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REVIEW ARTICLE

Trigeminal Neuralgia: Basic and Clinical Aspects

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Abstract: The trigeminal nerve is the largest of all cranial nerves. It has three branches that provide the main sensory innervation of the anterior two-thirds of the head and face. Trigeminal neuralgia (TN) is characterized by sudden, severe, brief, and stabbing recurrent episodes of facial pain in one or more branches of the trigeminal nerve. Pain attacks can occur spontaneously or can be triggered by non-noxious stimuli, such as talking, eating, washing the face, brushing teeth, shaving, a light touch or even a cool breeze. In addition to pain attacks, a proportion of the patients also experience persistent background pain, which along with autonomic signs and prolonged disease duration, represent predictors of worse treatment outcomes. It is now widely accepted that the presence of a neurovascular compression at the trigeminal root entry zone is an anatomic abnormality with a high correlation with classical TN. However, TN may be related to other etiologies, thus presenting different and/or additional features. Since the 1960s, the anticonvulsant carbamazepine is the drug of choice for TN treatment. Although anti-epileptic drugs are commonly used to treat neuropathic pain in general, the efficacy of carbamazepine has been largely limited to TN. Carbamazepine, however, is associated with dose-limiting side-effects, particularly with prolonged usage. Thus, a better understanding and new treatment options are urgently warranted for this rare, but excruciating disease.

Keywords: Neuropathic orofacial pain, symptomatology, epidemiology, pathophysiology, diagnostic, pharmacological treatment.

1. INTRODUCTION

According to the International Headache Society, TN is defined as "a disorder characterized by recurrent unilateral brief electric shock-like pain, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli" [1]. The last classification of IHS also considers that Classical TN (previously called Idiopathic Trigeminal Neuralgia) relates to TN that is caused exclusively by neurovascular compression, and it is classified into two subforms: 1) Classical TN, purely paroxysmal and 2) Classical TN with concomitant persistent facial pain; which will be discussed in this review.

Trigeminal neuralgia-like pain that is related to an underlying disease, including tumors, trauma, viral infection, and multiple sclerosis is classified as Secondary TN. Secondary TN has a similar clinical presentation as classical TN, but may present some additional and/or different features. For instance, TN attributed to multiple sclerosis may have a bilateral presentation and TN related to tumors frequently display abnormalities in electrophysiological tests, such as trigeminal brainstem reflexes [1].

2. EPIDEMIOLOGY

TN is considered a rare condition, and epidemiological studies are scarce. The first report on TN incidence was published in the US by Penman [2] in approximately 107 men and 200 women per 1 million people. Later, Katusic and colleagues estimated that the incidence of TN in Rochester, Minnesota, from 1945 through 1984 was 4.3 to 100,000 for men and women [3]. Similar findings have been reported by others (*i.e.*, 4 new cases/100.000/year), which suggest that the prevalence of TN in the US might be 15.000 new cases each year [4, 5]. Much higher incidence rates (*i.e.*, 27 in 100.000/year) were reported in UK primary care [6]. In the general population, an analysis of prevalence studies indicates that the range of TN incidence is 0.03% to 0.3% [7]. The historical aspects of trigeminal neuropathic pain have been the subject of excellent reviews [8-10] and will not be addressed here.

Early studies already indicated a slight female predominance in TN incidence considered nearly twice as common

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in women [3, 5], a finding that has been corroborated by recent studies [11-13]. Additionally, a systematic review of TN prevalence found a 3:1 proportion between women and men [14].

TN is rare below the age of 40, but it can affect the pediatric population, and cases have been reported even in patients as young as 1 year of age [15-18]. In 90% of the cases, symptoms begin after age 40, and incidence progressively increases with age, from 17.5/100 000/year between 60 and 69 years of age up to 25.6/100 000/year after age 70 [3, 5, 14].

