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Trigeminal Neuralgia

A Project Submitted to

The Council of the College of Dentistry at the University of Baghdad, Department of Oral Diagnosis in Partial Fulfillment of the Requirements for the Degree of B.D.S

By

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Certification of the Supervisor

I certify that this project entitled "Trigeminal Neuralgia "was prepared by the fifth-year student shahad saeed sahib under my supervision at the College of Dentistry/University of Baghdad in partial fulfilment of the graduation requirements for the Degree of B.D.S.

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DEDICATION

This project is dedicated to my lovely family for their love, support and prays

Acknowledgment

To Dr.Raghad Alhashimi ,the Dean of the college of Dentistry/Baghdad University

To Dr.Bashar Hamed ,the head of Oral Diagnosis Department ,college of Dentistry

To Dr.Rana Murthada, the supervisor of this project .For all of your support we're thankful.

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Acronym /Abbreviations	Meaning
CN V	Fifth cranial nerve
TN	Trigeminal neuralgia
MRI	Magnetic resonance image
NOP	Neuropathic orofacial pain
NP	Neuropathic pain
ICHD-3	International Classification of Headache Disorder-3
CTN	Classical trigeminal neuralgia
NVC	Neurovascular compression
ITN	Idiopathic trigeminal neuralgia
SUNHA	short-lasting unilateral neuralgiform headache attacks
V1	Ophthalmic nerve
V2	Maxillary nerve
V3	Mandibular nerve
QST	quantitative sensory test
SUNCT	short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

Introduction

The Trigeminal Nerve is the fifth cranial nerve. It is also represented as CN V. It is the largest of all the cranial nerves. It is the most complex of all the cranial nerves due to it's extensive anatomic course. This nerve is a mixed nerve - having both sensory and motor fibres. The origin of the trigeminal nerve is the annular protuberance at the limit of the cerebellar peduncles **(Parral and Croibier , 2009).** It originates from three sensory nuclei (mesencephalic, principal sensory, spinal nuclei of trigeminal nerve) and one motor nucleus (motor nucleus of the trigeminal nerve) extending from the midbrain to the medulla (**Pazhniappan , 2020**).

The trigeminal nerve having three major branches: the ophthalmic nerve , the maxillary nerve, and the mandibular nerve . The ophthalmic and maxillary nerves are purely sensory, whereas the mandibular nerve supplies motor as well as sensory (or "cutaneous") functions **(Kamal et al., 2001**). Adding to the complexity of this nerve is that autonomic nerve fibers as well as special sensory fibers (taste) are contained within it.

The branches of trigeminal nerve and their cell bodies are located in the trigeminal ganglia and they make connections with second-order neurons in the trigeminal brainstem sensory nuclear complex. Ascending projections via the trigeminothalamic tract transmit information to The thalamus and other brain regions responsible for interpreting sensory information (**Gambeta et al., 2020**). One of the most common forms of craniofacial pain is trigeminal neuralgia.

Trigeminal neuralgia is characterized by sudden, brief, and excruciating facial pain attacks in one or more of the V branches, leading to a severe reduction in the quality of life of affected patients. Trigeminal neuralgia etiology can be classified into idiopathic, classic, and secondary. New diagnostic criteria, which subclassify TN on the basis of presence of trigeminal neurovascular conflict or an underlying neurological disorder, should be used as they allow better characterisation of patients and help in decision-making regarding medical and surgical treatments (**Gambeta et al., 2020).**

Classical trigemial neuralgia is associated with neurovascular compression in the trigeminal root entry zone, which can lead to demyelination and a dysregulation of voltage-gated sodium channel expression in the membrane**(Jones et al., 2019).**

These alterations may be responsible for pain attacks in trigeminal neuralgia patients. The antiepileptic drugs carbamazepine and oxcarbazepine are the first-line pharmacological treatment for trigeminal neuralgia.

MR imaging, including high-resolution trigeminal sequences, should be performed as part of the diagnostic workup.

Surgical treatment should be considered if the pain is poorly controlled or the medical treatments are poorly tolerated. Trigeminal microvascular decompression is the first-line surgery in patients with trigeminal neurovascular conflict while neuroablative surgical treatments can be offered if MR imaging does not show any neurovascular contact or where

patients are considered too frail for microvascular decomprssion or do not wish to take the risk **(Lambru et al., 2021**).

1. Literature Review

1.1 Pain

pain is a multifaceted experience involving physiological, cognitive, and emotional aspects. Reflecting this complexity, pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage **(Glick, 2015**). Acute pain resulting from injury or a painful stimulus generally results in a withdrawal reaction, ensuring minimal or no damage to the organism.

The injured area is painful during the healing phase, in most cases the pain is resolved with no residual disability following healing. Chronic pain, on the other hand, is not directly associated with injury; it continues beyond healing and has no value for the organism’s survival. It may be associated with primary or reactive changes in the nervous system that perpetuate the sensation of pain even in the absence of an active injury.

Chronic pain is often not a symptom but a disease in itself that inflicts severe physical and emotional suffering on the individual. Chronic orofacial pain may be subdivided into three main symptomatic classes: musculoskeletal, neurovascular, and neuropathic **(Sharav et al., 2008)**.

1.2 NEUROPATHIC PAIN

Neuropathic pain (NP) is defined as “pain arising as a direct consequence of any lesion or disease affecting the somatosensory system **(Haanpaa ,2011,Treede,2008**).which induces chronic pain that may originate from a peripheral nerve, a ganglion, the dorsal root, or from the central nervous system.

