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REVIEW ARTICLE

The changing face of trigeminal neuralgia—A narrative review

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Abstract

Objective: This narrative review aims to update the reader on the new classification of trigeminal neuralgia (TN), clinical signs, pathophysiologic evidence, and their implications on management. This review is based on the authors' collective experience and knowledge of the literature in addition to a literature search.

Background: In recent years, the phenotype of TN has been intensively studied leading to discrete groups of patients. These include patients with TN with additional continuous pain, and patients with and without neurovascular compression of the trigeminal dorsal root entry zone. A number of associated clinical signs such as tearing and sensory changes need further research.

Methods: The literature on TN was searched in PubMed with the aims of providing evidence for the recently published third edition of the *International Classification of Headache Disorders* (ICHD) and update the clinical phenotype and management of the TN subcategories.

Results: The ICHD's new classification for TN is based on reliable clinical data, imaging, and neurophysiologic studies. The TN classification reflects current knowledge and has improved the possibility for clinicians to choose adequate management options. However, there is a lack of effective, safe drugs for the management of TN and sparse, robust data on neurosurgical options.

Conclusion: Research into all aspects of TN—diagnosis, pharmacotherapy, surgery, long-term management prognosis, and natural history—is needed. Research should adhere to the ICHD's schema for TN. Improved drugs are needed along with rigorous research into surgical options and their efficacy for different subtypes of TN.

KEYWORDS
classification, neuropathic pain, trigeminal nerve

INTRODUCTION AND DEFINITION

Trigeminal neuralgia (TN) is a unilateral facial pain with pronounced physical signs and symptoms and a very typical clinical phenotype. The pain is excruciating, short-lasting, usually described as electrical or sharp and is "triggered" by light touch in the affected area.[1] Often pain is accompanied by a characteristic spasm in the ipsilateral part of the face and explains its previous names "tic convulsif" or "tic douloureux." The disorder is debilitating and significantly affects the quality of life (QoL).[2,3]

Over the last decade or so we have recognized that TN does not exclusively present as described above. A large proportion of patients have continuous pain between attacks; attack duration may last for longer than 2 min; some patients have ipsilateral tearing; and mild sensory changes are quite common even in the absence of a space-occupying

Abbreviations: CTN, classical trigeminal neuralgia; ICHD, *International Classification of Headache Disorders*; IHS, International Headache Society; ITN, idiopathic trigeminal neuralgia; NVC, neurovascular compression; QoL, quality of life; STN, symptomatic trigeminal neuralgia; TN, trigeminal neuralgia.

lesion or multiple sclerosis (MS). More recently, a large number of patients with TN have been shown to lack any significant neurovascular compression (NVC). The current schema for TN and its subtypes published by the International Headache Society (IHS) with the third edition of the *International Classification of Headache Disorders, 3rd edition* (ICHD-3)[1] is the result of intense collaboration between the IHS and the International Association for the Study of Pain (Table 1).

During the last decade, new "faces" of TN have been described with different phenotypes, variably including continuous pain, tearing, and longer attack duration, which are now also partly reflected in ICHD-3. This raises some important questions: Are the different clinical phenotypes a spectrum of the same disorder? Or are we seeing the emergence of clearly different subtypes with related but distinct pathophysiologies and possibly treatment protocols? These are the emerging faces of TN.

METHODS

This is a narrative review based on the authors' collective experience and knowledge of the literature in addition to a PubMed search. An electronic PubMed search aimed at updating the authors' literature bank and previous reviews was performed on December 22, 2020. The search was limited to publications in English appearing between January 1, 2015 and December 20, 2020 under the search terms "TN," "facial neuralgia," and "trigeminal neuropathic pain." The resulting publication list (title and abstract) was examined to verify if patients with TN were involved. Relevant publications were retrieved electronically and information cited as deemed relevant by the authors. As a narrative review, these are representative of the authors' opinions.

CLASSIFICATION

"TN" as a diagnosis can be established clinically (Table 2), but to subclassify the diagnosis, imaging is needed (Figure 1).[1] Classical trigeminal neuralgia (CTN) is defined as occurring with "demonstration on MRI or during surgery of NVC (not a simple contact), with morphological changes in the trigeminal nerve root."[1] Compression is typically associated with nerve atrophy or displacement. CTN remains subdivided into purely paroxysmal or with concomitant continuous pain (Table 3). Secondary trigeminal neuralgia (STN) is reserved for a typical TN phenotype associated with a space-occupying lesion or MS usually associated with demyelination of the trigeminal nerve root (Table 4 and Figure 1). A striking change is the introduction of a new, evidence-based subcategory: idiopathic trigeminal neuralgia (ITN). ICHD-3 defines ITN as "trigeminal neuralgia with neither electrophysiological tests nor MRI showing significant abnormalities." The use of "neither/nor" implies that both must be absent. Although MRI is widely available, electrophysiology equipment and trained staff are not. Our opinion is that ITN definition needs rewording, possibly: "Trigeminal neuralgia without significant morphological abnormalities on MRI. The diagnosis is strengthened by electrophysiological and other tests similarly showing no causative reason" (Table 5 and Figure 1). ITN is also subdivided into purely paroxysmal and those with concomitant continuous pain.[1] ICHD has now made the triggering phenomenon a compulsory criterion for TN[4] bringing the structure of the TN diagnostic criteria in line with those for other neuropathic pains.[5-7]

TRIGEMINAL NEURALGIA EPIDEMIOLOGY

Lifetime prevalence figures suggest around 70 TN cases per 100,000 population, and it is, therefore, a rare condition.[8] Recent data suggest an incidence of 12.6–27/100,000 patient-years.[9] The crude annual incidence of TN is 4.3–8 per 100,000; higher in females (5.7) than in males (2.5). However, in those >80-years-old, males have a very high incidence of 45/100,000.[8,10] Peak incidence begins at 50–60 years and increases with age; in 60- to 69-year-olds, it is 17.5/100,000, whereas in >80-year-olds, it is 25.9/100,000.[11]

TABLE 1 Subtypes of trigeminal neuralgia and their coding as per the International Classification of Headache Disorders, 3rd edition (ICHD-3)

13.1 Pain attributed to a lesion or disease of the trigeminal nerve			
13.1.1	Trigeminal neuralgia (TN)		Note: Clinically established
	13.1.1.1	Classical TN (CTN)	
		13.1.1.1.1	CTN, purely paroxysmal
		13.1.1.1.2	CTN with concomitant continuous pain
	13.1.1.2	Secondary TN (STN)	
		13.1.1.2.1	TN attributed to multiple sclerosis
		13.1.1.2.2	TN attributed to space-occupying lesion
		13.1.1.2.3	TN attributed to other cause
	13.1.1.3	Idiopathic TN (ITN)	
		13.1.1.3.1	ITN, purely paroxysmal
		13.1.1.3.2	ITN with concomitant continuous pain

TABLE 2 Diagnostic criteria for trigeminal neuralgia

Diagnostic criteria		Notes
A	Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond,[1] and fulfilling criteria B and C	In a few patients, pain may radiate to another division, but it remains within the trigeminal dermatomes Classical trigeminal neuralgia may be preceded by a period of atypical continuous pain termed "pretrigeminal neuralgia" in the literature Pain is overwhelmingly unilateral and does not cross the midline. Bilateral pain may indicate disease (e.g., multiple sclerosis) Most patients suffer pain in the distribution of the second or third division or both Pain may be accompanied by spasm of the facial muscles Periods of remission from days to years may occur
B	Pain has all of the following characteristics: 1. Lasting from a fraction of a second to 2 min 2. Severe intensity 3. Electric shock-like, shooting, stabbing, or sharp in quality	Duration can change over time, with paroxysms becoming more prolonged. A minority of patients will report attacks predominantly lasting for >2 min Attack duration, distribution, etc. may vary between patients but are highly consistent within cases, that is, attacks are stereotyped in the individual patient Pain may become more severe over time Mild autonomic symptoms such as lacrimation and/or redness of the eye may be present
C	Precipitated by innocuous stimuli within the affected trigeminal distribution	Some attacks may be, or appear to be, spontaneous, but there must be a history or finding of pain provoked by innocuous stimuli to meet this criterion. Ideally, the examining clinician should attempt to confirm the history by replicating the triggering phenomenon. However, this may not always be possible because of the patient's refusal, awkward anatomical location of the trigger, and/or other factors A short gap between trigger and pain may be observed (latency). Following an attack, a refractory period occurs where pain cannot be triggered
D	Not better accounted for by another ICHD-3 diagnosis	Other causes are ruled out by history, physical examination, and special investigations. Imaging (preferably MRI) should be done to exclude secondary causes and, in the majority of patients, to demonstrate neurovascular compression of the trigeminal nerve (i.e., establish classical trigeminal neuralgia) Sensory testing may reveal mild deficits in the distribution of the trigeminal nerve

