Review

Cephalalgia
An International Journal of Headache
International Headache Society

Cephalalgia
2017, Vol. 37(7) 648–657

DOI: 10.1177/0333102416687280
journals.sagepub.com/home/cep
SAGE

Trigeminal neuralgia – diagnosis and treatment

Stine Maarbjerg[1], Giulia Di Stefano[2], Lars Bendtsen[1] and Giorgio Cruccu[2]

Abstract

Introduction: Trigeminal neuralgia (TN) is characterized by touch-evoked unilateral brief shock-like paroxysmal pain in one or more divisions of the trigeminal nerve. In addition to the paroxysmal pain, some patients also have continuous pain. TN is divided into classical TN (CTN) and secondary TN (STN).

Etiology and pathophysiology: Demyelination of primary sensory trigeminal afferents in the root entry zone is the predominant pathophysiological mechanism. Most likely, demyelination paves the way for generation of ectopic impulses and ephaptic crosstalk. In a significant proportion of the patients, the demyelination is caused by a neurovascular conflict with morphological changes such as compression of the trigeminal root. However, there are also other unknown etiological factors, as only half of the CTN patients have morphological changes. STN is caused by multiple sclerosis or a space-occupying lesion affecting the trigeminal nerve.

Differential diagnosis and treatment: Important differential diagnoses include trigeminal autonomic cephalalgias, posttraumatic or postherpetic pain and other facial pains. First line treatment is prophylactic medication with sodium channel blockers, and second line treatment is neurosurgical intervention.

Future perspectives: Future studies should focus on genetics, unexplored etiological factors, sensory function, the neurosurgical outcome and complications, combination and neuromodulation treatment as well as development of new drugs with better tolerability.

Keywords

Trigeminal neuralgia, diagnostic criteria, guidelines, treatment, etiology, pathophysiology

Date received: 11 October 2016; revised: 21 November 2016; accepted: 7 December 2016

Definition

According to the beta version of the 3rd edition of the International Classification of Headache Disorders (ICHD-3 Beta) (1) (Table 1), trigeminal neuralgia (TN) is defined by recurrent unilateral brief electric shock-like pain that is abrupt in onset and termination. The pain is restricted to one or more of the trigeminal divisions and is triggered by innocuous sensory stimuli. TN is divided into either classical TN (CTN) or secondary TN (STN) caused by multiple sclerosis or a space-occupying lesion such as a tumor, cerebral aneurism or a megadolicho basilar artery.

Recently the International Association for the Study of Pain (IASP) has produced an independent classification, definition, and diagnostic process of trigeminal neuralgia (TN) (2). It is a main aim of both societies to find a bilaterally agreed compromise, for the sake of researchers and clinicians and ultimately of patients. Table 1 outlines the two classifications.

Symptomatology

In early descriptions of TN, the disorder was called tic douloureux (3), addressing the characteristic wince that TN patients may exhibit at a pain paroxysm; TN pain is not only extremely painful, it is also characteristic that the pain is sudden and unexpected, and short-lasting, hence the term pain paroxysm. The pain quality is stabbing, electrical shock-like, or shooting. Although one single

[1]Danish Headache Center, Department of Neurology, Rigshospitalet – Glostrup, University of Copenhagen, Denmark
[2]Department of Neurology and Psychiatry, Sapienza University, Rome, Italy

Corresponding author:
Stine Maarbjerg, Danish Headache Center, Department of Neurology, Rigshospitalet – Glostrup, University of Copenhagen, Nordre Ringvej 67, 2600 Glostrup, Denmark.
Email: stine.maarbjerg@regionh.dk

Table 1. Diagnostic criteria of trigeminal neuralgia according to the beta-version of the 3rd edition of the International Classification of Headache Disorders (ICHD3-beta) and to the International Association for the Study of Pain (IASP) (shortened and adapted versions).

	ICHD3-beta
Definition	Outlined in main manuscript
*Criteria**	A. At least three attacks of unilateral facial pain fulfilling criteria B and C
	B. Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
	C. Pain has at least three of the following four characteristics:
	1. recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes
	2. severe intensity
	3. electric shock-like, shooting, stabbing or sharp in quality
	4. precipitated by innocuous stimuli to the affected side of the face
	D. No clinically evident neurological deficit
	E. Not better accounted for by another ICHD-3 diagnosis
Subclassification	*Classical TN*
	- TN with purely paroxysmal pain
	- TN with concomitant persistent pain
	*Symptomatic TN***
	- TN associated to multiple sclerosis (MS): MS has been diagnosed and MRI demonstrates MS plaque affecting the trigeminal nerve root or electrophysiological studies indicate impairment of the affected nerve(s). Pain is not necessarily unilateral****
	- TN associated to space-occupying lesion: contact between a space-occupying lesion and the affected trigeminal nerve has been demonstrated by imaging and pain has developed after contact occurred between the lesion and the trigeminal nerve, or led to its discovery
Comments	*In the forthcoming final ICHD3 criteria C1, 2, 3 and 4 of ICHD3-beta will most likely be converted into individual monothetic criteria and criterion D of ICHD3-beta will most likely be deleted
	**In ICHD3-beta symptomatic TN is termed painful trigeminal neuropathy but this will most likely be changed back to symptomatic TN in the forthcoming final ICHD3
	*** In the forthcoming final ICHD3 the criteria demanding an MRI-verified plaque affecting the trigeminal root or electrophysiological cerification will most likely be removed
	IASP
Defintion	Orofacial pain restricted to one or more divisions of the trigeminal nerve. With the exception of TN caused by multiple sclerosis, the pain affects one side of the face. It is abrupt in onset and typically lasts only a few seconds (2 minutes at maximum). Patients may report their pain as arising spontaneously but these pain paroxysms can always be triggered by innocuous mechanical stimuli or movements. If patients experience additional continuous pain in the same distribution and same period as the paroxysmal pain it is considered to be TN with concomitant continuous pain and this phenotype may be present in each of the three subclassification categories
Criteria	A. Orofacial pain distributed within the trigeminal facial or intraoral territory
	B. Paroxysmal character of pain
	C. Pain triggered by typical maneuvers
Subclassification	- *Idiopathic TN:* no apparent cause
	- *Classical TN:* caused by vascular compression of the trigeminal nerve root resulting in morphological changes of the root
	- *Secondary TN:* caused by major neurological disease, e.g., a tumour of the cerebellopontine angle or multiple sclerosis