1.3 Neuropathic Orofacial Pain

Neuropathic orofacial pain (NOP), sometimes termed as trigeminal neuropathic pain is an umbrella term that includes conditions related to painful lesions of the cranial nerves **(Benoliel et al., 2015**) The most common clinical entities are trigeminal neuralgia, painful post-traumatic trigeminal neuropathies, and burning mouth syndrome. NOP may be generally classified as peripheral or central, or based on the symptomology as episodic and continuous. Episodic neuropathies are characterized by short, sharp, or electrical like paroxysmal pain similar to trigeminal neuralgia, while post-traumatic neuropathy or inflammation in nerve structures (neuritis) are commonly characterized by continuous burning pain. NOP shares mechanisms and features with spinal neuropathic pain, yet it demonstrates inimitable characteristics. Conditions such as burning mouth syndrome or trigeminal neuralgia occur solely in this region, while other conditions such as painful diabetic neuropathy, one of the most common neuropathic conditions, rarely affects the orofacial region. This may be explained in part by trigeminal nerve injury studies that show divergent responses to physical and inflammatory insults compared to spinal nerves injury **(Benoliel et al., 2001**).

2. Trigeminal Neuralgia

2.1 Definition :

Trigeminal neuralgia (TN) is the most common form of craniofacial neuropathic pain and is considered the cause of one of the most severe types of pain that a person can experience. The incidence is estimated at 4 to 13 people per 100,000/year **(Jhon et al.,2019**).

The International Association for the Study of Pain describes TN as "a sudden usually unilateral severe brief stabbing recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve **(Maarbjerg et al.,2019).**

Pain is usually described as stabbing, paroxysmal, reminiscent of electric shock, or burning and is limited to the area innervated by one or more branches of the trigeminal nerve. In approximately 60% of the cases, there is an involvement of only one branch, the maxillary or mandibular branch, whereas in approximately 35% of the cases, both are involved. On the other hand, the ophthalmic branch is rarely affected ,i.e., in fewer than 4% of patients **(Maarbjerg et al.,2019**).

Aging is a risk factor for the development of trigeminal pain, commonly occurring in patients over 50 years old **(Montano et al.,2015).**

The incidence in woman is higher, with a female–male ratio of approximately 2–3:1 **(Bangash,2011).** Pain attacks usually occur by stimulating trigger points, usually located in the territory innervated by the trigeminal nerve. Examples of stimuli that trigger attacks of pain include a slight touch of the face, tooth brushing, and activation of the masticatory and facial muscles during speech and feeding. Each episode of pain is followed by a refractory period that can last from a few seconds to several minutes.

When attacks of pain become very frequent, patients become unable to perform their daily activities, and even avoid eating and communicating for fear of triggering a new crisis. This, in turn, can lead to a severe impairment of life quality and mental health in these patients **(Türp and Gobetti ,1996).**

2.2 Classification of Trigeminal Neuralgia

According to the International Classification of Headache Disorder-3 (ICHD-3) classified TN into :

classical, secondary or idiopathic, depending on the underlying cause (figure 1.1). The classical type, which is the most common and accounts for 75% of cases, is diagnosed when there is trigeminal neurovascular compression

(figure2.2) with morphological changes ipsilateral to the side of the pain, demonstrated either on MR imaging with appropriate trigeminal sequences or during surgery. Simple trigeminal contact without morphological changes is not sufficient to underpin such a diagnosis as this is a common neuroimaging finding in healthy people. Indeed, prospective trigeminal MR imaging studies have shown that on the symptomatic side, classical TN is associated with neurovascular compression with morphological changes (distortion, indentation, atrophy) while these morphological changes are rare on the asymptomatic side **(Maarbjerg et al.,2015).**

The secondary type, accounting for approximately 15% of cases, is attributable to an identifiable underlying neurological disease (except trigeminal neurovascular compression) that is known to cause TN, such as cerebellopontine angle tumour, arteriovenous malformation and multiple

sclerosis. Approximately 2% of people with multiple sclerosis have symptoms similar to those of TN **(De Simone et al.,2005)**

The idiopathic type, accounting for approximately 10% of cases, is diagnosed when no apparent cause for TN can be found .

Idiopathic and classical TN are further subclassified in groups with purely paroxysmal pain or with concomitant continuous pain (depending on the presence or absence of continuous or near continuous interictal pain ,figure(1.1)