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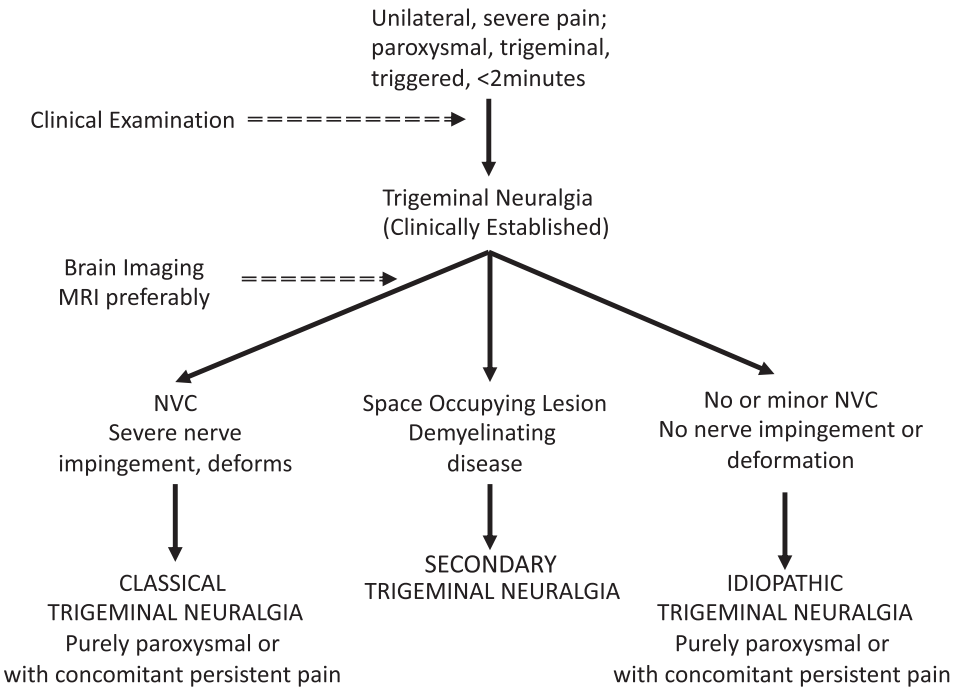

FIGURE 1 Flow diagram for the diagnosis of trigeminal neuralgia into subtypes (see also Table 1). MRI, magnetic resonance imaging; NVC, neurovascular contact

TABLE 3 Diagnostic criteria for classical trigeminal neuralgia

Criteria		Comments
A	Recurrent paroxysms of unilateral facial pain fulfilling criteria for 13.1.1 Trigeminal neuralgia	Typically nerve root atrophy and/or displacement due to neurovascular compression (NVC), which are independently associated with the signs and symptoms of trigeminal neuralgia. Classical trigeminal neuralgia is caused by neurovascular compression, most frequently by the superior cerebellar artery. The common site of neurovascular compression is at the root entry zone, with compression by an artery more clearly associated with symptoms than compression by a vein. MRI techniques to measure volume and cross-sectional area of the root are available. Atrophic changes may include demyelination, neuronal loss, changes in microvasculature, and other morphological changes
B	Demonstration on MRI or during surgery of neurovascular compression (not simply contact), with morphological changes in the trigeminal nerve root	
Diagnostic criteria for classical trigeminal neuralgia, which is purely paroxysmal or with concomitant continuous facial pain		
Purely paroxysmal		**With concomitant continuous facial pain**
A	Recurrent paroxysms of unilateral facial pain fulfilling criteria for 13.1.1.1 Classical trigeminal neuralgia	Recurrent paroxysms of unilateral facial pain fulfilling criteria for 13.1.1.1 Classical trigeminal neuralgia
B	Pain-free between attacks in the affected trigeminal distribution	Concomitant continuous or near-continuous pain between attacks in the affected trigeminal distribution

Note: With permission from the International Headache Society.

TABLE 4 Diagnostic criteria for secondary trigeminal neuralgia

Criteria		Comments
A	Recurrent paroxysms of unilateral facial pain fulfilling criteria for 13.1.1 Trigeminal neuralgia, either purely paroxysmal or associated with concomitant continuous or near-continuous pain	In many cases, clinically indistinguishable from classical or idiopathic trigeminal neuralgia Clinical examination shows sensory changes in a significant proportion of these patients
B	An underlying disease has been demonstrated known that is to be able to cause, and explaining, the neuralgia	1. Recognized causes are tumor in the cerebellopontine angle, arteriovenous malformation, and multiple sclerosis (MS)
C	Not better accounted for by another ICHD-3 diagnosis 1. Recognized causes are tumour in the cerebellopontine angle, arteriovenous malformation and multiple sclerosis 2. MRI is best equipped to detect an underlying cause for Secondary trigeminal neuralgia. Other investigations may include neurophysiological recording of trigeminal reflexes and trigeminal evoked potentials, suitable for patients who cannot undergo MRI	2. MRI is best equipped to detect an underlying cause for 13.1.1.2 Secondary trigeminal neuralgia. Other investigations may include neurophysiological recording of trigeminal reflexes and trigeminal evoked potentials, suitable for patients who cannot undergo MRI
Most common forms of secondary trigeminal neuralgia		
Trigeminal neuralgia attributed to MS		**Trigeminal neuralgia attributed to space-occupying lesion**
A	Recurrent paroxysms of unilateral facial pain fulfilling criteria for 13.1.1 Trigeminal neuralgia	Recurrent paroxysms of unilateral facial pain fulfilling criteria for 13.1.1 Trigeminal neuralgia
B	B. Both of the following: 1. MS has been diagnosed 2. An MS plaque at the trigeminal root entry zone or in the pons affecting the intrapontine primary afferents has been demonstrated by MRI, or its presence is suggested by routine electrophysiological studies showing impairment of the trigeminal pathways	Both of the following: 1. A space-occupying lesion in contact with the affected trigeminal nerve has been demonstrated 2. Pain has developed after identification of the lesion or led to its discovery
C	Not better accounted for by another ICHD-3 diagnosis	Not better accounted for by another ICHD-3 diagnosis

Note: A third type is defined by ICHD: "Trigeminal neuralgia attributed to other cause." This is designed to be a flexible diagnosis that may include various causes of secondary TN with criteria that clearly link the disorder to the signs and symptoms.
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CLINICAL FEATURES OF TRIGEMINAL NEURALGIA

The diagnosis of TN is initially clinical, based on the history, characteristic clinical signs, and symptoms. For such a dramatic clinical presentation, there are many misdiagnoses in TN. Possibly because clinical signs may vary across patients depending on which dermatome/s are affected, the exact duration of pain, and the absence/presence of background pain: numerous permutations of these can make diagnosis challenging.

TABLE 5 Diagnostic criteria for idiopathic trigeminal neuralgia

Criteria		Comments
A	Recurrent paroxysms of unilateral facial pain fulfilling criteria for 13.1.1 Trigeminal neuralgia, either purely paroxysmal or associated with concomitant continuous or near-continuous pain	A contact between a blood vessel and the trigeminal nerve and/or nerve root is a common finding on neuroimaging in healthy subjects. When such a contact is found in the presence of 13.1.1 Trigeminal neuralgia but without evidence of morphological changes (e.g., atrophy or displacement) in the nerve root, the criteria for 13.1.1.1 Classical trigeminal neuralgia are not fulfilled and the condition is considered idiopathic
B	Neither 13.1.1.1 Classical trigeminal neuralgia nor 13.1.1.2 Secondary trigeminal neuralgia has been confirmed by adequate investigation including electrophysiological tests and MRI	
C	Not better accounted for another ICHD-3 diagnosis	Electrophysiological tests nor MRI showing significant abnormalities
Diagnostic criteria for idiopathic trigeminal neuralgia, which is purely paroxysmal or with concomitant continuous facial pain		
Purely paroxysmal		**With concomitant continuous facial pain**
A	Recurrent paroxysms of unilateral facial pain fulfilling criteria for 13.1.1.3 Idiopathic trigeminal neuralgia	Recurrent paroxysms of unilateral facial pain fulfilling criteria for 13.1.1.3 Idiopathic trigeminal neuralgia
B	Pain-free between attacks in the affected trigeminal distribution	Concomitant continuous or near-continuous pain between attacks in the affected trigeminal distribution

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TRIGEMINAL NEURALGIA

Purely paroxysmal or with concomitant continuous pain

Most of the available data on clinical features have been published according to the definition of "CTN" in common use up till the publication of ICHD-3. Presently, according to ICHD-3, this would include the recently classified ITN. In general, the clinical features across the subtypes (CTN, ITN, STN) seem to be very similar and, as stated, support the use of imaging in all TN. Although most patients with TN report characteristic, paroxysmal attacks of pain, some patients present with a history of concomitant continuous pain and are classified separately (Tables 1 and 2). TN with continuous pain may account for up to 30% of patients[12,13]; it has historically been referred to as "atypical" or "type 2."