There are no reports of racial or geographic differences accounting for TN incidence, but there are some suggestions that some patient populations are at higher risk for TN development. It is well documented that the incidence of TN in multiple sclerosis (MS) patients is higher than in the general population. More than 2% of TN patients have associated MS [19, 20]. Although it has been reported that TN can precede MS, in the majority of the cases, MS is considered the underlying cause of TN. Interestingly, in both situations, the clinical presentation differs from the classical TN, and most patients suffer from bilateral pain attacks [3, 5, 21].

Familial cases of TN are even rarer, comprising about 1-2% of all cases, but have been consistently reported. Katusic *et al*., found that 5.3% of the patients had a family history of TN [3]. An autosomal dominant transmission of TN has been suggested, as reported by Duff and colleagues, who found seven members of the same family diagnosed with TN and by Herzberg, who reported a family with four cases of TN in three generations [22, 23]. Smyth and colleagues described 4 cases of TN in three generations [24], while Braga *et al*., presented a case of four siblings with TN, ranging between the ages of 24 and 31 [25]. Genetic clustering was also suggested by Savica *et al*., who described four members of the same family suffering from TN and by Kirkpatrick, who found three non-twin sisters with TN in the early middle-age [26, 27]. There is evidence that familial cases of TN may have an early onset and be associated with glossopharyngeal neuralgia and Charcot-Marie-Tooth neuropathy (for review see [24]).

The relationship between hypertension and TN has also been investigated by some groups, but the results are still inconclusive. Katusic *et al*., suggested that hypertension is associated with an elevated risk of TN, but Sandell and colleagues did not find a difference in the prevalence of arterial hypertension in the general population compared to TN patients [3, 28]. There is evidence that neurovascular compression is related to certain neurologic disorders, including TN, which might contribute to related conditions, such as essential hypertension, because surgical decompression was associated with a significant decrease in blood pressure [29, 30]. It has also been suggested that hypertension may be a predisposing factor for the development of TN, but the existing data is contradictory and inconclusive [31, 32].

3. SIGNS AND SYMPTOMS

TN is characterized by recurrent unilateral short-lasting pain attacks distributed in one or more branches of the trigeminal nerve. Pain is described as sharp, lancinating, shock-like or electric-like, severe, sudden and superficial and the pain attacks may be accompanied by tic-like cramps (*i.e.*, involuntary contraction or spasm) of the facial muscles, hence, the early description of TN is "tic douloureux". Pain attacks can occur spontaneously or can be triggered by non-noxious stimuli, such as talking, eating, washing the face, combing the hair, brushing teeth, shaving, a light touch, or even a cool breeze. Pain attacks can occur several times per day, and their frequency, duration, and severity may worsen over time (for review see [33-35]).

According to some clinical studies, the majority of TN patients experience as many as 10-50 pain attacks per day [13, 36, 37]. The duration of each pain attack ranges from a fraction of a second to two minutes and most patients are asymptomatic between paroxysms. This patient population is now considered to suffer from Classical TN which is purely paroxysmal. On the other hand, pain attacks can be followed by a persistent background, dull pain of moderate-to-severe intensity, which is now, termed Classical TN with concomitant persistent facial pain [1].

TN usually affects the maxillary (V2) and mandibular (V3) trigeminal branches. The ophthalmic branch (V1) is afflicted less commonly, occurring in 1-5% of patients. The frequency of involvement of the V2 and V3 divisions varies in different studies, with some reporting higher incidence for the V2 and others for the V3 division [13, 14, 33, 38]. The involvement of V1+V2 and V2+V3 divisions also accounts for approximately 10 and 20%, respectively, of TN cases [33], and the involvement of all three nerve branches have been reported [13, 39]. It has been suggested that the high incidence of V2 and V3 involvement might be due to the somatotopic distribution of the sensory fibers in the trigeminal root, as vascular compression was more frequently found in a superior-lateral or inferior position in relation to the circumference of the nerve root [40].