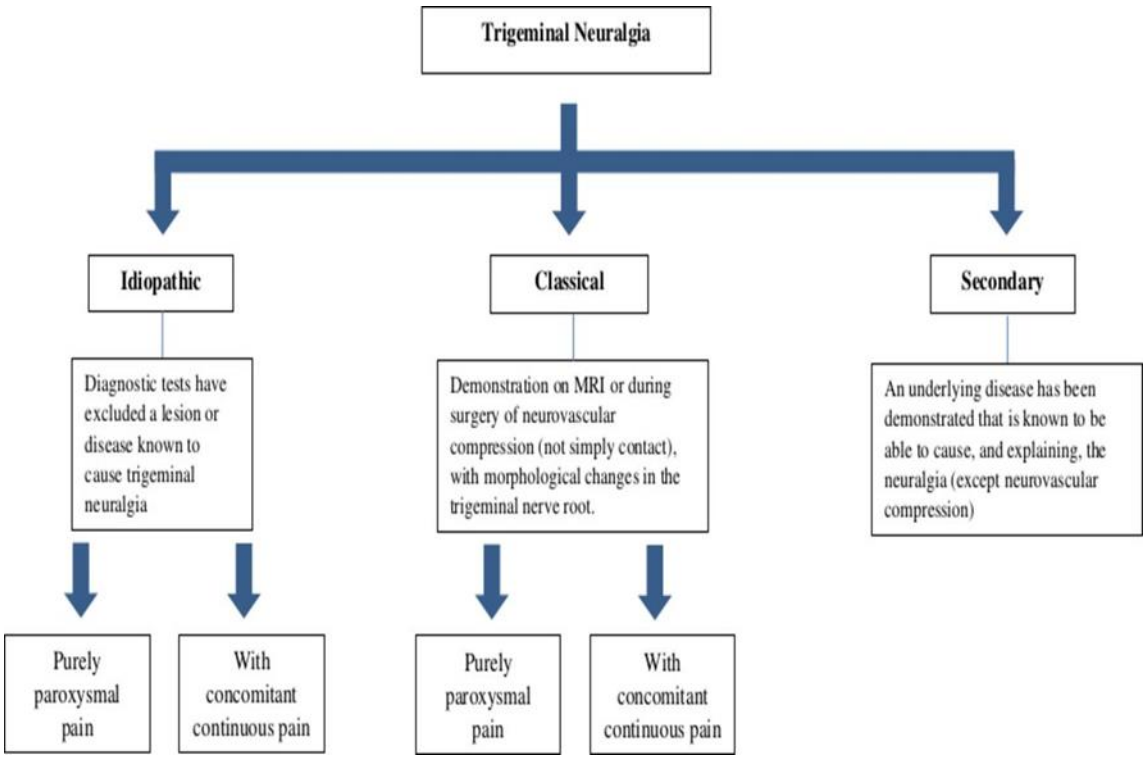


Figure 1.1

International Classification of Headache Disorders Edition 3 subclassification of trigeminal neuralgia (Lambru , et,al., 2021).

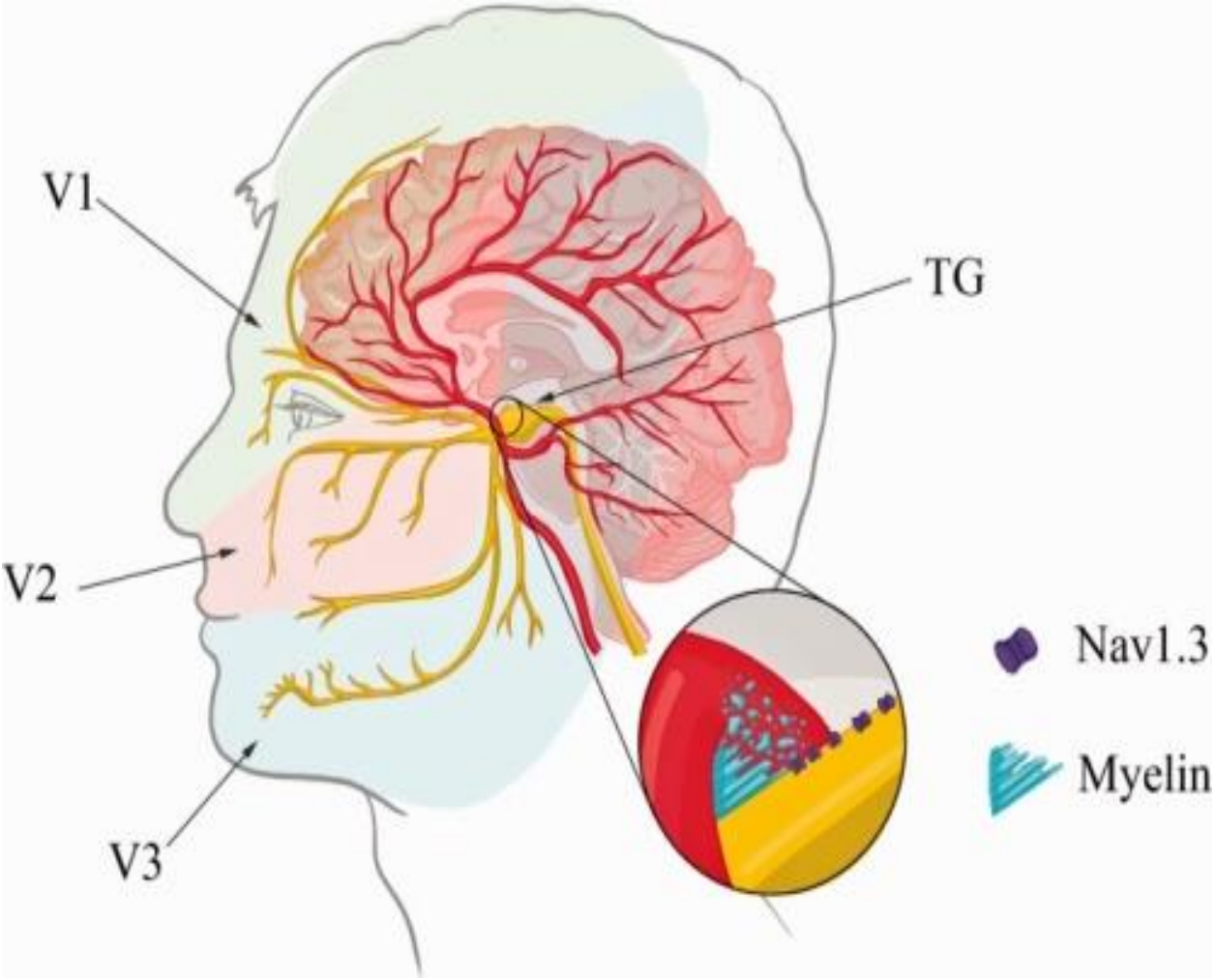


Figure 2.2

Representation of the trigeminal system and classical trigeminal neuralgia etiology. The area of innervation for the ophthalmic (V1), maxillary (V2), and mandibular (V3) branches is indicated. Neurovascular compression by the superior cerebellar arteries observed at the root entry zone of the trigeminal nerve (Gambeta et al ., 2020).