Location

TN is a unilateral facial pain syndrome.[1,12,14,15] Bilateral cases have been reported in 2%–5% of cases, but one side usually precedes the onset of pain on the contralateral side by years.[13,16,17] Bilateral pain is considered an ominous sign that needs rapid investigation. Reviews of case series suggest that the right side is involved more often, but the clinical significance is doubtful. Pain location is usually described according to the major branches of the trigeminal nerve.[18] Pain in one branch is reported by 36%–42% of patients: in 17%–19%, pain occurs in the maxillary or the mandibular branch, whereas pain solely in the ophthalmic occurs in about 2% (Figure 2). Most commonly, pain involves the maxillary and mandibular branches jointly (35%), and pain in all three branches occurs in 14% of patients. The jaws are, therefore, involved in most cases (Figure 3, dashed oval),[11,12,15,19-22] explaining why patients with TN so often seek help from dentists. Pain radiation is usually within the dermatome of origin.

Although the location, intensity, and triggers of TN vary across patients, they may be *stereotyped* within individual patients with TN, that is, each attack is similar in location, duration, and intensity.[15] However, some patients may report differences in location within the same affected area as well as differences in duration and intensity.

Quality and severity

Pain in TN is most often described as shooting, sharp, piercing, stabbing, or electrical in nature (70%–95%).[11,12,15,20,21,23] Pain severity in TN is extreme; with ratings of 9–10 on a 10-cm visual analog scale (VAS).[14,24] Less severe attacks may also occur.

Triggering

The diagnostic criteria for TN include that pain is precipitated by light, innocuous stimuli in *trigger* areas (Figure 3). Spontaneous pain is reported by some patients (68%–98%),[15,25,26] but it is unclear whether these reflect triggering by subconscious day-to-day activities, such as swallowing and lip movement, that may go unnoticed. When attacks are reported as spontaneous, the precise location of the trigger areas may be difficult to identify clinically.[27] A short gap between stimulation of a trigger area and pain onset may be observed and is termed *latency*. Trigger areas in TN are usually in the distribution of the affected trigeminal branch (Figure 3), particularly around the lips but may rarely be extratrigeminal,[4,14,25] usually multiple and even change location. The triggering stimuli are innocuous and include talking (76%), chewing (74%), touch (65%), temperature (cold 48%, heat 1%), wind, and shaving.[14,15] The most common extraoral trigger areas are the nasolabial fold, the lips, the cheek, and the chin.[25] Intraoral TN triggers and pain are more often associated with the alveolar gingivae[14,28] (Figure 3).

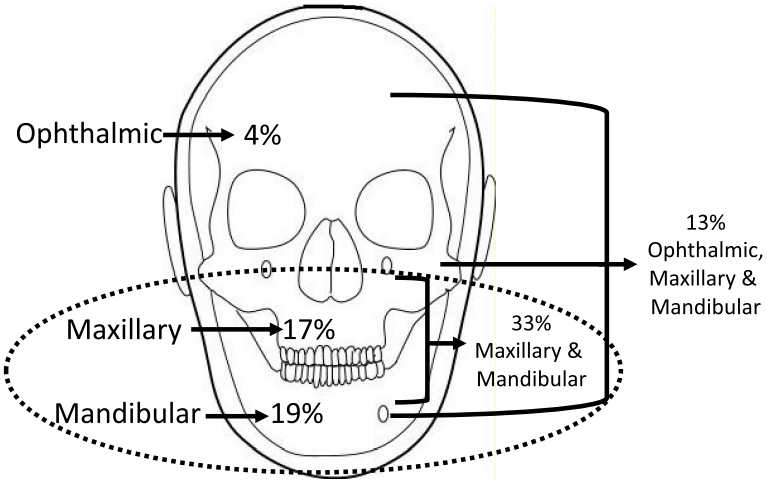

FIGURE 2 Distribution of pain in classical or idiopathic trigeminal neuralgia. Pain is unilateral in the overwhelming majority of patients (>95%). On the right side of the face, the percentage of pain reported affecting single branches of the trigeminal nerve is shown. On the left side of the face, the percentage of pain occurring in combined branches is shown. The separation of percentages to the two sides of the diagram is for clarity only. The total as per the figure is not 100%: partly explained by the fact that the figures were drawn from multiple sources and that bilateral cases are not included. These figures are however secondary to the message they convey: The majority of patients with TN (about a sizable proportion) experience pain in trigeminal divisions II and III concomitantly. Isolated pain in either division II or III is very common. Thus, pain occurring singly in the mandible and/or maxilla accounts for 69% of patients (included within the dashed oval), partly explaining why patients often approach dental practitioners for an opinion. (This figure is an original drawing by the author (RB) using computer software.) [Color figure can be viewed at wileyonlinelibrary.com]

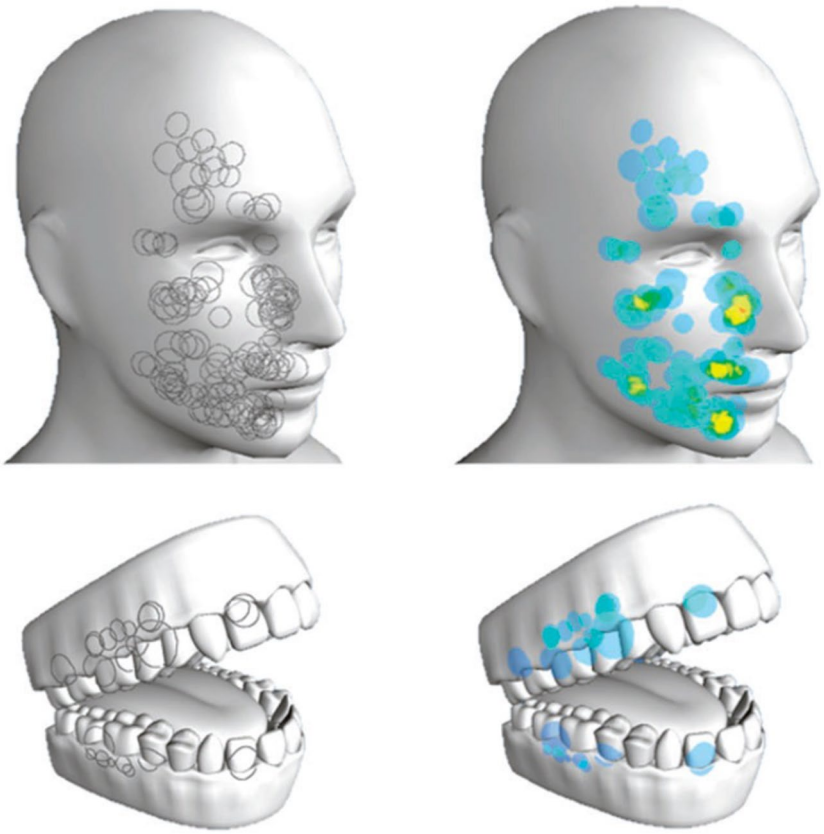

FIGURE 3 Trigger zone distribution in a cohort of 70 prospectively enrolled patients with classical or secondary trigeminal neuralgia. Upper panel: Extraoral territories. Lower panel: Intraoral territories. Left column: Trigger-zone contours. Right column: Trigger-zone overlap profiling. The number of superimpositions ranges from 2 (cyan) to 15 (dark orange). The number of trigger zones in the intraoral territory is smaller in comparison with the number of patients reporting talking or chewing as the main trigger maneuvers because of the patients' difficulty in identifying a circumscribed trigger-zone region within the mouth. From Di Stefano et al., 2018, with permission from the International Headache Society [Color figure can be viewed at wileyonlinelibrary.com]

Figure 3 clearly illustrates the density of trigger areas around the lips, nasolabial folds, and intraoral areas.[25] These are typical areas for pain of dental or otolaryngologic origin and, together with pain location (Figure 2), partly explain the misdiagnoses made between TN, dental, and otolaryngologic pain.

The triggering of TN-like pain by gustatory stimuli[29] is an interesting phenomenon that has been described as both primary and secondary (postsurgical) syndromes. The initiation of pain by sweet or salty foods is usually associated with dental pathology so that these cases present a difficult diagnosis.