Interestingly, it has also been repeatedly demonstrated that the right side of the face is more commonly affected by TN than the left [3, 5, 12, 14, 39, 41]. In addition, it has recently been reported that right-sided TN is more frequent in patients with purely paroxysmal pain compared to those with concomitant persistent facial pain [41]. It has been hypothesized that pain lateralization in TN is due to a narrower foramen rotundum and foramen ovale on the right side [42], but this suggestion is yet to be validated.

Bilateral TN has also been reported, but most of these patients suffer from multiple sclerosis, as discussed below [5, 33]. Likewise, V1 involvement is not frequent and needs to be carefully evaluated in order to establish a correct diagnosis. TN affecting the V1 branch can be confused with trigeminal autonomic cephalalgias, as both conditions often present autonomic symptoms. The prevalence of autonomic symptoms in TN patients varies in different studies (31-67%) and is usually considered mild including mainly conjunctival injection and lacrimation. In the presence of pronounced autonomic signs, it is also important to investigate if the patient suffers from both conditions [13, 43, 44].

In addition to pain attacks and dull persistent pain, which are common for some patients, studies employing quantita-

tive sensory testing (QST) have documented significant sensory alterations that seem to affect 15-25% of TN patients [45]. Increased tactile thresholds for touch and temperature were described in the affected division of the trigeminal nerve, while in the unaffected adjacent divisions, only the tactile threshold was altered [46, 47]. In different studies, increased detection thresholds for cold and warm were observed more frequently [45, 48, 49]. Despite the unilateral character of pain attacks in TN, bilateral thermal and mechanical hyperalgesia have also been reported [48]. In line with these previous observations, a very elegant study by Younis and colleagues described bilateral facial thermal and mechanical hyperalgesia, as well as increased facial mechanical detection threshold suggesting subclinical hypoesthesia in TN patients. In this study, it was shown for the first time that the sensory alterations are not restricted to the face, as they were also detected with the same characteristics on the patients' hands [41].

3.1. Natural History

The pain-free intervals in TN patients may range from days to years [43]. Spontaneous remission of TN pain attacks can occur unexpectedly, which contributes to the uncertain natural history of the disease [5]. The reported median active period is about 50 days, followed by remission of months (36%), weeks (16%) or even days (16%). Only 6% may look forward to remissions of more than a year and about 20% may suffer from incessant attacks [50]. Another important observation showed that abnormal QST was detected for TN patients both in and out of remission [41].

Although some studies have suggested that it represents a progressive disorder [51, 52], there is growing evidence indicating that worsening of pain with time and the development of late resistance only occurred in a very small minority of patients [53, 54]. Some studies have reported significant pain reduction over time in patients receiving pharmacological treatment for TN [50, 54].

It has been reported that the presence of some features, including long attack duration, autonomic signs, prolonged disease duration, and atypical pain descriptors are considered indicators of a poor therapeutic outcome [1, 50].

If patients on medication are pain-free for 4-6 weeks, tapering of medication should be considered [5]. However, it remains to be elucidated if, in this situation, the patient is in remission or enjoying the benefits of therapy. These features of TN, combined with the fact that it is a relatively rare condition with uncertain natural history, have contributed to the vast list of difficulties in clinical studies on this pain condition [33].

3.2. Impact of TN on the Patients 'Lives'

TN patients present a marked reduction in the quality of life due to the nature and severity of pain. There is mounting evidence that TN frequently leads to psychological distress that sometimes results in suicide attempts [55-58]. It has been reported that the suffering of TN patients is related to delays in diagnosis, fear of pain recurring suddenly, side effects of medications, and lack of psychological support [59]. Recent clinical studies have identified levels of depression and anxiety in TN affected individuals [58, 59]. Indeed, the incidence of depression and anxiety in TN patients is estimated to be nearly three times than that observed in matched controls and it positively correlates with pain scores and disease duration [55, 60, 61].

It is noteworthy that mood disorders may be improved when the pain is relieved/reduced, resulting in improved quality of life. This observation highlights the importance of a multidisciplinary team in the management of TN [60].