2.3 Trigeminal Neuralgia Etiology and Pathogenesis

Approximately 10% of TN cases are symptomatic and have detectable underlying pathology, such as a tumor of the cerebellopontine angle, a demyelinating plaque of multiple sclerosis, or a vascular malformation. The most common tumor associated with TN is a meningioma of the posterior cranial fossa.The most widely accepted theory is that a majority of cases of classic TN are caused by an atherosclerotic blood vessel (usually the superior cerebellar artery) pressing on and grooving the root of the trigeminal nerve. This pressure results in focal demyelinization and hyperexcitability of nerve fibers, which will then fire in response to light touch, resulting in brief episodes of intense pain **(Nurmikko and Eldridge, 2001**). Evidence for this theory includes the observation that neurosurgical decompression of the nerve root from the vessel eliminates the pain in a majority of cases **(Zakrzewska and Coakham, 2012**).

Additional evidence for this theory was obtained from a study using tomographic magnetic resonance imaging, which showed that contact between a blood vessel and the trigeminal nerve root was significantly more frequent on the affected side.

Evidence against this theory explaining all cases of classic TN includes the observation by neurosurgeons that vascular compression is not always detected and manipulation of the area of the nerve root may eliminate the painful episodes even when an atherosclerotic vessel is not pressing on the nerve root. Neurovascular compression (NVC) is not identifiable in a significant number of CTN patients. For example, in a series of 219 patients with paroxysmal TN, 28.3% had no imaging evidence of NVC **(Lee et al., 2014).**

And up to 17% of patients undergoing surgery for TN had no NVC **(Ishikawa ,2002, Sindou,2002).** Moreover, NVC is prevalent both on the symptomatic and asymptomatic side (89%versus 78%) in TN patients, but severe NVC is more prevalent on the symptomatic side (53% versus 13%).Furthermore, 17% of age-matched TN-free controls have imaging evidence of NVC. Moreover, 14% of cadavers with no history of CTN demonstrate vascular contacts, although these had minimal grooving. Classifying CTN and ITN separately allows further study of these groups **(Antonini et al., 2014).**

TN patients with no NVC are typically younger and three times more likely to be female **(Ko AL et al., 2015).**Supporting the clinical value of the new classification. Observing neurovascular contact of itself, therefore, has low predictive value in establishing a diagnosis of CTN.

The presence of anatomical changes associated with the neurovascular contact increases specificity and positive predictive value. Although NVC clearly plays a role in individual patients, at a population level, the high prevalence of NVC and the rarity of CTN suggest that a finding of NVC in CTN may often be insignificant. Current evidence postulates that TN is a far more complex disease (or cluster of diseases) than previously appreciated **(Antonini et al., 2014).**

The pathophysiology of TN seems complex. Around 2% of all TN cases may be familial, and family clusters of TN indicate that it may have a genetic origin **(Fernandez et al., 2017).**

Some of the suggested causes include: inherited anatomical changes affecting the base of the skull, which would promote compression of the trigeminal nerve by vascular structures; mutations in the gene encoding calcium channels resulting in hyperexcitability; as well as mutations in the serotonin transporter gene (5-HTTLPR**) (Cui W et al.,2014).**

Therefore, certain individuals may be prone to develop pain following neurovascular compression while others may be resistant, as in traumatic neuropathies.

2.4 Epidemiology of Trigeminal Neuralgia

The lifetime prevalence of TN is estimated to be 0.16%–0.3% **(Sjaastad ,2007, Mueller, 2011)**. While the annual incidence is 4–29 per 100 000 person-years. It is more prevalent in women than in men (F:M ratio 3:2). The incidence increases with age, with a mean age of onset of 53–57 years and range of 24–93 years in adult series Furthermore, a recent paediatric headache clinic of 1040 identified five children in the age range 9.5–16.5 years with TN **(Brameli et al., 2021).**

2.5 Clinical features of Trigeminal Neuralgia

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 figure (3.3) 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 **(Bennetto et al ., 2007).**

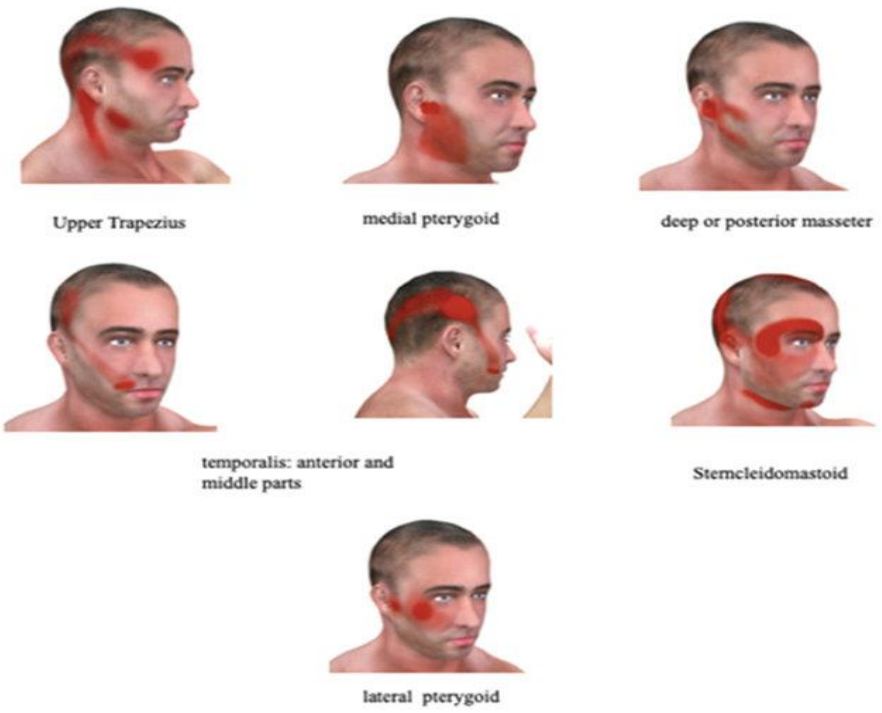


Figure 3.3

The referred pain patterns of relevant neck and head muscles that refer pain to the face in the trigeminal nerve distribution **(Gerwin , 2020).**