Temporal pattern

TN may begin abruptly, and the patient usually recalls the exact day,[26] or via a rarer preceding syndrome termed pre-TN described below.[30] Individual attacks are characterized by a rapid onset and peak, and then subside, lasting overall from a few seconds up to 2 min.[31] Longer-lasting attacks have been reported, but the significance is unclear.[1,12] Pain is followed by a *refractory period* during which pain is impossible or extremely difficult to trigger.[32] Attacks occur mostly during the day, but there are reports of nocturnal TN.[33,34]

Long-term follow-up of patients with TN reveals that there are well-defined periods of pain attacks variably followed by periods of remission that may last from weeks to years. This pattern complicates the research and management of TN as often temporary remission is misinterpreted by patients/carers as treatment success. The median active period is reported at about 49 days followed by remission of some months (36%), weeks (16%), or even days (16%). Only 6% may look forward to remissions of more than a year, and about 20% experience incessant attacks.[11,35,36] Following a first attack of TN, it has been calculated that 65% of patients will have a second attack within 5 years and 77% within 10 years.[11]

Natural history and prognosis

TN has historically been considered a progressive disease with a poor prognosis.[37] The available data at the time suggested that 90% of TN cases eventually reported increased attack frequency and severity.[14,38] It must be stressed that the inclusion criteria of the historical data may not reflect current classification groupings. Based on the same type of data, the initial response to carbamazepine was cited at around 70% and by 5–16 years the response rate dropped to 20% with 44% of patients requiring drug combinations or alternative medication.[39] Long-term follow-up of oxcarbazepine (OXC)-treated TN cases demonstrated a high failure rate necessitating surgery.[38]

More recent data suggest that typical paroxysmal TN acts quite differently.[40] Of 95 patients treated with carbamazepine and 83 with OXC (at usually acceptable dosages), the initial response was 98% and 94%, respectively.[40] Side effects were common in both drugs and reduce QoL that may lead to cessation of therapy.[40,41] Drug resistance at the 13-month time point was rare, and 7% required a neurosurgical intervention. This suggests that the immediate response rate is better than previously thought and that the short-term prognosis is good. The data, which were collected from paroxysmal patients with TN exclusively, strengthen current thinking that different TN subgroups respond differentially to standard therapy. We are still in need of long-term, high-quality studies on the natural history of TN in its various forms and the long-term response to various therapies.

Associated sensory signs

Although clinically detectable neurological changes suggest STN, mild sensory disturbances, particularly hypoesthesia, have been documented in TN. These deficits, that may go unnoticed in gross examination, may be more readily detected when using sophisticated examination techniques, particularly quantitative sensory testing (QST).[15,42-45] Reflex and evoked potential studies reveal nociceptive fiber dysfunction in TN.[46] Following successful microvascular decompression (MVD), nerve conduction properties return to normal, but clinical improvement is often delayed.[47] More recently, examination of a large series of patients with TN revealed sensory abnormalities in around 30%.[48] The authors suggest that clinically detected sensory abnormalities should form part of the spectrum of TN.[48]

Interesting findings emerge from a blinded QST study on patients with TN with no clinically detectable sensory abnormalities.[49] They found generalized subclinical hypoesthesia (increased mechanical detection threshold), which was more pronounced on the symptomatic side, in trigeminal and extratrigeminal sites relative to controls. This would suggest generalized, rather than segmental, somatosensory plasticity.

Accompanying autonomic signs

Characteristically lacrimation is not considered a sign of neuropathic type pain. However, lacrimation and rhinorrhea have been reported in TN. Lacrimation has been described in ophthalmic, maxillary, and mandibular TN.[12,50-52] This presentation is diagnostically challenging vis-à-vis the short-lasting trigeminal autonomic cephalgias (see below). The appearance of lacrimation in TN is inconsistent occurring in about a quarter of cases and seems to correlate with increasing pain severity—possibly by initiating the trigeminal autonomic reflex. The presence of lacrimation indicates a poorer prognosis for surgery and pharmacotherapy.[51,53] Evidence of autonomic activity in TN is also found in reports of facial flushing (vasodilation), increased salivation, and swelling.[51,54] The true significance of tearing in TN is, however, unclear.

Investigations

There are no specific diagnostic tests for TN. Mostly, tests are aimed at excluding alternate diagnoses. A neurologic examination should

be routine and thorough evaluation with adequate testing by relevant specialists is appropriate. In all cases, dental examination with radiographs of oral structures should be considered to rule out oral pathology.

Preparing for pharmacotherapy

All patients to be treated with anticonvulsants need baseline and follow-up of hematologic, electrolyte, and liver function tests. Baseline ECG is highly recommended. Anticonvulsants increase the risk for suicidality and careful follow-up of patients, particularly of at-risk individuals and close collaboration with the family physician should be maintained. In patients of Asian ancestryto be treated with carbamazepine, HLA-B*1502 testing to assess the risk of Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is recommended by the FDA. Patients at risk for SJS/TEN with carbamazepine also carry an increased risk with other antiepileptic drugs (AEDs). Women in child-bearing years should be informed of the teratogenic potential of AEDs and advised regarding contraception and pregnancy.[55,56]

Imaging

Imaging in TN has two aims: to establish and assess NVC and to exclude disease and tumors in the central nervous system (CNS), thereby establishing diagnosis. Some clinical centers do not or are not equipped to image their patients with TN on a routine basis. However, the European Academy of Neurology states, "magnetic resonance imaging (MRI), using a combination of three high-resolution sequences, should be performed as part of the work-up in TN patients, because no clinical characteristics can exclude secondary TN."[57] The ICHD-3 does not specifically address the issue other than to stress that imaging is the only way to establish the precise diagnosis.[1] The American Academy of Neurology rates imaging as level C diagnostic evidence.[58] Their data reiterate that STN will occur in about 15% of TN[58] cases and, thus, our recommendation would be to always image when possible.[59]

For routine diagnosis and treatment planning in TN, MRI is the method of choice.[57] NVC is clearer using 3-Tesla resolution although lower resolutions may be used and are good enough at depicting space-occupying lesions. To reliably detect and accurately grade the severity of neurovascular contact, three high-resolution sequences are recommended: 3D T2-weighted, 3D time-of-flight, and MR angiography with 3D T1-weighted gadolinium.[57]

Neural structure is best studied with diffusion tensor imaging, for now largely restricted to the research field. This technique has shown altered nerve structure as a result of NVC. Fractional anisotropy, an indicator for white matter integrity, is altered in the nerve root entry zone of patients with TN.[60-64] This would suggest demyelination or dysmyelination as is seen in histological samples of nerve root biopsies from patients with TN.[65,66]

Quality of life

The severity of TN has resulted in patients committing suicide; however, TN does not alter life expectancy. QoL is much reduced in patients with TN either as a direct effect of the pain or secondary to drug side effects.[14,41] Patients with TN are often depressed and anxious[67] and need family and possibly professional support.[26]

FEATURES IN TN WITH CONCOMITANT CONTINUOUS PAIN

Patients with TN may describe two types of pain: paroxysmal attacks of short, sharp pain and a background pain that may last from hours to days.[13,33] Background pain may be described as dull, throbbing, aching, and burning,[68] and is of varying intensity with a mean VAS of 4.6.[13] Some patients with TN with continuous pain also report longer attacks of paroxysmal pain. Continuous pain may be triggered in about 50% of cases, typically by chewing, cold wind, talking, touch, or toothbrushing.[13] In one recent series, bilateral pain was significantly more common in TN with background pain.[13] Patients with TN with background pain are younger and more often female than in purely paroxysmal TN.[13] Continuous background facial pain is a clinical predictor of poorer treatment response.[53,69-71]

SECONDARY TN

In most cases STN is clinically indistinguishable from CTN or ITN, hence the need for imaging.[57]

TN ATTRIBUTED TO MULTIPLE SCLEROSIS

More than half of patients with MS report some type of pain during the course of their disease.[72,73] More than a quarter will experience central pain that is bilateral, constant, aching, burning, or pricking. Nonfacial pain may be a presenting symptom of MS in 5.5% of cases, alone or in combination with other signs.

TN in MS may be due to demyelination of the trigeminal nerve. Additionally, findings of NVC of the nerve root and positive outcome of MVD for these cases suggest that vascular malformations may also contribute to the appearance of TN in MS,[74] but the available studies are contradictive.[75] MS increases the risk of developing TN by a factor of 20. Clinical signs predictive of MS in patients with TN are bilateral pain (14% in MS) and young age.[76] Very rarely does TN herald the onset of MS; this was observed in only 0.3% of MS cases. In one cohort study of patients with TN with MS, TN preceded MS diagnosis in 19% of the cases.[74] Usually, TN develops in a person already diagnosed with MS, on average about 12 years after the onset of MS and occurs in 1.5%–7.9% of those with MS.[72,73,77]

TRIGEMINAL NEURALGIA ATTRIBUTED TO SPACE-OCCUPYING LESIONS

Trigeminal nerve dysfunction has been observed in 33% of patients with middle and posterior cranial fossa tumors but in only 13% was this the presenting symptom.[78] About 10% of cases with intracranial tumors experienced TN-like symptomatology. Pain may mimic TN, persistent idiopathic facial pain, and temporomandibular disorders.[79] Posterior fossa tumors and meningiomas are most likely to cause TN-like symptoms.[78,80] Cerebellopontine angle tumors (e.g., acoustic neuromas) may also cause TN, and this diagnosis is more likely when the patient is young and suffers pain in more than one trigeminal branch. In patients with TN under the age of 29 years, the possibility of underlying pathology is significantly increased.[81] Specifically, 10%–13.4% of patients with TN may have intracranial tumors, and MRI is the most sensitive diagnostic technique.[82] Most of these patients are usually younger than expected for TN and develop subtle or frank neurologic deficit.[83] A reduced corneal reflex and hypesthesia were typical of cranial masses. Gamma knife stereotactic (GKS) radiosurgery has recently been used to treat benign intracranial tumors.[84,85] However, although tumor control may be successful, the facial pain does not always resolve.