Other accompanying symptoms of TN patients include impairment in the performance of daily activities, avoidance of social interactions, sleep disorders, fatigue and anorexia [36, 55, 58]. TN patients also showed high catastrophizing scores, which may be related to the fear and unpredictability of the pain attacks, as well as impotence to deal with the crisis [58].

4. PATHOPHYSIOLOGY

According to the ICHD-3, Classical TN is caused by neurovascular compression, most frequently by the superior cerebellar artery [1]. This physiopathological mechanism was first proposed by a neurosurgeon named Walter Dandy in 1929, who noticed that the trigeminal nerve root was indented by an artery during the partial sectioning of the root as a treatment for classical TN (for a complete review on the historical aspects of TN please see [8]). Since then, many studies have been developed aiming to identify vascular compression and to correlate this finding with the major TN characteristic; the paroxysmal pain attacks. It has been considered that around 80-90% of the patients suffering from TN exhibit vessel contact within the nerve, while vascular contact in the asymptomatic control group seems to occur in 40% of cases [39, 62, 63]. Thus, vascular compression of the trigeminal nerve is suggested to be an anatomical abnormality with a high correlation with TN.

It has also been reported that the most common origin of nerve compression is the superior cerebellar artery, involving about 50% of the cases [39, 64-67]. In 25% of the cases, the origin seems to be exclusively venous, while in a few cases, the involvement is considered mixed. Other vessels that may be responsible for the compression include the anterior inferior cerebellar artery, basilar artery, and pontine veins [39, 62]. The most common location of the vascular compression was identified in the trigeminal root entry zone, that is the point where the trigeminal roots enter the brainstem (*i.e.*, more than 50% of the cases), but compression has also been described in the mid-third of the nerve and at the exit of the nerve from the trigeminal or Meckel cave [40, 62]. Several degrees of compression severity have been described including simple contact with the nerve, a marked indentation, nerve atrophy and nerve distortion or deformity. Nerve deformity has often been observed in some studies therefore, the side of the deformed nerve correlated well with the side of TN [39, 40].

Several alterations have been described as a result of the vascular compression, but as first proposed by Jannetta, focal demyelination at the entry zone of the trigeminal nerve seems to be one of the main mechanisms that could promote neuralgia-like pain [68]. Focal demyelination of compressed

fibers was observed in TN patients and may result in the facilitation of ephaptic conduction of nerve impulses [63, 69]. The pattern of demyelination differs from that seen in multiple sclerosis, since it is not associated with inflammation and is characterized by focal loss of myelin and close apposition of the demyelinated axons with few intervening astrocytic processes [69, 70].

Other structural changes that have been reported in the compressed zone of TN patients include alterations of peripheral axons, such as atrophy or hypertrophy, the presence of great number of collagen fibers in the extracellular matrix, alterations in oligodendrocytes, damage to Schwann cells and peripheral myelin. In addition to demyelination, alterations in the myelin include deformation, thickening, as well as aberrant remyelination, in which a single thin myelin sheath involves many adjacent axons [63, 69-71].

In attempting to correlate the paroxysmal pain attacks with the structural alterations observed in compressed trigeminal neurons, Devor and colleagues formulated the ignition hypothesis, which has been widely accepted to explain TN physiopathology [72]. This hypothesis states that sensory neurons partially damaged become hyperexcitable and susceptible to cross excitation, as a result of the physical proximity of the neurons in the site of root compression. Therefore, the explosions of post-trigger neuronal activity recruit additional neighboring neurons leading to a rapid accumulation of electrical activity, which can be amplified by ephaptic interaction among neurons, since myelin sheath was damaged and nerve fibers maintain close contact among them. Thus, the stimulus of a single sensory fiber may lead to activation of many others, and the explosions of neuronal activity triggered by an external stimulus may extend beyond the stimulus duration [72]. According to this hypothesis, pain paroxysms experienced by TN patients would be the result of this synchronized phenomenon, which can be stopped by hyperpolarization from potassium ion influx making the neurons refractory to new excitation and would partly justify the refractory period after the crisis [71-73].