pain paroxysm may only last a fraction of a second, these paroxysms may recur, after a refractory period, many times a day, and they may come in a series of attacks with many paroxysms close together.

Approximately half of the TN patients also have concomitant continuous pain: an aching or dull or burning background pain of lower intensity in the same area as the paroxysmal pain (4–6). The continuous pain is usually present during the same periods as the paroxysmal pain. This background pain is most common in women (4,7,8).

Refractory period and trigger factors

Many patients experience a refractory period after a paroxysmal attack where new attacks cannot be elicited. The

pathophysiological mechanism of this phenomenon is unknown. It has been proposed that it is caused by hyperpolarisation of the sensory neuron (9). In early studies by Kugelberg and Lindblom, the presence and duration of the refractory period in TN was a function of the intensity and duration of the preceding attack (10).

It is highly characteristic that pain is triggered by innocuous sensory stimuli to the affected side of the face. Sensory stimuli may be extraoral and intraoral. The most frequent trigger factors involve normal daily activities such as light touch, talking, chewing, brushing teeth and cold wind against the face (11,12). It has been suggested that apparently spontaneous pain paroxysms may in fact be elicited by very subtle sensory stimuli or movements.

Localisation

TN most frequently affects the 2nd and/or 3rd trigeminal division and the right side is slightly, but significantly, more often affected than the left side (11). Bilateral TN is very rare in classical TN, and should raise suspicion of secondary TN.

Natural history

There are very few studies examining the natural history of TN. It has been proposed that pain may worsen with time and that TN in its chronic state is characterised by longer lasting, medically refractory pain, sensory disturbances and progressive neuroanatomical changes of the trigeminal root (8). Several studies have now challenged this notion; Di Stefano et al. found that in the majority of TN patients the pain does not increase in frequency or duration, nor did it become refractory to medication, and the dosage needed to relieve pain did not increase with time (13). Maarbjerg et al. found that concomitant persistent pain and neuroanatomical morphological changes were not related to age or to duration of disease (4,7).

A feature that is also very characteristic to the course of TN is unpredictable periods of complete remission that may last months or even years. This unusual phenomenon in neuropathic pain is most likely attributed to a reduction in excitability and partial remyelination (9).

Autonomic symptoms in facial pain

Traditionally, autonomic symptoms such as tearing and rhinorrhea have not been associated with TN. However, it is now known that a large proportion of TN patients have autonomic symptoms from time to time (11,12,14). Keeping in mind that the trigeminovascular reflex can be elicited by intense facial pain in general (15), it is not surprising that there can be sporadic autonomic symptoms in TN. The challenge is related to differential diagnosis; short-lasting triggered stabbing pain with pronounced and consistent autonomic symptoms is characteristic of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA) (16).

Epidemiology

TN is frequently both misdiagnosed and underdiagnosed. The incidence of TN is variably reported between studies, with a range from 4.3 to 27 new cases per 100,000 people per year (17–19). The incidence is higher among women, and increases with age (17). The lifetime prevalence was estimated to be 0.16–0.3% in population-based studies (18,20). The average age of onset is 53 years in classical TN and 43 years in secondary TN, but the age of onset can range from early to old age (11,21). In tertiary care-based studies, STN accounted for 14–20% of TN patients (11,22).

Etiology and pathophysiology

As early as 1934, Dandy proposed that in at least 30% of TN patients the pain was caused by a blood vessel compressing the trigeminal nerve (23). Today, it is generally agreed that the most common cause of classical TN is compression or other morphological changes of the trigeminal nerve by a blood vessel, usually an artery, in the cerebellopontine cistern. This is termed a neurovascular conflict with compression. Anatomical studies documented that the transition from Schwann cell myelination to oligodendroglia myelination in many specimens tapers gradually along the proximal 25% of the nerve (24). Possibly, this ''transition zone'' represents a particularly vulnerable area to, for example, pressure from a blood vessel.