IDIOPATHIC TRIGEMINAL NEURALGIA

Clinical signs and symptoms, at this time, seem to be identical with those of CTN, but further research is needed. Comparing demographics of ITN with CTN, females are affected more commonly, and the patients are younger at disease onset.[86,87]

It is of interest to compare the efficacy of MVD between the two groups. Most previous studies do not distinguish efficacy rates based on morphological changes of the trigeminal nerve, but a few studies indicate that MVD is more efficacious in CTN versus ITN.[88-91] In one Danish neurosurgical study of 59 primary patients with TN, MVD was significantly more efficacious in men as opposed to women,[88] but this possible sex difference is yet to be replicated in other similar high-quality studies.

The striking issue with ITN is that by definition there is no compression from a NVC and no other known causative factors. Further research is needed to elucidate pain mechanisms. Furthermore, neuropathic pain is defined as "pain arising as a direct consequence of any lesion or disease affecting the somatosensory system."[92] Diffusion tensor imaging studies provide early data to indicate that patients with ITN also have de- and dysmyelination of the trigeminal root of unknown origin.[64] These studies need replicating and expanding so that ITN can confidently be regarded as a neuropathic pain.

PRETRIGEMINAL NEURALGIA

An early form of CTN termed "pretrigeminal neuralgia" (pre-TN) has been reported in 18% of patients with CTN and is characterized by a dull continuous pain in one of the jaws that lasts from days to years.[30] Pre-TN pain often mimics dental pathology leading to possible misdiagnosis.

Our clinical experience confirms that there are cases with highly atypical features that respond to carbamazepine and eventually develop into CTN. However, the lack of clear and consistent diagnostic criteria makes this a problematic entity to recognize; it is usually diagnosed when all other possibilities are exhausted or in retrospect once CTN develops.

TRIGEMINAL NEURALGIA COMORBIDITY

TN most often occurs as a single pain syndrome. However, it has been reported rarely to occur with cluster headache and with paroxysmal hemicrania; these are termed cluster-tic and chronic paroxysmal hemicrania-tic syndromes, respectively. Around 10% of patients with glossopharyngeal neuralgia suffer comorbid CTN.[93]

DIFFERENTIAL DIAGNOSIS OF TRIGEMINAL NEURALGIA

The numbers of misdiagnosed TN cases suggest that the clinical presentation may not always be clear or typical, or there is a general lack of awareness of the features of TN in spite of TN having a typical and dramatic clinical presentation.

The diagnostic pitfall of suspecting TN in any facial pain patient merely because of an MRI-verified neurovascular contact is frequently observed in clinical practice. As previously stated, TN diagnosis is clinical and is based on clear diagnostic criteria. It is only if the diagnostic criteria for TN are fulfilled that it is of interest to look for a neurovascular contact.

Depending on location, the presence of background pain and other signs such as tearing, patients attend the most appropriate clinician in their own judgment. A recent survey found that most patients with TN consult medical professionals including primary care physicians (43.1%), dentists (in 30.4%), otorhinolaryngologists (3.9%), neurosurgeons (3.9%), and neurologists or headache specialists (14.7%).[94] The common misdiagnoses are surprising and include migraine (n = 5, 6.5%), cluster headache (n = 4, 5.2%), temporomandibular joint dysfunction (n = 3, 3.9%), tension-type headache (n = 1, 1.3%), glaucoma (n = 1, 1.3%), otitis (n = 1 1.3%), and tonsillitis (n = 1, 1.3%).[94,95]

The mean diagnostic delay from disease onset was 10.8 ± 21.2 months. Misdiagnoses at first consultation were found in 42.1% of the cases, whereas only 19 subjects (18.4%) received a correct diagnosis.[94] The number of TN cases presenting with extensive misdiagnosis suggests that there is a need to increase education and awareness among all medical professionals.

DENTAL

TN can mimic dental pain quite well, and up to a quarter of cases will initially consult a dentist.[28] Indeed, 33%–65% of TN cases may

undergo unwarranted dental interventions; up to 12% may be eventually rendered edentulous.[14,28] Invasive dental treatment must not be performed when no positive anamnestic, clinical, and radiographic signs indicate it.

SHORT-LASTING UNILATERAL NEURALGIFORM HEADACHES WITH AUTONOMIC SIGNS

Short-lasting unilateral neuralgiform headaches with autonomic signs (SUNHA), which includes SUNCT and SUNA as subclassifications in ICHD, combines characteristics of neuralgiform pain with autonomic signs, such as lacrimation. The differential diagnosis versus cases of TN with lacrimation is extremely difficult. ICHD allows for both diagnoses to be given in a single patient.

Based on the strikingly similar clinical phenotype and associated signs, discussion continues on whether SUNHA is a neuropathic pain related to TN.[96-98] The evidence for this is mixed. The demography is different, as in SUNHA, there is an equal representation of men and women, and the average age of onset is 44 years, whereas in TN, there is an overrepresentation of women and an average age of onset of 52 years.[99] Mechanical precipitation of attacks is a hallmark of TN but is also seen in SUNHA.[100] Refractory periods are considered typical of TN and are very rare in SUNCT patients.[100] Supraorbital nerve blockade has been relatively unsuccessful in SUNCT,[100] whereas nerve blocks are effective in CTN cases with lacrimation. CTN reliably responds to carbamazepine, whereas SUNCT syndrome is characterized by drug resistance from its onset.[100] Imaging studies suggest that SUNHA is related to the trigeminal autonomic cephalalgias,[101] but recent discoveries point to an association between NVC and the painful side in SUNHA.[99] The absence of trigeminal sensory pathway abnormalities would support the view that it is not a neuropathic type of pain.[102]

PAINFUL POSTTRAUMATIC TRIGEMINAL NEUROPATHY (PREVIOUS TERM: ANESTHESIA DOLOROSA)

A unilateral or bilateral facial or oral pain that follows trauma to the trigeminal nerve(s).[20,103] Pain is accompanied by prominent sensory deficits and other symptoms or clinical signs of trigeminal nerve dysfunction.[1,20]

Pain is usually continuous and burning with occasional spontaneous or touch evoked paroxysms. Together with hallmark allodynia, it should be a straightforward diagnosis, not to be confused with TN.

PATHOPHYSIOLOGY OF TRIGEMINAL NEURALGIA

Paroxysmal, short-lasting pain is the common feature across the subtypes of TN. We must keep in mind that the "idiopathic" subgroup is differentiated by the absence of NVC and "continuous pain" is part of the phenotype in a large proportion of both CTN and ITN.

Neurovascular compression

For CTN, there are several lines of evidence supporting compression of the trigeminal root at or near the dorsal root entry zone (DREZ) by a blood vessel as a major causative or contributing factor.[47,68,104,105] The DREZ is the point where the peripheral and central myelin sheaths of Schwann cells and astrocytes meet and is postulated to be significantly more susceptible to pressure effects. The compression is often arterial but may be venous or combined.[106] Early studies, searching for the etiology in TN not due to disease or pathology, revealed a high rate of vascular compression of the DREZ when using imaging methods and surgical observations.

This etiologic concept received wide support from imaging and correlated surgical findings[107-109] and ultrastructural analysis of neuronal tissue[65,66,110] that confirm NVC in many patients with resultant clear histologic damage to neurons and their myelin sheaths. Biopsy specimens of trigeminal roots demonstrate pathologic changes such as axonal loss and demyelination.[47,110] Within zones of demyelination, groups of axons are closely apposed without an intervening glial process. The location of the zone of demyelination matches the point of vascular indentation and extends about 2 mm in each direction.[47] Juxtaposed axons have also been demonstrated in MS patients with CTN. Using the nociceptive blink reflex and pain-related evoked potentials, impairment of the trigeminal nociceptive system due to demyelination and/or axonal dysfunction on the symptomatic side was located close to the DREZ in the brainstem.[111]

There must be significant NVC with related, secondary anatomical/structural changes in the nerve to establish CTN. This also increases the specificity and positive predictive value of imaging.[104] Neurovascular contact is reported in pain-free controls and in patients with ITN, but with no significant secondary anatomical/structural changes in the nerve.[104,112-115] These studies underscore the use of accurate imaging techniques.