The ignition hypothesis appears to account, in part, for mechanisms that promote paroxysmal attacks, a primary feature of TN. It is important to point out, however, that pain attacks are usually evoked by innocuous stimulation of the trigger points, especially by light touch. In this regard, it has been postulated that vascular compression would first impair large myelinated Aβ fibers [74-76]. It has also been proposed that the shock-like pain evoked by innocuous tactile stimulation represents a feature of initial stages of the disease and, as it persists, there is a progressive change in the character of pain and sensory impairment [74, 76].

In line with this hypothesis, several clinical studies indicated that sensory abnormalities occurred more frequently in TN patients with concomitant persistent background pain [77, 78]. Such sensory alterations include increased thresholds to tactile stimuli, which can indicate peripheral and/or central neuronal deafferentation of Aβ fibers, as well as decreased thresholds for nociceptive stimuli that are coded by Aδ and C fibers. Thus, as the disease progresses, the function of Aδ and C fibers is impaired resulting in constant and diffused pain, in addition to the sensory abnormalities [41, 48, 76]. As background pain, hyperalgesia and other sensory alterations are bilateral, suggesting that they reflect central facilitation of trigeminal nociceptive pain processing [77].

It is also noteworthy that other physiopathological processes may contribute to paroxystic pain in TN. One possibility is that alterations in voltage-gated sodium channels (Nav) may account for greater neuronal excitability and ectopic shooting of afferent trigeminal fibers, which has been widely demonstrated in pre-clinical models of neuropathic pain, including trigeminal neuropathic pain models [79, 80]. Indeed, increased expression of Nav1.3 sodium channels was detected in gingival tissue samples of TN patients, corroborating this idea [81]. The contribution of sodium channels to the pain paroxysm in TN helps to explain the efficacy of antiepileptic drugs that stabilize cell membranes to control pain in this condition.

Changes in central nervous system structures have also been reported in TN patients. Some groups detected a significant reduction in the grey matter volume of many structures associated with pain processing and perception, such as the thalamus, somatosensory cortex, insula, *etc.*, which seem to correlate well with the disease duration [82-84]. The results of these studies suggest that the duration of TN may be a critical factor associated with brain alterations, which may reflect an adaptation mechanism to persistent peripheral input.

5. DIFFERENTIAL DIAGNOSIS

According to the IHS, the diagnosis of classical trigeminal neuralgia should comprise at least 3 pain attacks with the following characteristics: 1) Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond; 2) Pain lasting from a fraction of a second to two minutes, severe intensity and electric shock-like, shooting, stabbing or sharp in quality; 3) Precipitated by innocuous stimuli within the affected trigeminal [1]. It is important to mention that in the majority of patients, classical TN has a memorable onset of pain.

In the purely paroxysmal form of TN, there is no background pain between the attacks, while in the TN with concomitant persistent facial pain. there is persistent facial pain of moderate intensity in the affected area, which is less likely to be triggered by innocuous stimulation [1]. Additionally, according to the ICHD-3, classical TN patients usually failed to demonstrate sensory abnormalities, unless advanced methods are employed. In fact, studies that have applied QST in classical TN patients have documented sensory abnormalities [41, 45, 48, 49].

The presence of sensory abnormalities during clinical evaluation may represent a confounding factor in the diagnosis of TN. On the other hand, QST enables the assessment of particular features of each TN patient, like other pain measurement tools, contributing to approaches for improved pain control [85].

There are several painful facial conditions that can be confounded with TN, which together with the rare nature of

TN can delay the diagnosis. Some conditions, such as those of dentoalveolar or musculoskeletal origin, are easily differentiated from TN, but others, including some types of headaches and migraines, as well as some types of neuropathic pain, such as post-herpetic neuralgia and glossopharyngeal neuralgia, require more attention. The main features that differentiated TN from other forms of orofacial pain are the short duration of the pain attacks, their unilateral character, and their limitation to trigeminal nerve branches. The investigation of multiple sclerosis should always be considered in the differential diagnosis, especially in bilateral cases or in younger patients. Magnetic resonance imaging (MRI) scans can determine if there is a symptomatic cause, such as multiple sclerosis or tumors, and whether surgery is indicated. Finally, response to carbamazepine, the most effective drug in TN treatment has also been considered as a useful tool in the differential diagnostic [34, 35, 86].