2.5.1. Laterality and site of pain

The right side of the face (60%) is affected more than the left side. Bilateral simultaneous pain in TN is rare (1.7%–5%) and more often these patients experience side-alternating unilateral pain paroxysms. In view

of its rarity, bilateral simultaneous or side-alternating trigeminal paroxysmal pains should raise concern about an underlying neurological disorder or

a non-neurological disorder affecting the cranium. It therefore warrants careful exclusion of secondary pathology. If investigations are normal, then idiopathic cases of constant or long-lasting bilateral trigeminal pain include: temporomandibular joints dysfunction, persistent idiopathic facial pain and rarely migraine with facial pain **(Maarbjerg ,2015).**

In cases with paroxysmal short-lasting pain episodes, trigeminal autonomic cephalalgias such as short-lasting unilateral neuralgiform headache attacks (SUNHA) should be considered if pain is associated with cranial autonomic symptoms or idiopathic stabbing headache if the pain is predominantly in the ophthalmic (V1) trigeminal distribution.The pain of TN most frequently affects the distribution of the maxillary (V2) and mandibular (V3) divisions of the trigeminal nerve, though approximately a quarter of the cases have ophthalmic (V1) division involvement **(Maarbjerg ,2015).**

2.5.2. Frequency and duration of attacks

The frequency and duration of TN attacks are highly variable. While the pain usually lasts from less than a second up to 2 min in the majority (74%), a significant minority reports attacks lasting 2–10 min **(Haviv et al.,2016).** Furthermore, up to 70% of patients occasionally have series of paroxysms lasting up to 1 hour, which can cause diagnostic confusion.In patients with long-lasting attacks (>2 min) but with a phenotype otherwise consistent with TN, it is imperative to rule out other neuralgiform disorders. The number of attacks is highly variable even in the same patients and ranges from a few attacks to several hundred attacks daily; approximately 40% of patients report more than 10 attacks daily **(De Toledo et al.,2016).** Obtaining a good descriptive history of frequency and duration of attacks in

short-lasting trigeminal neuralgiform pain conditions is often challenging. Using pain diagrams may help to clarify our definition of a single paroxysm as opposed to a group of paroxysms.

TN follows a relapsing–remitting pattern in approximately two-thirds of patients but has a chronic pattern in the remaining one-third. Both the frequency and duration of the remission periods vary greatly, with the remission periods lasting months (37%) or years (63%)

(De Toledo et al.,2016).

2.5.3. Triggers and trigger zones

One of the hallmark clinical features of TN is the trigger ability of the attacks by innocuous mechanical stimulation of the face and intraoral mucosa ipsilateral to the side of the pain. Around 91%–99% of patients report triggered attacks and these are often considered to be pathognomonic of TN (Patients usually report a mixture of triggered and spontaneous attacks **(Cruccu,2017).** With 68%–98% of cases having spontaneous attacks
A complete lack of triggerable attacks should prompt careful assessment to exclude an alternative diagnosis including a trigeminal autonomic cephalalgia or craniofacial pathology.

Light tactile stimulation is the most potent trigger and, conversely, painful and thermal stimulation seems ineffective at eliciting pain in TN.

Common triggers include light touch, talking, chewing, brushing teeth, washing or drying, drinking and shaving. Most patients have several trigger factors. The location of the pain does not always concord with the site of trigger zone **(Di Stefano et al., 2018).**

The most common trigger zones include the nasolabial fold, upper lip, lateral part of the lower lip, chin, cheek and the alveolar gingiva (figure 5.5)