Neurophysiology and sensory changes

Despite the findings indicating dysfunction of the trigeminal system, patients with CTN do not always have clinically detectable neurosensory dysfunction. When present, any dysfunction is mild and primarily involves touch and thermal sensation. The findings are usually in the symptomatic division but may occur in the other two ipsilateral trigeminal branches, which suggests central mechanisms.[45] Brainstem reflexes are usually normal in CTN, but not in TN due to systemic disease or regional pathology and are, therefore, useful for diagnosis. Patients with STN usually all have abnormal laser-evoked potentials (LEPs), whereas only a proportion of patients with CTN showed this abnormality,[42] and thus brainstem reflexes are more consistent in distinguishing CTN from

symptomatic TN. In terms of elucidating neuronal dysfunction in CTN, LEPs are obviously superior. Indeed, the finding that some patients with CTN have abnormal LEPs indicates a dysfunction of nociceptive fibers or of CNS pathways evoked by nociceptive afferent stimulation. Nociceptive fiber dysfunction may be a peripheral mechanism for the establishment of trigger points in CTN (pain induced by innocuous stimuli).

MVD of the nerve leads to prolonged pain relief in more than 90% of the cases[116,117] and reversal of sensory loss in many patients.[118] The outcome is often related to the presence and degree of NVC.[119,120] Moreover, MVD results in sustained pain relief for about 10 years in ~70% of patients with TN,[16,121] supporting NVC as the source of neuronal damage and pain.

Neuronal and CNS changes

Volumetric assessment of the affected trigeminal nerve in patients with CTN shows it to be significantly reduced.[122,123] This reflects atrophy of the nerve, often seen during surgery. Nerve degeneration, neuroinflammation, and edema have also been confirmed on diffusion tensor imaging.[61,62,124]

Reduced gray matter volume was observed in a cohort of patients with CTN,[125] similar to those described in other nerve injury models. The reduction of gray matter in some areas correlated with longer disease duration, suggesting a possible role for these structures in the long-term changes associated with CTN, such as increased pain and resistance to pharmacotherapy. Microstructural alterations in white matter have also been shown in CTN, and it is proposed that this is possibly a reactive change to the damage at the level of the root entry zone.[124]

A case–control functional magnetic resonance imaging study compared patients with CTN before and after MVD surgery with healthy controls.[126] The researchers assessed activation of primary (SI) and secondary (SII) somatosensory cortices on nonpainful tactile stimulation of lips and fingers in 18 patients with TN and 10 patients with TN relieved from pain after successful neurosurgical intervention in comparison with 13 healthy subjects. SI and SII activations in patients did not depend on the affected side of TN nor differ between operated and nonoperated patients. However, SI and SII activations, but not thalamic activations, were significantly reduced in patients compared with controls. These differences were most prominent for finger stimulation, an area not associated with TN. For lip stimulation, SI and SII activations were reduced in patients with TN on the contralateral side but not on the ipsilateral side to the stimulus. These findings suggest a general reduction of SI and SII processing in patients with TN, indicating a long-term modulation of somatosensory function and pointing to an attempt of cortical adaptation to potentially painful stimuli.

An earlier study investigated the changes in opioid receptor binding in patients with CTN before and after successful surgical treatment.[127] The volume of distribution of opioid binding was significantly increased after thermocoagulation of the relevant trigeminal division in the anterior cingulate and prefrontal cortices (and other cortical areas), basal ganglia, and thalamus bilaterally. The changes in binding most likely resulted from the postsurgical pain relief. The significant increase in opioid binding within some of the cortical and subcortical components of the pain matrix is consistent with the concept of decreased occupancy by endogenous opioid peptides when pain free. Endogenous opioids are involved in modulating nociceptive responses, and these results reinforce the concept of an altered CNS in patients with TN.

The studies described in the sections above support a pathophysiologic model involving nerve injury, with a significant secondary contribution of CNS structures in the complex pathophysiology of CTN. Although no such injury is present in ITN, CNS mechanisms need to be researched and may play a role in ITN.

Triggering and the trigeminal ganglion

Intriguingly, the pain trigger in TN is often innocuous stimulation. How is the trigeminal system altered so that light mechanical touch results in disproportionate pain? The trigeminal ganglion of patients with TN demonstrates degenerative hypermyelination and microneuromata with no significant damage to neuronal soma[128,129]; although unclear, the initiating event may be related to the injury induced by NVC.

Experimentally, following nerve injury, there is an increased proportion of neurons with subthreshold oscillations (pacemaker activity) that bring neurons close to firing threshold. These neurons often generate ectopic discharges spontaneously or following external stimuli.[130] Ectopic discharges often last a number of seconds, termed “afterdischarge.” Stimulation of the peripheral nerve (particularly A-β fibers) or the dorsal root produces a transient depolarization in passive neighboring C-fiber neurons in the same ganglion.[131] In experimental setups, about 90% of neurons sampled responded with this “cross-depolarization.” In injured nerves, this cross-depolarization leads to prolonged activity in neighboring neurons (crossed afterdischarge). These findings demonstrate a mechanism by which afferent nociceptors could be stimulated by activity in low-threshold mechanoreceptors, particularly following nerve injury. The “ignition hypothesis” was formulated based on these findings.[132] According to the hypothesis, injury renders axons and axotomized somata hyperexcitable resulting in synchronized afterdischarge activity, cross-excitation of nociceptors, and pain paroxysms. CNS neuroplasticity will no doubt occur in the presence of such peripheral changes and will ultimately affect the clinical phenotype and response to therapy. Although explaining many of the phenomena in CTN, the ignition hypothesis awaits definitive proof.

In a study examining the effects of triggering pain in CTN on CNS structures,[133] evidence was found for pathological hyperexcitability of the trigeminal nociceptive system. The pain neuromatrix showed significant activation during nonpainful stimulation of the trigger

zone, suggesting a state of persistent sensitization of the trigeminal nociceptive system in CTN.[133] This finding supports the involvement of central mechanisms in the triggering phenomenon of CTN.

Trigeminal neuralgia with concomitant continuous pain

In a substantial number of patients with CTN and ITN, a constant background pain accompanies paroxysmal pain. Possibly, central mechanisms may be more involved in these cases. One study showed no differences in CNS structures in patients with CTN with or without continuous pain,[125] but further imaging, neurophysiological, and psychophysical studies are needed on these subgroups.

The etiology of such continuous pain is unclear, and a faulty pain modulation system or central sensitization has been proposed.[134,135] Patients with CTN with continuous pain experienced no experimental induction of conditioned pain modulation, suggesting a deficient descending inhibitory system.[135] Additionally, they had more tender points relative to both controls and purely paroxysmal CTN patients, indicating central sensitization extending beyond the trigeminal system.[135] Central facilitation of trigeminal nociceptive processing was observed in patients with TN with continuous chronic facial pain indicating overactivation of central sensory transmission.[111]

There are indications that continuous background facial pain is a clinical predictor of poorer treatment response, both pharmacologic and surgical.[13,68,69,91,136] Nearly half of these patients have clinical sensory loss,[13] and this is a negative predictor for the long-term outcome of MVD[137] and gamma knife surgery.[138] MVD provided absolute postoperative pain relief in CTN for 80%–87% of cases and for 47%–79% of CTN cases with background pain.[91,137] Long-term follow-up (>5 years) revealed excellent results in 75%–80% of paroxysmal but only in 35%–54% of CTN cases with continuous facial pain.[91,137] The presence of background pain is also a negative prognostic factor in patients with CTN treated by rhizotomy.[139] In contrast, other centers report no differences in surgical or gamma knife outcomes,[140,141] and this may be related to different inclusion criteria.