Emerging evidence indicates that a neurovascular conflict involving morphological changes of the trigeminal nerve such as distortion, dislocation, distension, indentation, flattening or atrophy is highly associated with classical TN and is present in about half of the TN patients (Figure 1) (25–27). Conversely, it is debated whether a neurovascular conflict without morphological changes of the trigeminal nerve, a ''simple contact'', where the two structures are merely touching, is important to TN etiology. On the one hand, a simple neurovascular contact was also, however much less, associated to TN (25,26) and microvascular decompression was also reported to be effective in TN patients with a simple neurovascular contact (28). On the other hand a simple contact was a very prevalent finding in cadavers without a history of TN, in healthy

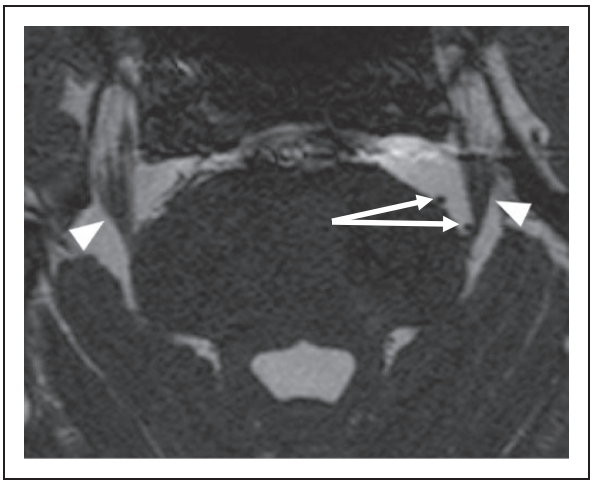

Figure 1. MRI in a patient with left-sided classical trigeminal neuralgia. Balanced fast field echo sequence of the fossa posterior, axial plane, at the level of the pons. The left trigeminal nerve (right-sided arrowhead) is displaced by an arterial loop (arrows) from the anterior inferior cerebellar artery.

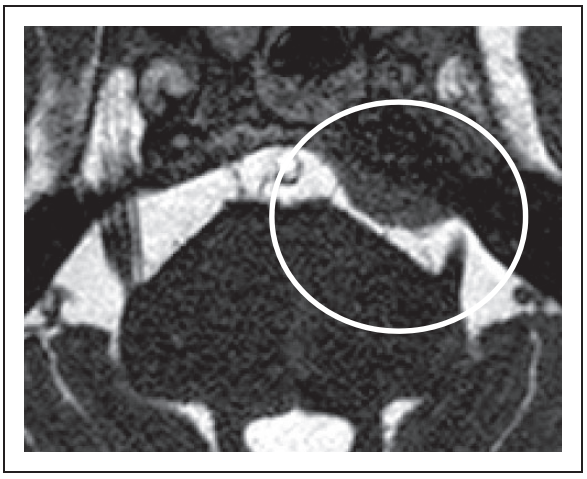

Figure 2. MRI in a patient with left-sided symptomatic trigeminal neuralgia. Balanced fast field echo sequence of the fossa posterior, axial plane at the level of the pons. The peripheral part of the left trigeminal nerve is displaced by a meningioma (both structures encircled).

subjects and on the asymptomatic side in TN patients (25,29–31). In patients with persistent idiopathic facial pain, an important differential diagnosis to TN, the prevalence of neurovascular conflict is similar to that found in asymptomatic nerves (32). Thus, a neurovascular conflict should be considered a normal neuroanatomic variant in patients with facial pain not fulfilling the TN diagnostic criteria. A hypothetical exception to this rule is that some TN patients only have persistent pain at onset, previously termed ''pretrigeminal neuralgia'', and thereafter develop the classical paroxysmal pain (4,33). Such patients do not initially fulfill the TN diagnostic criteria.

Although it is not yet clear which other etiological factors might contribute to or cause TN, there are numerous neurophysiological, neuroimaging and histological studies pointing to focal demyelination of primary trigeminal afferents near the entry of the trigeminal root into the pons as the underlying pathophysiological mechanism in TN (34–36). The consequences of the demyelination are not fully clarified, but it has been hypothesised that the focally demyelinated primary afferents become hyperexcitable when demyelination reaches such a level that ions can move in and out of the axon, also away from the Ranvier node zones, at which point the axons do not have enough energy to promptly re-establish the resting potential. Hence the axons tend towards a depolarisation level, which makes them hyperexcitable. Ectopic impulses, which are generated either spontaneously along the sensory afferent or because of a local direct mechanical stimulus such as arterial pulsation, are probably also involved in the hyperexcitability. Moreover, supported by evidence in animal models of focal demyelination of the trigeminal root, ephaptic transmission, i.e. cross-talk from close, healthy nerve fibres, and the generation of high-frequency discharges are also suggested to contribute to the hyperexcitable nervous state in TN (9,37,38).

Finally, there is some evidence suggesting that the hyperactivity of primary afferents secondarily induces central sensitisation of wide-dynamic-range neurons in the spinal trigeminal nucleus or even more central changes (36,39). Future investigations are needed.

In secondary TN, the pathophysiological mechanism is most likely the same as in classical TN but the etiology is dependent on the specific structural lesion, most frequently an MS plaque affecting the trigeminal root or a space-occupying lesion in the cerebellopontine cistern such as epidermoid tumours, meningiomas, neurinomas, arteriovenous malformations or aneurysms (Figure 2) (40,41).

Diagnostic considerations

The diagnosis of TN is primarily based on patient history, as there are no definitive laboratory or diagnostic tests. When obtaining patient history, special attention should be paid to the potential pitfalls leading to misdiagnosis such as a symptomatic cause of pain, odontogenic pain and associated autonomic symptoms (Table 2). When obtaining patient history, one should pay special attention to the *onset* of pain; if the pain was preceded by or coincided with a *herpes zoster* rash in the ipsilateral trigeminal distribution, painful trigeminal neuropathy attributed to acute herpes zoster

Table 2. Differential diagnosis in trigeminal neuralgia.

The symptomatology of trigeminal neuralgia is typically very characteristic, with patients reporting intense stabbing touch-evoked unilateral facial pain in the cheek, the area of the nostrils, teeth or jaw. Primary and secondary, i.e. pain secondary to multiple sclerosis or space-occupying lesion, TN may be indistinguishable based on pain characteristics. Meanwhile, in patients with secondary TN, neurological deficits, extra-trigeminal symptoms, bilateral pain and young onset are more frequent.