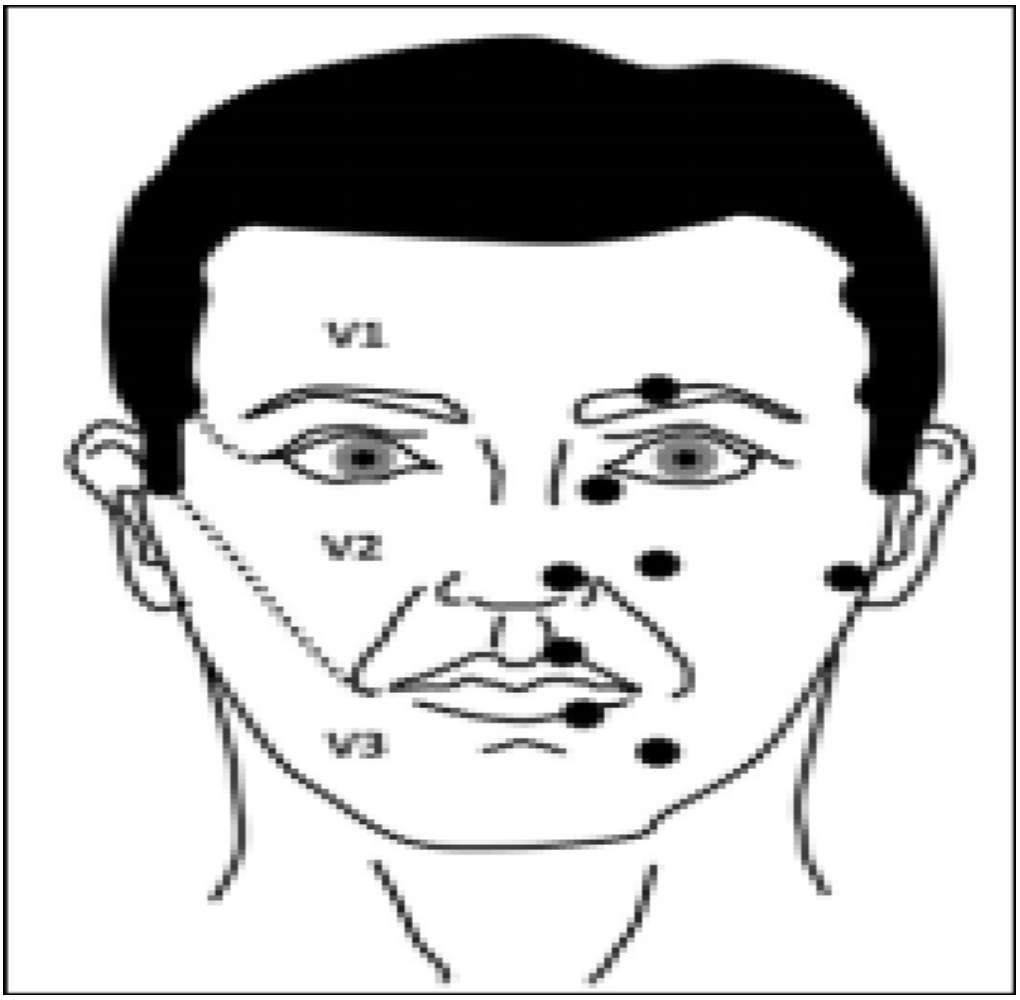


Figure 4.4 Represent Trigeminal Nerve Distribution and Trigger Points

(Bhaduri et al., 2011).

2.5.4. Refractory period

In most people with TN, a triggered attack is normally followed by a period of seconds or minutes during which further attacks cannot be provoked, a phenomenon called refractory period. This contrasts with the trigeminal

autonomic cephalalgia, SUNHA, in which there is mostly no refractory period after exposure to a trigger **(Lambru,2019).**

2.6. Trigeminal Neuralgia diagnosis and differential diagnosis

The diagnosis of TN is based on the history of shooting, electric shock-like pain along a branch of the trigeminal nerve, the presence of trigger zones and refractory periods **(Goh BT et al.,2001)**. A routine cranial nerve examination will be normal in patients with idiopathic TN, but sensory and/or motor changes may be evident in patients with underlying tumors or other CNS pathology. A clinical examination alone may be insufficient to distinguish symptomatic from classic TN; in some cases, electrophysiological testing of trigeminal reflexes is more accurate. Local anesthetic nerve blocks, which temporarily eliminate the trigger zone, and painful episodes are also good diagnostic tools. Since approximately 10% of TN cases are caused by detectable underlying pathology, enhanced MRI of the brain is indicated to rule out tumors, multiple sclerosis, and vascular malformations . Magnetic resonance angiography may also be needed to detect difficult to visualize vascular abnormalities **(Goh BT et al.,2001).**

The International Classification of Headache Disorders third edition (ICHD-3) criteria for TN :

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 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 (HIS ,2018). 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 quantitative sensory test (QST) in classical TN patients have documented sensory abnormalities **(Maier, 2010, Ichida, 2015).**

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 **(Kumar et al., 2013).**

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 **(Van Kleef , 2009).**

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 **(Krafft , 2008).**

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 (Lambru G ,2014) .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 **(Paliwal et al.,2015**). In addition, a case of TN and SUNCT coexistence has been reported in a patient afflicted by a hemorrhagic infarct of the dorsolateral medulla. This observation is in agreement with early studies that pointed to a relationship between TN development and brainstem infarct. 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 **(Warren et al.,2009).**

2.7 Trigeminal Neuralgia Treatment

Initial therapy for TN should consist of trials of drugs that are effective in eliminating the painful attacks. Anticonvulsant drugs are most frequently used and are most effective.The mainstay of management is pharmacological preventive treatments. However, acute treatments that work rapidly have to be used occasionally for severe exacerbation. Surgical interventions are reserved for patients who fail to respond to or adequately tolerate medical therapies **(Cruccu et al., 2020).**

2.7.1. Pharmacological preventive treatments :

The arsenal of preventive treatments for TN has now been in use for several decades but the quality of the evidence base is poor and there are few high-quality randomised controlled trials. Though these treatments are not supported by good quality randomised controlled trials, the clinical experience with some of these drugs (particularly carbamazepine, oxcarbazepine, lamotrigine, gabapentin, pregabalin, baclofen and botulinum toxin type A) is good, resulting in meaningful pain control although with still a substantial unmet need for more effective and better tolerated drugs

(O'Callaghan et al.,2020).

2.7.1a. Carbamazepine and oxcarbazepine

Carbamazepine and oxcarbazepine are the first-line treatment options for TN and offer meaningful initial pain control in almost 90% of patients, although this may not be sustained in the long term. The benefit of these drugs is offset by adverse effects, which lead to withdrawal in up to 40% of patients **(O'Callaghan et al.,2020).** Carbamazepine is known for its metabolic interaction with other medications, which can be problematic

in elderly people with comorbidities. Oxcarbazepine causes fewer side effects and has lower potential for drug interactions than carbamazepine, though it is more likely to cause excessive central nervous system depression or dose-related hyponatraemia. The tolerability of both these drugs is gender related; women are significantly less tolerant.

The individual response to both drugs varies considerably, hence if one is not effective, then the other one can be tried. If changing over from carbamazepine to oxcarbazepine, then 200 mg of carbamazepine is equipotent to 300 mg of oxcarbazepine. It is important to be aware that the modified-release (retard) version of carbamazepine available is best used when patients have stabilised. Liquid versions of both drugs are useful when patients find it hard to swallow due to pain severity **(Araya et al.,2020).**

Contraindications to using these agents include cardiac conduction problems and allergic reactions. There is a high degree of cross-reactivity between the aromatic antiseizure medications (carbamazepine, oxcarbazepine, phenytoin, phenobarbital).

Carbamazepine and oxcarbazepine do not generally require regular monitoring of serum drug concentrations; in most patients, the drug doses can be titrated or tapered by clinically considering the balance between the efficacy and adverse effects. However, we advocate regular monitoring of renal, calcium and liver function tests. Patients may develop hyponatraemia and a cholestatic picture on liver function testing which, while not usually of clinical concern, need careful monitoring to ensure that they do not progressively worsen. Older women are already at increased risk of osteoporosis and this needs to be monitored in long-term use (Araya et al.,2020).