Recently, there has been some debate regarding the classification and differential diagnosis of TN and some trigeminal autonomic cephalalgias, especially, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA). In spite of being considered and classified as different disorders, there is emerging clinical and imaging evidence of significant overlap among these conditions [87-89]. In fact, aberrant vascular loops have been reported around the ipsilateral trigeminal nerve in patients with SUNCT as seen in patients with TN, and, as already mentioned, mild autonomic symptoms may be seen in up to 50% of patients with TN [44, 88]. In addition, a case of TN and SUNCT coexistence has been reported in a patient afflicted by a hemorrhagic infarct of the dorsolateral medulla [90]. This observation is in agreement with early studies that pointed to a relationship between TN development and brainstem infarct [91-93]. In light of these considerations, it has been argued that these conditions may constitute a continuum of the same disorder, rather than separate clinical entities, but further research is needed to support this idea.

6. TREATMENT

6.1. Pharmacological Treatment

It has only been within the past 40 years that reasonable pharmacological and surgical therapies were introduced for TN treatment. Before that, the most effective treatments consisted of destruction of the nerve branch affected by injection of caustic substances or section of the sensory trigeminal root behind the gasserian ganglion [8].

The first drug introduced for the treatment of TN was the anticonvulsant phenytoin in 1942 [94], which is still employed in the treatment of refractory TN by intravenous route [95]. However, it soon became apparent that carbamazepine, an anticonvulsant introduced in the clinic in 1959, was a more effective option for the treatment of TN [96]. This observation was supported by three placebo-controlled clinical trials [97-99], and since the early 1960s, carbamazepine continues to be the drug of choice for the treatment of TN [97, 100-102]. However, as TN is a rare disease, the largest of these initial trials included 77 patients [97]. More recent clinical studies included a limited number of patients, which together with the uncertain natural history of the disease, represent major limitations in understanding TN.

Carbamazepine is highly effective in reducing TN pain symptoms, showing efficacy in up to 70% of the treated patients. Accordingly, it has been estimated that carbamazepine's number needed to treat (NNT) in TN is equal to 1.8 [103, 104]. The onset of carbamazepine effects on pain paroxysms is generally very rapid and seems to be related mainly to the blockade of sodium channels in neuronal membranes during high-frequency stimulation, thereby reducing the propagation of the electrical signal and limiting the spread of ectopic activity. Several additional mechanisms may contribute to carbamazepine analgesic effect, which has been reviewed elsewhere [105]. However, long-term treatment with carbamazepine has been associated with many side effects, including sleepiness, tiredness, dizziness, nausea, vomiting, ataxia, renal and hepatic toxicity, allergic reactions and symptoms relapse in up to 50% of the patients. Therefore, its number needed to harm (NNH) is estimated as 3.7 [53, 103].

It is important to highlight that carbamazepine use has been associated with a variety of hypersensitivity reactions, ranging from mild maculopapular exanthemas to hypersensitivity syndrome, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis; the latter four phenotypes are referred to as serious cutaneous adverse reactions [106, 107]. Frequently, these reactions require the discontinuation of carbamazepine, due to the discomfort caused to patients or due to its severity and life-threatening character [108]. These unpredictable clinical phenotypes are T-cell-mediated, in which carbamazepine and/or its metabolites bind specific human leukocyte antigen (HLA) molecules triggering a T-cell response. Two genetic risk variants for carbamazepine-induced hypersensitivity reactions have been identified: HLA-B*15:02 and HLA-A*31:01, but the precise mechanism of how carrying each variant results in an increased risk of hypersensitivity to the drug remains to be elucidated [108]. It is estimated that the incidence of Stevens-Johnson syndrome is 1 in 1000 in the general population, with an alarming incidence of 1 in 400 at-risk populations [107, 109, 110]. Thus, testing is recommended for HLA-B*15:02 and HLA-A*31:01 alleles in patients with Asian ancestry before starting carbamazepine therapy [108].