Primary and secondary headache and facial pain differential diagnosis includes:

- **Glossopharyngeal neuralgia** causes evoked stabbing pain located to the back of the tongue, the pharynx or deep in the ear. Trigger factors are somewhat different from TN and include swallowing, coughing, sneezing
- **Painful posttraumatic trigeminal neuropathy** can cause stabbing and touch-evoked pain similar to TN, but pain is by definition preceded by trauma and there are usually clear-cut neurological abnormalities of both gain and loss of function corresponding to the affected peripheral nerve
- **Persistent idiopathic facial pain** causes touch-evoked or spontaneous dull or aching constant pain
- **Painful trigeminal neuropathy attributed to acute herpes zoster** causes burning and stabbing pain preceded by a herpetic rash in the trigeminal distribution. Tingling sensations and neurological abnormalities with both gain and loss of function are frequent
- **Short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)** or **paroxysmal hemicrania** cause touch-evoked and spontaneous stabbing orbital, supraorbital or temporal pain accompanied by ipsilateral autonomic symptoms. Unlike TN, pain may change side
- **Cluster headache** causes orbital, supraorbital or temporal pain accompanied by ipsilateral autonomic symptoms and restlessness. Duration is from 15–180 minutes. Unlike TN, pain may change side
- **Primary stabbing headache** causes stabbing spontaneous pain in the scalp and is not accompanied by autonomic symptoms

Odontogenic differential diagnosis:

- **Cracked tooth** can cause evoked shooting pain when chewing hard foods
- **Caries** or **pulpitis** can cause evoked pain at intake of sweet, cold or hot foods. The pain can last from ten minutes up to hours

*Autonomic symptoms are conjunctival injection, lacrimation, rhinorrhea, nasal congestion, sweating, miosis, ptosis and eyelid edema.

should be considered (42). In pain preceded by a relevant *trauma* to the ipsilateral side of the face, such as invasive dental procedures or fractures, painful posttraumatic trigeminal neuropathy (PPTN) is more likely the correct diagnosis. Studies have shown that pain in PPTN may be comparable to TN pain with short, intense triggered pain, but in PPTN there are usually clear cut sensory abnormalities, including both loss and gain of function, corresponding to the damaged peripheral nerve (29). Also important when obtaining the patient history is the *location* of pain; pain originating distinctly or diffusively from the *teeth* should be evaluated by a dentist because, for example, a cracked tooth may present with TN-like pain evoked by chewing hard foods. In *bilateral* constant pain located in the temporomandibular area, tension-type headache, temporomandibular joint disorder and persistent idiopathic facial pain should be considered. If the short-lasting, intense stabbing pain is isolated to the *scalp or occipital area*, diagnoses such as occipital neuralgia, primary stabbing headache and paroxysmal hemicrania should be considered. Glossopharyngal neuralgia is located to the back of the *tongue, the soft palate and the pharynx*, and nervus intermedius neuralgia is located deep in the *ear*. Finally, *associated symptoms* are important; if each pain attack is accompanied by *autonomic symptoms* such as conjunctival injection, miosis or lacrimation, SUNA, SUNCT or paroxysmal hemicrania are important differential diagnoses.

Treatment

Figure 3 outlines a proposed work-up and treatment algorithm in TN. As a part of the early work-up, we suggest including an MRI of the brain and brainstem, ECG and laboratory testing. As symptomatic and classical TN cannot be confidently separated based on history and examination (43), an MRI is important early on to exclude a symptomatic cause of pain that could warrant specific treatments, such as tumors or multiple sclerosis. Laboratory testing is performed to ensure normal renal and liver function and normal sodium level prior to prescription of medication. ECG is warranted because carbamazepine and oxcarbazepine are contraindicated in patients with atrioventricular block. First line treatment is sodium channel blockers, either carbamazepine or oxcarbazepine. They have the same mechanism of action, namely the blockade of voltage-gated sodium channels in a frequency-dependent manner. Treatment recommendations are generally the same in classical and secondary TN (43). Generally, sodium channel blockers are effective in most TN patients and the number needed to treat for carbamazepine is 1.7 (44–46). However, side effects including somnolence, drowsiness, dizziness, rash, and tremor are frequent and the number needed to harm for carbamazepine is 24 for severe side effects and 3.4 for minor side effects (43). Oxcarbazepine may be preferred because of a minor risk of drug interactions and its