2.7.1b.Lamotrigine

Lamotrigine has been reported to be helpful as an add-on therapy in a small randomised cross-over trial **(Mockenhaupt et al., 2005).** Lamotrigine can be used in patients who cannot tolerate carbamazepine and oxcarbazepine, or as add-on therapy to increase efficacy. It is generally associated with fewer side effects than carbamazepine and oxcarbazepine. The dose of lamotrigine should be escalated slowly as the incidence of lamotrigine-induced rash is well recognised to be dose and titration dependent. About 10% of people taking lamotrigine develop benign adverse cutaneous reactions. However life-threatening conditions, like Stevens-Johnson syndrome, can rarely occur. Since the introduction of a slow-dose titration protocol, the rate of severe rashes has reduced to 0.1%–0.01% In view of the need for this slow-dose titration, lamotrigine is not appropriate for managing severe TN exacerbation to those who need rapid pain control

(Mockenhaupt et al.,2005).

2.7.1c. Gabapentin and pregabalin

There are 16 randomised controlled trials for gabapentin, all published in Chinese, comparing it with carbamazepine. However, it is difficult to draw any meaningful conclusions as the inclusion criteria, endpoints and dosage are either not clarified or very varied. There are no such trials for pregabalin, but a long-term study suggests that it may be effective **(Obermann et al.,2005).**

Clinical experience shows that gabapentin and pregabalin are less effective but have fewer side effects than carbamazepine and oxcarbazepine.

They can therefore be used in place of or in addition to carbamazepine or oxcarbazepine

2.7.1d.Baclofen

Baclofen can help in TN especially in people with multiple sclerosis who may be using the drug for spasticity.

2.7.1e.Botulinum toxin type A

Recent randomised controlled trials of botulinum toxin type A have provided evidence for efficacy in TN. The botulinum toxin type A was injected subcutaneously and occasionally over the gingival mucosa. The dose varies among trials between 25 and 100 units applied following the pain distribution, 1 cm apart, often for a total of 10–20 injection points. Most trial outcomes were evaluated at 3 months **(Lambru et al.,2020).** All trials showed consistent significant superiority of botulinum toxin type A compared with placebo. Responders to botulinum toxin type A ranged between 68% and 86% compared with 15%–32% of placebo. Adverse effects were mild to moderate and included transient facial weakness and transient facial oedema. Overall, these studies point towards a clear efficacy of botulinum toxin type A in TN **(Lambru et al., 2020).**

2.7.1f.Other treatments

Other drugs reported in small open-labelled studies include phenytoin, tizanidine, levetiracetam, misoprostol (especially in patients with multiple sclerosis), topiramate, pimozide, duloxetine and eslicarbazepine. A novel sodium channel blocker, vixotrigine, has been tested in one randomised

controlled trial and phase three trials are due to start shortly **(Lambru et al., 2020).**

2.7.2. Acute treatment for severe exacerbation

Severe exacerbation during which there is a marked increase in the frequency and intensity of pain, resulting in an inability to eat or drink and may require admission to hospital for rehydration, maintenance of nutrition, short-term pain management and long-term optimisation of preventive treatments. Though opioids are frequently used, they are generally ineffective and should be avoided. Topical lidocaine or local anaesthetic injections into the trigger zones can provide transient relief. Intravenous infusions of fosphenytoin (15 mg/kg over 30 min) and lidocaine (5 mg/kg over 60 min) under cardiac monitoring can be highly effective but should be administered by specialised teams with expertise in their use and in the setting of a high dependency unit **(Moore et al., 2019).**

2.7.3. Surgical treatments

Surgical treatments are generally reserved for patients with debilitating pain refractory to pharmacological treatments. There are three types of surgical intervention available:

(1) invasive, non-ablative (microvascular decompression),

(2) invasive, ablative (controlled lesioning of the trigeminal ganglion or root by mechanical (balloon compression), thermal (radiofrequency

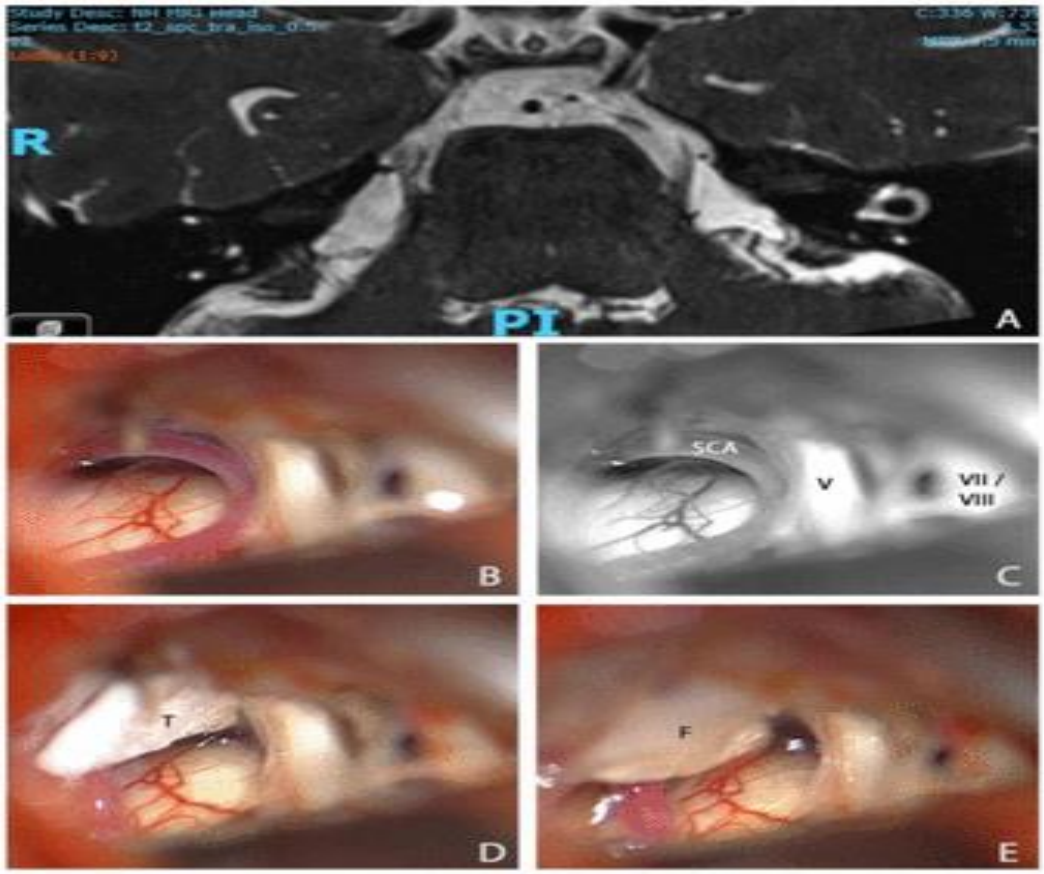
thermocoagulation) or chemical means (glycerol rhizolysis), separation of trigeminal nerve fascicles in the posterior fossa (internal neurolysis)) and