It has been suggested that oxcarbazepine, a drug related to carbamazepine, may well be as effective, but its comparative efficacy lacks evidence in TN. However, according to some international guidelines carbamazepine and oxcarbazepine are considered the first-line treatment for TN patients, especially due to a more favorable safety and pharmacokinetic profile of the latter [111]. Unlike carbamazepine, which is metabolized by cytochrome P450 oxidative processes, oxcarbazepine is metabolized by cytosolic enzymes, presenting a lower potential for drug interactions. Other advantages of oxcarbazepine over carbamazepine are the lack of auto-induction so that its elimination does not change significantly over time (for review [112]). Some recent com-

parative studies have shown similar efficacy of oxcarbazepine and carbamazepine in the treatment of TN patients, but the superiority of the safety profile of oxcarbazepine was not evident [54, 113]. Side effects like skin rash and hyponatremia are considered major adverse reactions associated with oxcarbazepine treatment [114]. Hyponatremia is often asymptomatic, but it can lead to symptoms ranging from unsteadiness and mild confusion to seizures, headache and coma. It may occur in patients taking both carbamazepine or oxcarbazepine, but some recent evidence indicates that it is more frequent with the latter [115]. Hyponatremia is probably due to the antidiuretic properties of both drugs, and to date, there is no evidence that a genetic risk variant is associated with this effect [116, 117]. However, there is evidence of an association of HLA-B*15:02 with Stevens-Johnson syndrome induced by oxcarbazepine, which is estimated to be 30-40 fold lower compared to carbamazepine in Taiwan Han Chinese patients [108].

Due to the side effect profile and pharmacokinetic features of carbamazepine, the effectiveness of other drugs for the treatment of TN has been evaluated. Second-line agents for TN include the anticonvulsant lamotrigine and the muscle relaxant baclofen (level C evidence) [111]. Newer anticonvulsants, including gabapentin, pregabalin and topiramate have also been tested in TN patients in the past few years [37, 118, 119]. However, evidence supporting their use is scarce and the methodological quality of most studies is relatively poor.

In addition to systemic treatment options, some studies have shown the efficacy of locally applied agents in TN. The injection of botulinum toxin to trigger zones seems to provide rapid pain relief with minimal side effects [120, 121]. Likewise, the topical application of capsaicin over the painful area showed promising results in some clinical studies [122-124]. A peripheral nerve block with different local anesthetics may be beneficial for some TN patients [125, 126]. More recently, it has been suggested that the association of peripheral nerve block with systemic TN pharmacotherapy may result in better pain control with reduced side effects, due to the possibility of lowering anticonvulsant doses [127-129]. Finally, a few studies have proposed the application of local anesthetic trough medicated plasters, intranasal sprays and epidural catheters [130, 131]. However, as already stated regarding the systemic treatments, there is no high-quality evidence to support the use of locally applied therapeutic agents, either as monotherapies or as an adjuvant in the treatment of TN.

Some conditions have been described as predictors of worse treatment outcomes, such as TN with concomitant background pain, prolonged disease duration and the presence of autonomic signs [1, 132]. Thus, studies aiming to investigate pharmacological options for the treatment of TN patients, especially those with negative prognostic signs, are urgently needed.

Advances in the pharmacological treatment of TN include the assessment of an extended-release formulation of oxcarbazepine and the evaluation of a new selective Nav1.7 channel blocker (BIIB074 or Vixotrigine), which are currently in progress (ClinicalTrials.gov, Identifiers # NCT03374709 and NCT03637387, respectively).