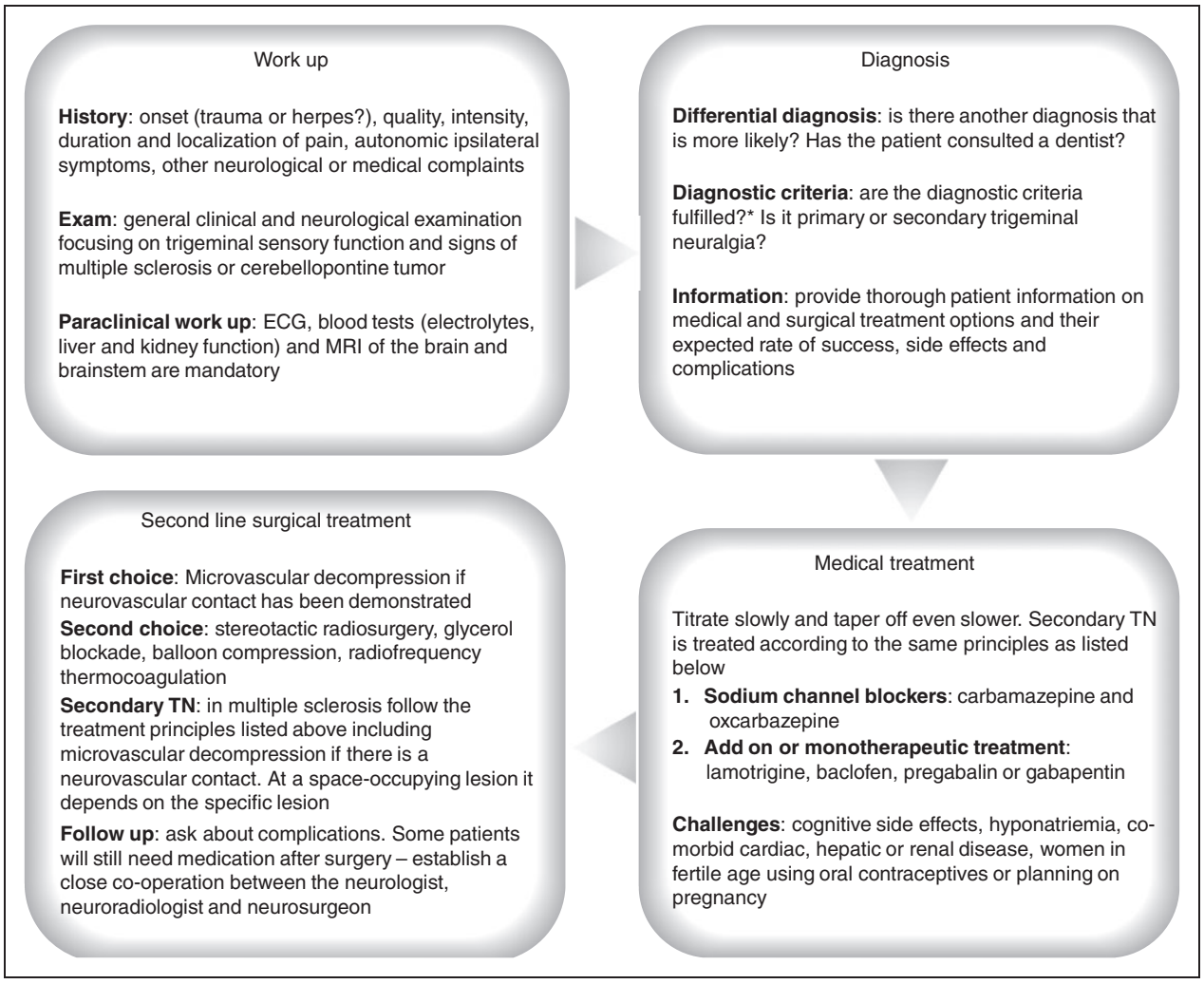

Figure 3. Work up and treatment algorithm in trigeminal neuralgia (TN) – presented in short. Diagnostic criteria of TN are outlined in Table 1.

better tolerability in comparison with carbamazepine. Carbamazepine was reported to have a higher percentage of discontinuation due to all kinds of side effects, except for sodium depletion, for which discontinuation only occurred with oxcarbazepine (13).

Very often high dosages are necessary for sufficient pain relief, so many patients suffer from disabling side-effects. Treatment failure is typically not due to drug inefficacy, but rather due to undesired side effects that causes interruption of treatment or dosage reduction to an insufficient level. In one study, worsening of pain with time and development of late resistance only occurred in a very small minority of patients (13).

According to the international guidelines it is advised that "if any of these sodium-channel blockers is ineffective, referral for a surgical consultation would be a reasonable next step" (43). Surgery should also be considered when drugs, although effective, cannot reach the therapeutic dosage due to adverse events. From a clinical perspective, it may also be reasonable to try out both carbamazepine and oxcarbazepine sequentially. Furthermore, many TN patients benefit from add-on treatment combining carbamazepine or oxcarbazepine with lamotrigine, baclofen, pregabalin or gabapentin. Combination treatment should be considered when carbamazepine or oxcarbazepine cannot reach full dosage because of side effects. Each of the above-mentioned drugs may also have efficacy as monotherapeutic agents, although the available evidence is very weak (43). At severe exacerbations, in-hospital treatment may be necessary for titration of antiepileptic drugs and rehydration. In many centres, severe exacerbation is treated with intravenous loading of fosphenytoin, but there is a lack of scientific evidence for this treatment.

In medically refractory patients, with a neurovascular conflict, microvascular decompression (MVD) is the first choice treatment (43). This procedure implies

craniotomy and posterior fossa exploration for identification of the affected trigeminal nerve and the conflicting blood vessel(s). Microvascular decompression provides the longest duration of pain freedom in comparison with other surgical techniques, as it reportedly provides significant pain relief in 73% of patients after five years. Minor complications such as new aching or burning pain, sensory loss and other mild or transient cranial nerve dysfunction occur in 2–7%. Major complications such as major cranial nerve dysfunction (2%), stroke (0.3%) and death (0.2%) are rare, yet it is important to inform patients of the potential risks (47). In most previous studies, the surgical complications were not reported by independent assessors and therefore the complication rates may be higher. The conventional opinion that multiple sclerosis is a contraindication to microvascular decompression has recently been refuted by a study showing that in some multiple sclerosis patients with TN, a neurovascular conflict may act as a concurring mechanism in producing focal demyelination of the primary afferents at the root entry zone (48).