Genetics

Familial clustering[142-145] has been observed, and a recent review suggests that familial TN is more common than previously considered.[143] Genetic variants within a 173-gene panel, comprising channel genes encoding sodium, potassium, calcium, chloride, transient receptor potential channels, and gap junction channels were studied in 11 patients with TN with a positive family history.[143] They demonstrated variants in genes encoding voltage-gated ion channels and transient receptor potential channels within these patients. A correlation has been observed between the serotonin transporter gene, pain severity, and response to carbamazepine.[146] Together with previous genetic studies,[147-151] it seems that there is a significant genetic component in signal transduction channels involved in this disorder's pathophysiology.[15,152]

MANAGEMENT

The therapeutic or management options are different for the subtypes of TN (Figure 4). Whether CTN is a progressive disease remains unclear. The improved morbidity rates of neurosurgical techniques such as MVD coupled with high efficacy rates suggest that many patients may benefit from surgery, possibly at an earlier stage. At present, medical management is the basis for many patients with CTN; even for surgical candidates medical therapy is essential preoperatively and is often needed postoperatively, albeit in reduced doses.[68]

PHARMACOLOGICAL,[153] SEE TABLE 6

Carbamazepine is highly efficacious in CTN and is usually the first drug tested. The number needed to treat (NNT) for any pain relief for carbamazepine in CTN is 1.9, and for significant effectiveness is 2.6.[154,155] Its success in CTN has been extrapolated by some clinicians to serve as a diagnostic test. However, a number of patients may be initially resistant, and others become refractory to carbamazepine therapy.[27] On the other hand, recent studies established that, over a 2-year follow-up, patients with TN do not generally become refractory to medication.[156] Oxcarbazepine, a carbamazepine derivative, is also efficacious in CTN[40,157] with less side effects, other than hyponatremia, but patients may also develop resistance.[38] Barbemazepine (CBZ) and OXC are the most commonly used drugs in the management of TN, but both can cause serious cognitive impairment. Their most common significant side effects include tiredness 31.3%, sleepiness 18.2%, memory problems 22.7%, disturbed sleep 14.1%, difficulty concentrating and unsteadiness 11.6%.[158] These are largely more common in CBZ. Interestingly, females reported significantly more side effects than males, and this effect remained when controlling for body mass index, concomitant drugs, body weight, percentage body fat, increased vigilance, and desire to report side effects.[158] The potential toxic dose for females is approximately 1200 mg of OXC and 800 mg of CBZ and 1800 mg of OXC and 1200 mg of CBZ for males. Pharmacokinetic and pharmacodynamic differences are thus likely to be the reason for these sex differences. Therefore, females may need to be prescribed lower doses in view of their tendency to reach toxic levels at lower dosages. When transferring patients between OXC and CBZ, an OXC dose of +30% relative to CBZ is usually required.[159]

Baclofen, with a low side effect profile, may be titrated to relatively high doses (80 mg/day) with a NNT of 1.4. However, a strong synergistic effect with both carbamazepine and phenytoin is reported, making baclofen suitable for combined therapy, which is its more common use. Gabapentin has not been rigorously tested in CTN but may be useful in selected CTN cases.[160,161] Pregabalin (150–600 mg/day) significantly

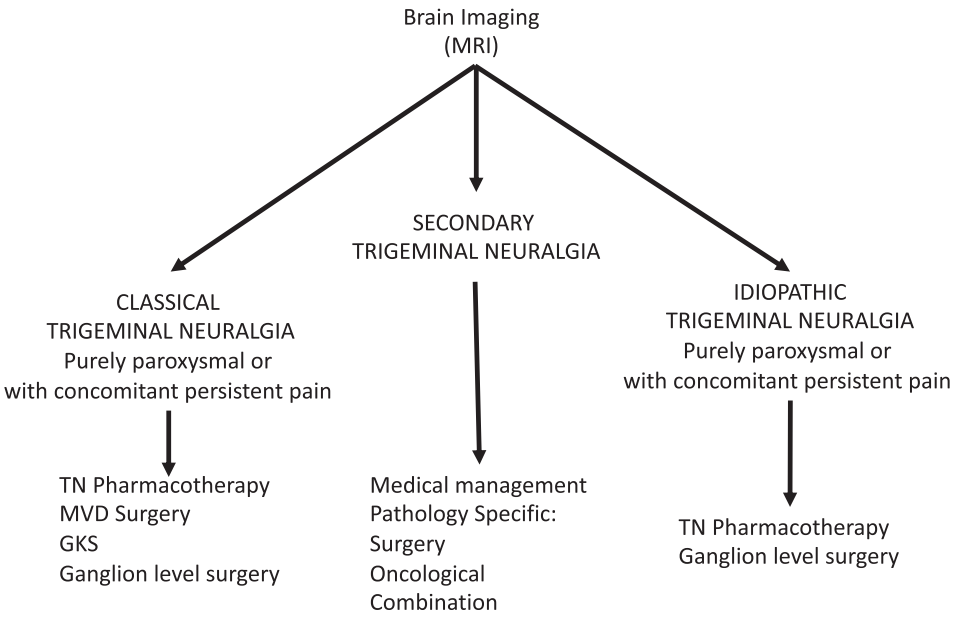

FIGURE 4 Therapeutic options based on the specific trigeminal neuralgia diagnosis. GKS, gamma knife surgery; MRI, magnetic resonance imaging; MVD, microvascular decompression; TN, trigeminal neuralgia

TABLE 6 Drugs commonly used in the treatment of trigeminal neuralgia

Drug	Initial dose (mg)	Target dose (mg)[a]	#Dose increase (titration)	Schedule
Carbamazepine	100–200	1200–1800	100–200 mg/2 days	x2-4/days
Carbamazepine-CR	200–400	1200	Usually transfer from regular format at equivalent dose	x2/days
OXC	300	1200–2400	300–600 mg/week	x2-3/days
Baclofen	5–15	30–60	5 mg/3 days	x3/days
Gabapentin	300	900–2400	300 mg/2–3 days	x3/days
Pregabalin	150	300–600	50 mg/2–3 days	x2-3/days
Lamotrigine	25	400–600	25–50 mg/week	x1-2/days

Abbreviations: CR, controlled release. OXC, oxcarbazepine; X, number of times daily.
[a]Titrate according to response and side effects.

improved pain in patients with CTN after 8 weeks in 60%–70% of treated cases.[69,162] Lamotrigine is effective as add-on therapy but needs slow titration.[163] It is unclear whether topiramate is effective for CTN.[164,165] Phenytoin was the first drug for CTN and is prescribed at 150–200 mg twice daily but has a relatively low success rate (25%). Side effects such as drowsiness and dizziness occur in 10% of patients even at low doses. Long-term use can induce osteomalacia.

Based on the current evidence, we initiate therapy with carbamazepine and transfer patients at the earliest opportunity to the controlled release formulation that has less side effects. If carbamazepine causes troublesome side effects, we reduce the dose and add baclofen, gabapentin, pregabalin, or lamotrigine. Alternatively, oxcarbazepine as monotherapy or with add-on therapy may be tried. In refractory cases, drug combinations as above should be tried. It is important to appreciate that breakthrough pain may occur in successfully treated patients and require temporary dose adjustment; in extreme cases, inpatient care with intravenous phenytoin may be needed.[166] The issue is that no matter which protocol is used, patients' QoL can be severely affected by significant motor, cognitive, sensory, and biological side effects.[167]

ONABOTULINUMTOXIN A

Onabotulinumtoxin A is one of the seven antigenically distinct serotypes of botulinum neurotoxins (BoNT, A to G) making up the

clostridial family. BoNT-A is available commercially in the United States (Botox®, Allergan, Irvine, CA, USA). BoNT-A is FDA approved for chronic migraine, cervical dystonia, axillary hyperhidrosis, adult upper limb spasticity, strabismus, and blepharospasm associated with dystonia.

The toxin affects the nervous system predominantly by inhibiting the release of neurotransmitters from nerve terminals. This occurs through a three-stage process that begins with binding to the target nerve terminal membrane and internalization, translocation, and finally, cleavage of a target protein that is involved in neurotransmitter release.[168]

A number of studies have examined the effect of BoNT-A in TN.[169] The majority of studies used 20–50 U injected into the trigger zones, although lower (5–9 U)[170,171] and higher doses (75 U)[172] have been successfully used. Overall, more than 60% of patients reported an improvement of ≥50% in both pain frequency and intensity. The major events reported were transient facial paresis/asymmetry, edema, ptosis, dysesthesia, and chewing difficulties, but all were rare.[169] A recent meta-analysis found a superior effect for BoNT-A versus placebo in terms of proportion of responders (risk ratio [RR] = 2.87).[173] The effect is achieved less rapidly than by using pharmacotherapy and usually appears after 1–2 weeks. This would suggest to us that combined approaches may be indicated including early pharmacotherapeutic intervention for rapid control continued until the BoNT-A effect occurs. More research is needed, particularly to replicate existing studies so as to confirm efficacy and elucidate the minimum effective dose and the number and sites of injection points. Data so far suggest that BoNT-A may bea significant addition to the ways in which we manage TN.