(3) non-invasive ablative (stereotactic radiosurgery which focuses radiation at the trigeminal root entry zone).

Microvascular decompression is the surgery of first choice in classical TN (see figure 5.5). Data in over 5000 patients showed a pain-free rate of 62%–89% after 3–10 years of follow-up **(Bendtsen et al., 2019).**

The annual risk of recurrence is less than 2% 5 years after the operation and less than 1% after 10 years. TN with concomitant continuous pain has poorer outcome, with pain freedom rates dropping to 23.5%–51% at 5 years of follow-up, although that is not a consistent finding. While previous studies of microvascular decompression did not distinguish effectively between classical and idiopathic TN, the emerging evidence unsurprisingly suggests that it is more effective in classical than idiopathic TN **(Lambru et al.,2020).**

The data on decompression in TN secondary to multiple sclerosis are conflicting. The responder rates in the published series varied between 39% and 100% with follow-up periods of 12–65 months. The general advice in these patients would be to consider microvascular decompression if the MR scan shows morphological changes and in absence of a plaque in the pons, given that very recent evidence suggested that a brainstem lesion related to the TN on MR is a negative prognostic factor for microvascular decompression **(Montano et al., 2020).**Trigeminal microvascular decompression is a major procedure that can be carried out successfully in the elderly provided they have no significant comorbidities, but results are poorer in those younger than 25 years. Severe complications are rare but there is small risk of mortality (0.3%).



(Figure 5) MR scan of the trigeminal nerve and intraoperative pictures during microvascular decompression in patient with classical trigeminal neuralgia. (Lambru , et,al., 2021).

When there is no evidence of trigeminal neurovascular contact or there are significant comorbidities, ablative procedures are the preferred choice. The least invasive procedure is stereotactic radiosurgery. However, pain relief can be delayed by up to 6 months and sensory loss occurs frequently. Emerging evidence suggests that trigeminal internal neurolysis is highly effective in the long term but has a high complication rate (facial hypoaesthesia 96%, anaesthesia dolorosa 3.9%). The percutaneous neuroablative procedures (radiofrequency thermocoagulation, balloon compression, glycerol rhizolysis) provide on average 3–4 years of pain relief and repetitive ablative procedures are commonly required. Complication rates are high, especially with repetitive

procedures. There is no evidence for preference of one procedure over another **(Lambru et al., 2020).**

There is no clear guidance on the number of medical treatments that a patient has to fail before surgical approaches should be offered. It is important to make patients aware of the management options available, including both the medical and surgical approaches, early in the treatment pathway.

In patients with classical TN, consider microvascular decompression when patients report a poor quality of life and there is either failure to respond or significant adverse effects with up to three groups of drugs. Carbamazepine and/or oxcarbazepine followed by lamotrigine and a gabapentinoid (gabapentin or pregabalin) can be tried. These can be used in combination. If these patients fail to respond to microvascular decompression **(Lambru et al., 2020).** Then offer trials of other drugs not tried until then before considering neuroablative procedures. In both idiopathic and secondary TN (without evidence of neurovascular conflict), tend to try more pharmacological treatments before considering neuroablative procedures, mainly because of the risk of long-term complications particularly with repetitive percutaneous neuroablative procedures. Patients who develop superimposed severe trigeminal neuropathy secondary to the neuroablative procedures can be very challenging to manage in the long term **(Lambru et al., 2020).**

3. Conclusions

► Recent advances in TN have led to an improvement in its classification on the basis of the neuroimaging findings. Better understanding and description of other neuralgiform disorders such as SUNCT and SUNA have made the differential diagnosis clearer.

► Trigeminal neuralgia is currently classified into three subgroups: idiopathic, classical and secondary, based on imaging findings; MR brain imaging with trigeminal sequences is therefore essential in the diagnostic work-up.

► An accurate diagnosis is crucial because the clinical management differs among the various forms of facial pain.

► Carbamazepine and oxcarbazepine remain the medications of choice; lamotrigine, gabapentin, pregabalin, botulinum toxin type A and baclofen can be used as second-line treatments in monotherapy or polytherapy.

► In pharmaco-resistant cases, trigeminal microvascular decompression is the first-line surgery in patients with classical trigeminal neuralgia, whereas neuroablative surgical treatments and microvascular decompression can be considered in idiopathic trigeminal neuralgia

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