Second choice neurosurgical treatments are lesioning peripheral procedures targeting the trigeminal ganglion chemically by glycerol blockade, mechanically by balloon compression, or thermically by radiofrequency thermocoagulation. In stereotactic radiosurgery (''gamma knife'') the target is the trigeminal root, which is lesioned by convergent beams of radiation. The procedures are efficacious in approximately 50% of patients after five years, and minor complications such as sensory loss (12–50%), masticatory problems (balloon compression (up to 50%)) and new burning or aching pain (12%) are relatively prevalent (43).

The above-mentioned treatment recommendations are mainly based on expert opinion. There is a lack of robust scientific evidence for effect and side-effects of both medical and surgical treatment of TN.

Expert opinion: Open questions and burning desires

There are a number of open questions in TN that remain to be answered. Questions relate both to pathophysiology, etiology, genetics, natural history, treatment and classification.

Pathophysiology and etiology

To date, only very few animal models of TN have sought to mimic demyelination of the prepontine segment of the trigeminal nerve (38), other models have been based on more peripheral trigeminal nerve trauma. Proper animal models of TN could help elucidate the pathophysiological mechanisms behind TN. As previously discussed, neurovascular conflict with morphological changes of the trigeminal root was identified as a major etiological factor in TN, confirming the vast amount of neurosurgical studies supporting that microvascular decompression is effective in TN. However, firstly, only half of TN patients have morphological changes of the ipsilateral trigeminal nerve, and 12% of patients do not even have a neurovascular conflict (25,26), and secondly, the recurrence rate after microvascular decompression is about 2% annually, and in approximately 30% of patients the procedure does not provide long-term pain relief (47). This indicates that either microvascular decompression was not able to reverse the hyperexcitable state of the trigeminal root induced by a neurovascular conflict, or that the de- and dysmyelination of the trigeminal root can also be caused or maintained by other unknown etiological factors.

There are no confirmed risk factors in TN as studies (11,12) have failed to reproduce hypertension as a risk factor, which was reported by Katusic (17). There is a slight preponderance of women with TN; women generally have a younger age of onset and less frequently have morphological changes of the ipsilateral trigeminal root. Therefore, factors relating to the female sex, such as differences in sex hormone levels, may be risk factors in TN, but this has yet to be explored. Another virtually unexplored risk factor may be gain-of-function mutations of voltage gated sodium channels. Mutations were identified in other pain conditions somewhat resembling TN, such as paroxysmal extreme pain disorder, erythromelalgia, and small fiber neuropathy (49–51). A recent study identified a single $Na_V1.6$ de novo missense mutation causing increased trigeminal excitability in a CTN patient (52).

Classification

The terminology of TN type 1 (more than 50% paroxysmal pain) and 2 (more than 50% constant pain) (53) is widely used, especially in neurosurgical literature. A possible drawback to this proposed classification system is that patients with idiopathic constant facial pain and no paroxysmal pain, could be classified as TN type 2, where other classification systems would designate the diagnosis of persistent idiopathic facial pain (formerly atypical facial pain) to such patients.

Recently, it was suggested that classical TN should be divided into an idiopathic form and a classical form where there are morphological changes of the trigeminal root (2). If in fact the etiology is multifactorial in some patients, involving both neurovascular conflict and other factors that may lead to demyelination or

hyperexcitability, such a classification scheme is challenging and there is a need for studies exploring whether this proposed division is meaningful in a clinical and scientific context.

Maarbjerg et al. reported evidence of sensory abnormalities in TN, in particular hypesthesia, at clinical examination (11). Younis et al. demonstrated sensory abnormalities by quantitative sensory testing blinded to symptomatic side even in patients with no clinically evident sensory abnormalities (54). Similar results were also reported by others (21,47,55). Findings may be explained by central pain-induced functional changes (56).

Clinical practice

There is a need for prospective studies into TN natural history to clarify whether TN progress with time, stays the same, or improves with old age. There is a huge lack of well-designed studies investigating the efficacy and side-effects of prophylactic medications for TN. Further studies should also look into the efficacy of intravenous fosphenytoin loading, combination treatments, botolinum toxin and neurostimulation. It is debated when and which patients should be referred to surgery. There is a lack of well-designed prospective neurosurgical trials using independent evaluators of diagnosis and outcome (57).

Expert opinion: Where the field needs to go

Future studies should focus on co-operation between neurologists, neurosurgeons and neuroradiologists as well as co-operation between multiple centres to ensure a high quality, continuing discussion among specialised centres and large patient volumes in the much needed medical trials, longitudinal surgical and medical follow up and interventional studies. New sodium channel blockers are in the pipeline, but neurostimulation and botolinum toxin may also represent promising treatments in medically refractory patients (58–60).