ALTERNATIVE AND FUTURE PHARMACOTHERAPY FOR CLASSICAL TRIGEMINAL NEURALGIA[174]

Some nonantiepileptic or new drugs show promise in the management of CTN.[175] Pimozide is a centrally acting dopamine D2-receptor antagonist with evidence of efficacy that is greater than carbamazepine at 6 weeks.[176] Up to 83% of participants reported adverse effects, but these did not lead to withdrawal. Tizanidine is an alpha-2 adrenergic receptor agonist structurally related to clonidine and increases presynaptic inhibition of motor neurons. In a small trial, tizanidine was well tolerated, but the clinical effects were inferior to those of carbamazepine.[177] A later study revealed that patients experienced recurrence of TN within 1–3 months.[178]

Levetiracetam is an antiepileptic whose mechanism may involve inhibition of voltage-dependent N-type calcium channels, facilitation of GABA-ergic inhibitory transmission, reduction of delayed rectifier potassium current, and/or binding to synaptic proteins that modulate neurotransmitter release. Refractory CTN cases were treated with levetiracetam (3–4 g/day) as add-on therapy and experienced a reduction in the number of daily attacks by 62.4%. However, seven of the 23 patients withdrew from the study due to side effects.[179] The results in patients with central pain due to MS or with painful polyneuropathy were disappointing and therefore the potential of levetiracetam in neuropathic pain management is unclear.[180,181] Lacosamide is a functionalized amino acid whose precise antiepileptic mechanism is unknown. It enhances sodium channel inactivation, normalizes activation thresholds, decreases pathophysiological neuronal activity, and is beneficial in animal models of neuropathic pain.[182] Lacosamide has a modest effect in painful diabetic neuropathy, but increasing dosages induced significant side effects with little clinical benefit.[183] Early clinical findings suggest some benefit for refractory patients with CTN.[184] Eslicarbazepine is an AED that targets voltage-gated sodium channels. In a retrospective, open-label, multicenter, intention-to-treat study, 18 patients with TN were studied. The dose of eslicarbazepine ranged between 200 and 1200 mg/day and attained a response rate of 88.9% with 71% of patients reporting adverse events and 22% of patients discontinuing treatment.[185]

A new Nav1.7 selective state-dependent, sodium channel blocker (vixotrigine) has been developed.[186] Nav1.7, a major sodium receptor in the nociceptive system, is not located in the brain, thus preventing any side effects associated with depression of CNS excitability.[187] Vixotrigine demonstrates good tolerability at therapeutic doses, time to treatment failure, number of paroxysms, and average daily pain score. The new drug was well tolerated, and no severe or serious adverse events were reported.[188]

SURGICAL

The decision to opt for surgery is based on response to, and side effects from, medical treatment, the patient's age, and the surgical facilities and expertise available. The candidate must be in a physical condition that will allow safe general anesthesia and neurosurgery. Patients should be given concise and clear explanations of the potential surgical complications and the alternative neurosurgical procedures.

Surgery may be aimed peripherally at the affected branch or centrally at the trigeminal ganglion or the nerve root. Any surgical procedure seems to have a better prognosis when carried out as a first procedure particularly on patients with purely paroxysmal CTN; in MVD, best effects are obtained when performed within 7 years of CTN onset.[189] The changing trend in neurosurgical options in the United States was studied in a 20-year retrospective analysis.[190] The use of MVD has nearly doubled from 1988 to 2008, while rhizotomy interventions have dropped to about a tenth of the numbers being performed previously. Radiosurgery, introduced in the early 1990s, peaked in 2004 but has since declined. For ethical reasons, there are no sham-controlled neurosurgical studies and only a few quality trials on neurosurgical procedures for TN, particularly comparative studies that may aid in making individual choices.[191]

PERIPHERAL PROCEDURES

Local anesthetics

Nerve blocks may provide some hours of absolute pain relief in CTN, and we have used these to permit patients to participate in important personal activities. Within a hospital setting, continuous infusion of local anesthetic may be feasible but depends on the nerve branches involved.[192]

Peripheral procedures include neurectomy, cryotherapy, and glycerol injection. All have high recurrence and complication rates and give no benefit over ganglion-level procedures. All peripheral procedures aim at inducing nerve damage and carry the risk of developing neuropathic pain. Peripheral procedures should be reserved for emergency use or in patients with significant medical problems that make other procedures unsafe.[193]

CENTRAL PROCEDURES

Percutaneous trigeminal rhizotomy

Three techniques are available: radiofrequency, glycerol injection, and balloon compression. The basis of these techniques is that controlled heat (69–90°C), a neurotoxin or ischemic and mechanical pressure, respectively, will damage trigeminal neurons. Advantages to percutaneous techniques include shorter procedure duration and minimal anesthesia risk. A recent pooled analysis revealed that 55%–80% of patients are pain free at 4–11 years after balloon compression, 26%–82% after radiofrequency thermocoagulation, and 19%–58% after glycerol injection.[57] Initial pain relief (around 90%) across these is approximately equal, but each one is associated with different rates of recurrence and complications.[194-199]

With the large difference in success rates reported across centers for the same procedures, it is hard to unequivocally recommend a superior intervention. Radiofrequency thermocoagulation reaches high rates of pain relief but is associated with high frequencies of facial and corneal numbness.[200] Radiofrequency does allow for somatotopic nerve mapping and selective division lesioning.[198] Multiple treatments not only improve outcomes but also increase morbidity. Balloon compression is similar in outcomes with potentially high, long-term success rates.[57] Glycerol injection offers similar pain-free outcomes, but complication rates have been reported as higher (25% vs. 16%)[198] and lower (11% vs. 23%)[201] compared with balloon compression. Median time to recurrence was 21 months for the balloon procedure and 16 months for the glycerol procedure.[201] In summary, data suggest that these procedures may be dependent on patient selection and/or may be surgeon sensitive.

MICROVASCULAR DECOMPRESSION

The procedure essentially separates between the intracerebral arteries and the trigeminal nerve root preventing pulsatile injury leading to chronic demyelination and subsequently TN. The relatively high surgical morbidity (10%) reported in 1996 declined to about 0.3%–3% in 2003, making MVD a safer option, but mortality remains a risk.[116] Complication rates are lowest in high-volume hospitals and when the surgeon performs a large number of MVDs yearly.[116] Pooled analysis supports the reliability of MVD, with 62%–89% of CTN patients pain free at 3–11 years.[57] In the long term, MVD seems the most cost-effective surgical approach to CTN[202-204]. A literature review on surgical modalities for CTN concludes that MVD is associated with the lowest rate of pain recurrence and the highest rate of patient satisfaction.[205] Patient satisfaction with MVD is particularly high when performed as a first intervention for CTN.[206] There is currently no clear evidence or recommendation to perform surgery early.[57,88,157] Some studies would indicate that early MVD surgery carries advantages, and patient satisfaction with neurosurgery is higher than that with pharmacotherapy.[189,207,208]

GAMMA KNIFE

GKS radiosurgery is a minimally invasive technique that precisely delivers radiosurgical doses of 70–90 Gray units to the trigeminal nerve root at the point of vascular compression. The technique relies on accurate MRI mapping and sequencing. If no compressing vessels are identified, the site of exit of the trigeminal nerve from the pons or other preselected position on the trigeminal nerve is treated.

A recent pooled analysis reveals that 30%–66% of patients are pain free at 4–11 years after GKS.[57] Comparing GKS with glycerol rhizotomy injection, it was concluded that despite greater facial numbness and a higher failure rate, glycerol provided more rapid pain relief than GKS. Indeed, the percentage of patients with GKS becoming pain free often increases over time (~24 months), suggesting cumulative effects.[209-211] GKS shows better long-term pain relief with less treatment-related morbidity than glycerol rhizotomy and may be indicated in patients who are poor candidates for MVD.[212,213] Although posterior fossa surgery (MVD or partial nerve section) was shown to be superior to GKS over a mean follow-up duration of about 2 years,[213,214] there are reports that GKS may be the procedure of choice for recurrent CTN.[215] There are insufficient data at present to assess the long-term outcomes or complications of GKS, particularly the unknown effects of radiation in the area of the trigeminal root. With GKS, better outcomes are associated with higher dosages that, however, induce higher rates of sensory loss.[138]

CONCLUSION

TN is a disorder with multiple “faces” or presentations. The classification of TN has recently caught up with the clinical reality, and we have subgroups based on background pain and NVC. In addition, we are aware that the 2-minute cutoff for pain duration needs investigating along with the presence of lacrimation and sensory changes. Could these make up future subgroups? The enormous advances

in imaging and genetics may contribute significantly to our understanding of TN. Certainly, a reliable and representative animal model for TN would be advantageous. This may assist in drug development; we are in need of new, efficient drugs with minimal side effects. Our present armamentarium is "old" and needs replenishing.

Most studies collect data on pain and side effects. However, very few collect data on the impact of the disorder and its treatment on physical functioning, emotional status, and patient satisfaction.[216] This is a disorder that can cause depression and suicidal thoughts, and such outcomes are important. It is important to standardize outcome measures used for pain relief, pain intensity, and the rarely collected frequency of pain episodes.

The definition of ITN is a fascinating opportunity. What causes the pain? In the absence of a clear lesion, can it be considered a full neuropathic pain condition? This is an exciting time in the research of TN.

CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to the planning and writing of the manuscript, including the literature search.

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