Vixotrigine is a Nav1.7-selective, state-dependent sodium-channel blocker, that can be administered in therapeutic doses without titration, and has shown good tolerability in healthy individuals in phase 1 and phase 2a studies [133]. In the latter study, which enrolled 67 patients; eligible patients received vixotrigine (150 mg, 3 times per day, orally) for 21 days. The new drug was well-tolerated. Headache and dizziness were the most frequent adverse events. The primary endpoint, which was treatment failure, was not significantly different between placebo and vixotrigine-treated groups, but significant treatment differences versus placebo were found in secondary endpoints including time for treatment failure, the number of paroxysms, average daily pain score, the assessments of overall function and quality of life [133]. As already discussed, conclusions are limited by challenges in conducting TN clinical studies, but the results encourage the move to a Phase 3 study, which is currently in progress (ClinicalTrials.gov, Identifier # NCT03070132).

6.2. Surgical Interventions

The surgical procedures are indicated for patients with incapacitating symptoms of TN, refractory or recurrent TN or in the case of intolerable adverse effects related to the medication. TN surgical management is either non-ablative, which consists of the decompression of the nerve, preserving its normal function or ablation, which results in the destruction of sensory function of the trigeminal nerve. Some features are briefly discussed here including the main surgical options, but detailed indications and more information on the surgical procedures may be found in guidelines and have been reviewed by others [111, 134, 135].

Microvascular decompression (MVD) was based on Dandy's hypotheses of a vascular compression on the trigeminal root as the cause of TN, since its aim is to remove the suspected compression of the nerve by the artery or vein [136]. Although the procedure was performed by some neurosurgeons worldwide, it gained evidence and vast acceptance in the medical community when Dr Peter Jannetta improved it by using an operating microscope [136]. Dr Jannetta performed the first microvascular decompression surgery in 1966, but it took about a decade for the procedure to gain acceptance [137]. Over time, long-term studies have reported the efficacy and durability of the MVD procedure, with long term success rate, which is estimated at around 70%. The incidence of complications varies between 0.2 and 5% and includes loss of hearing, which is usually transient, infection, bleeding, hematomas, and cerebrospinal fluid leakage [138, 139]. Among the surgical options, MVD has proven to be the most successful and durable surgical approach for TN, but complications may limit its utility especially in elderly patients.

Gamma knife radiosurgery uses a focused radiation beam to sever the trigeminal root in the posterior fossa. This procedure is less invasive, allows patients to get discharged from the hospital on the same day of the treatment, and does not have the risk of open surgeries [140]. Some disadvantages of

this procedure include high cost, longer periods to get relief from pain after the procedure (*i.e*. up to several weeks) and a high rate of pain recurrence compared to MVD. The most frequent complications reported are paraesthesias and facial numbness [135, 140, 141].

The ablative methods include all percutaneous techniques directed to the trigeminal ganglion and consist mainly in glycerol rhizotomy; radiofrequency thermocoagulation and percutaneous balloon compression. They are designed to interrupt afferent pain fibers by causing injury to the trigeminal nerve root or ganglion [142]. Pain relief was reported in 90% of patients undergoing these procedures, but pain recurrence is estimated to afflict up to 50% of the patients after 5 years [134, 135]. All three percutaneous therapies are considered safe and are associated with low mortality rates, but sensory loss is highly incident (50%), followed by dysesthesias (6%), corneal numbness with a risk of keratitis (4%), and anesthesia dolorosa (4%) [135, 142].

All surgical options present risks and benefits, as well as different success rates and indications for patients. These should be carefully considered to determine the most appropriate procedure for each situation.

CONCLUSION

TN is a rare but excruciatingly painful condition that presents a clinical challenge. Fundamental questions related to the cause, prevalence, natural history, and underlying mechanism of TN are still open. Pre-clinical and clinical studies have provided substantial knowledge about all aspects of TN, but further studies are clearly warranted to fulfill the remaining gaps and contribute to the improvement of available treatments and search for new therapeutic options.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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