Article highlights

- Trigeminal neuralgia (TN) is characterised by unilateral, intense, touch-evoked, stabbing paroxysmal pain. It typically affects the second and third trigeminal branch.
- Trigeminal neuralgia can be either idiopathic or secondary to multiple sclerosis or a space-occupying lesion.
- A neurovascular conflict with morphological changes of the trigeminal nerve is highly associated to classical TN, however this finding is only present in half of the patients with classical TN.
- First line treatment is prophylactic medication with sodium channel blockers, and in medically refractory patients surgical treatment is the next step.
- Future research should focus on uncovering risk factors in classical TN, on prospective studies using independent assessors of surgical outcome, on exploring new drugs and on investigating the efficacy of neurostimulation, botulinum toxin and combination treatment with existing drugs.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 629–808.
2. Cruccu G, Finnerup N, Jensen TS, et al. Trigeminal neuralgia: New classification and diagnostic grading for practice and research. *Neurology* 2016; 87: 220–228.
3. Cole CD, Liu JK and Apfelbaum RI. Historical perspectives on the diagnosis and treatment of trigeminal neuralgia. *Neurosurg Focus* 2005; 18: 1–15.
4. Maarbjerg S, Gozalov A, Olesen J, et al. Concomitant persistent pain in classical trigeminal neuralgia – evidence for different subtypes. *Headache* 2014; 54: 1173–1183.
5. Rasmussen P. Facial pain. II. A prospective survey of 1052 patients with a view of: Character of the attacks, onset, course, and character of pain. *Acta neurochir* 1990; 107: 121–128.
6. Brisman R. Constant face pain in typical trigeminal neuralgia and response to gamma knife radiosurgery. *Stereotact Funct Neurosurg* 2013; 91: 122–128.
7. Maarbjerg S, Wolfram F, Gozalov A, et al. Association between neurovascular contact and clinical characteristics in classical trigeminal neuralgia: A prospective clinical study using 3.0 Tesla MRI. *Cephalagia* 2015; 35: 1077–1084.

8. Burchiel KJ and Slavin KV. On the natural history of trigeminal neuralgia. *Neurosurgery* 2000; 46: 152–154.
9. Devor M, Amir R and Rappaport ZH. Pathophysiology of trigeminal neuralgia: The ignition hypothesis. *Clin J Pain* 2002; 18: 4–13.
10. Kugelberg E and Lindblom U. The mechanism of the pain in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry* 1959; 22: 36–43.
11. Maarbjerg S, Gozalov A, Olesen J, et al. Trigeminal neuralgia – a prospective systematic study of clinical characteristics in 158 patients. *Headache* 2014; 54: 1574–1582.
12. Rasmussen P. Facial pain. IV. A prospective study of 1052 patients with a view of: Precipitating factors, associated symptoms, objective psychiatric and neurological symptoms. *Acta neurochir* 1991; 108: 100–109.
13. Di Stefano G, La Cesa S, Truini A, et al. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain. *J Headache Pain* 2014; 15: 1–5.
14. Simms HN and Honey CR. The importance of autonomic symptoms in trigeminal neuralgia. Clinical article. *J Neurosurg* 2011; 115: 210–216.
15. May A and Goadsby PJ. The trigeminovascular system in humans: Pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. *J Cereb Blood Flow Metab* 1999; 19: 115–127.
16. Cohen AS, Matharu MS and Goadsby PJ. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA) – a prospective clinical study of SUNCT and SUNA. *Brain* 2006; 129: 2746–2760.
17. Katusic S, Beard CM, Bergstralh E, et al. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. *Ann Neurol* 1991; 27: 89–95.
18. Mueller D, Obermann M, Yoon MS, et al. Prevalence of trigeminal neuralgia and persistent idiopathic facial pain: A population-based study. *Cephalalgia* 2011; 31: 1542–1548.
19. MacDonald BK, Cockerell OC, Sander JW, et al. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000; 123: 665–676.
20. Sjaastad O and Bakketeig LS. The rare, unilateral headaches. Vågå study of headache epidemiology. *J Headache Pain* 2007; 8: 19–27.
21. De Simone R, Marano E, Brescia Morra V, et al. A clinical comparison of trigeminal neuralgic pain in patients with and without underlying multiple sclerosis. *Neurol Sci* 2005; 26: 150–151.
22. Cruccu G, Biasiotta A, Galeotti F, et al. Diagnostic accuracy of trigeminal reflex testing in trigeminal neuralgia. *Neurology* 2006; 66: 139–41.
23. Dandy WE. Concerning the cause of trigeminal neuralgia. *Am J Surg* 1934; 24: 447–455.
24. Peker S, Kurtkaya O, Uzun I, et al. Microanatomy of the central myelin-peripheral myelin transition zone of the trigeminal nerve. *Neurosurgery* 2006; 59: 354–359.
25. Maarbjerg S, Wolfram F, Gozalov A, et al. Significance of neurovascular contact in classical trigeminal neuralgia. *Brain* 2014; 138: 311–319.
26. Antonini G, Di Pasquale A, Cruccu G, et al. MRI contribution for diagnosing symptomatic neurovascular contact in classic trigeminal neuralgia. A blinded case-control study and meta-analysis. *Pain* 2014; 155: 1464–1471.
27. Masur H, Papke K, Bongartz G, et al. The significance of three-dimensional MR-defined neurovascular compression for the pathogenesis of trigeminal neuralgia. *J Neurol* 1995; 242: 93–98.
28. Sarsam Z, Garcia-Finana M, Nurmikko TJ, et al. The long-term outcome of microvascular decompression for trigeminal neuralgia. *Br J Neurosurg* 2010; 24: 18–25.
29. Ramesh VG and Premkumar G. An anatomical study of the neurovascular relationships at the trigeminal root entry zone. *J Clin Neurosci* 2009; 16: 934–936.
30. Peker S, Dinçer A and Necmettin Pamir M. Vascular compression of the trigeminal nerve is a frequent finding in asymptomatic individuals: 3-T MR imaging of 200 trigeminal nerves using 3D CISS sequences. *Acta neurochir* 2009; 151: 1081–1088.
31. Miller JP, Acar F, Hamilton BE, et al. Radiographic evaluation of trigeminal neurovascular compression in patients with and without trigeminal neuralgia. *JNeurosurg* 2009; 110: 627–632.
32. Maarbjerg S, Wolfram, Frauke Heinskou TB, Rochat P, et al. Persistent idiopathic facial pain – a prospective systematic study of clinical characteristics and neuroanatomical findings at 3.0 Tesla MRI. *Cephalalgia*. Epub ahead of print 27 October 2016. DOI: 10.1177/0333102416675618.
33. Fromm G. Pretrigeminal neuralgia. *Neurology* 1990; 40: 1493–1495.
34. Rappaport ZH, Govrin-Lippmann R and Devor M. An electron-microscopic analysis of biopsy samples of the trigeminal root taken during microvascular decompressive surgery. *Stereotact Funct Neurosurg* 1997; 68: 182–186.
35. Lutz J, Thon N, Stahl R, et al. Microstructural alterations in trigeminal neuralgia determined by diffusion tensor imaging are independent of symptom duration, severity, and type of neurovascular conflict. *J Neurosurg* 2015; 124: 823–830.
36. Obermann M, Yoon M-S, Ese D, et al. Impaired trigeminal nociceptive processing in patients with trigeminal neuralgia. *Neurology* 2007; 69: 835–841.
37. Calvin WH, Loeser JD and Howe JF. A neurophysiological theory for the pain mechanism of tic douloureux. *Pain* 1977; 3: 147–154.
38. Burchiel K. Abnormal impulse generation in focally demyelinated trigeminal roots. *J Neurosurg* 1980; 53: 674–683.
39. Dubner R, Sharav Y, Gracely R, et al. Idiopathic trigeminal neuralgia: Sensory features and pain mechanisms. *Pain* 1987; 31: 23–33.

40. Nomura T, Ikezaki K, Matsushima T et al. Trigeminal neuralgia: Differentiation between intracranial mass lesions and ordinary vascular compression as causative lesions. *Neurosurg Rev* 1994; 17: 51–57.
41. Jensen TS, Rasmussen P and Reske-Nielsen E. Association of trigeminal neuralgia with multiple sclerosis: Clinical and pathological features. *Acta Neurol Scand* 1982; 65: 182–189.
42. Dworkin RH and Portenoy RK. Pain and its persistence in herpes zoster. *Pain* 1996; 67: 241–251.
43. Cruccu G, Gronseth G, Alksne J, et al. AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol* 2008; 15: 1013–1028.
44. Wiffen PJ, Derry S, Moore RA, et al. Carbamazepine for acute and chronic pain in adults. *Cochrane Database Syst Rev* 2011; 1–40.
45. Killian JM and Fromm G. Carbamazepine in the treatment of neuralgia. *Arch Neurol* 1968; 19: 129–136.
46. Nicol CF. A four year double blind study of Tegretol in facial pain. *Headache* 1969; 9: 54–57.
47. Barker FG, Jannetta PJ, Bissonette DJ, et al. The long-term outcome of microvascular decompression for trigeminal neuralgia. *N Engl J Med* 1996; 334: 1077–1083.
48. Truini A, Prosperini L, Calistri V, et al. A dual concurrent mechanism explains trigeminal neuralgia in patients with multiple sclerosis. *Neurology* 2016; 86: 2094–2099.
49. Fertleman CR, Baker MD, Parker KA, et al. SCN9A mutations in paroxysmal extreme pain disorder: Allelic variants underlie distinct channel defects and phenotypes. *Neuron* 2006; 52: 767–774.
50. Yang Y, Wang Y, Li S, et al. Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. *J Med Genet* 2004; 41: 171–174.
51. Huang J, Han C, Estacion M, et al. Gain-of-function mutations in sodium channel NaV1.9 in painful neuropathy. *Brain* 2014; 137: 1627–1642.
52. Tanaka BS, Zhao P, Dib-Hajj FB, et al. A gain-of-function mutation in Nav1.6 in a case of trigeminal neuralgia. *Mol Med*. Epub ahead of print 3 August 2016. DOI: 10.2119/molmed.2016.00131.
53. Burchiel KJ. A new classification for facial pain. *Neurosurgery* 2003; 53: 1164–1166.
54. Younis S, Maarbjerg S, Reimer M, et al. Quantitative sensory testing in classical trigeminal neuralgia – a blinded study in patients with and without concomitant persistent pain. *Pain* 2016; 157: 1407–1414.
55. Maier C, Baron R, Tolle TR, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 2010; 150: 439–450.
56. Geber C, Magerl W, Fondel R, et al. Numbness in clinical and experimental pain – a cross-sectional study exploring the mechanisms of reduced tactile function. *Pain* 2008; 139: 73–81.
57. Zakrzewska JM and Lopez BC. Quality of reporting in evaluations of surgical treatment of trigeminal neuralgia: Recommendations for future reports. *Neurosurgery* 2003; 53: 110–120.
58. Zakrzewska JM, Palmer J, Ettlin DA, et al. Novel design for a phase IIa placebo-controlled, double-blind randomized withdrawal study to evaluate the safety and efficacy of CNV1014802 in patients with trigeminal neuralgia. *Trials* 2013; 14: 402. DOI: 10.1186/1745-6215-14-402.
59. Jürgens TP, Müller P, Seedorf H, et al. Occipital nerve block is effective in craniofacial neuralgias but not in idiopathic persistent facial pain. *J Headache Pain* 2012; 13: 199–213.
60. Cruccu G, Truini A. Refractory Trigeminal Neuralgia : Non-Surgical Treatment Options. *CNS Drugs* 2013; 27: 91–96.