Clinical aspects of Trigeminal Neuralgia: A systematic Review

[1]Pratik U. Parikh, [2]Shivkumar R. Yadav, [3]Tanmay H. Tajane, [4]Ravi S. Khandare

[1, 2, 4]Student, Department of Pharmaceutical biotechnology, Sanjivani College of Pharmaceutical Education and Research, Shingnapur, Kopargaon, Tal. Kopargaon, Dist. Ahmednagar, Maharashtra (423603)
[3]Student, Department of Quality Assurance, MVP samaj's college of pharmacy, Nashik, Tal. & Dist. Nashik, Maharashtra (422002)

***Abstract*: The fifth cranial nerve, the Trigeminal nerve, is amongst the most widely distributed nerves in the human body. Trigeminal neuralgia (TN) is characterized by recurring occurrences of unilateral, intense, lancinating, stabbing discomfort in the distribution of one or more branches of the trigeminal nerve. When compared to men, women are more likely to develop Trigeminal Neuralgia. The trigeminal nerve is compressed and demyelinated, which causes Trigeminal Neuralgia. Diagnostic tests for Trigeminal Neuralgia include physical examinations, neuroimaging techniques, and neurophysiological studies. Initially, the patient was given a low daily intake of anti-epileptic drugs, with carbamazepine being the first-line treatment for Trigeminal Neuralgia. Surgery is a realistic and successful alternative if medical therapy has failed. Microvascular decompression, gamma knife radio surgery, percutaneous treatments at the Gasserian ganglion level and peripheral approaches are some of the surgical procedures used. The clinical symptoms, aetiology, diagnostic testing, and treatment for TN are all detailed in this review.**

***Keywords*: Trigeminal neuralgia, Gasserian ganglion, anti-epileptic drugs, Microvascular decompression**

Introduction

Tic douloureux is also a term as trigeminal neuralgia (TN). One of the most widely distributed nerves in the skull is the trigeminal nerve, often known as the 5th cranial nerve. It is made up of three enormous branches, as the name suggests. The ocular (V1, sensory), maxillary (V2, sensory), and mandibular (V3, motor and sensory) branches are the three branches. The V2 and V3 branches of the trigeminal nerve are the most commonly affected. Neuralgia is a stabbing, searing, and frequently severe pain caused by nerve compression or demyelination. Trigeminal neuralgia is defined as repeated bouts of pain that are unilateral, intense, short, electric-shock like, lancinating, stabbing, and occur within the distribution of one or more trigeminal neuralgia branches.[1] TN is most usually unilateral, however it can also be bilateral in 5% of cases. Secondary reasons such as multiple sclerosis are suspected when it develops at a young age or manifests with bilateral indications or an uncommon neurological examination, lack of provoked pain, and absence of a refractory period.

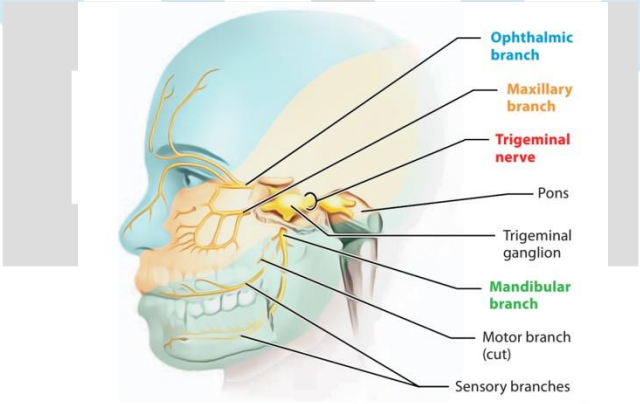

Fig. 1. Diagrammatic Presentation of Trigeminal nerve [2]

Prevalence:

The prevalence of TN is 0.015 percent among the overall population. The annual incidence of TN has been consistent, ranging from 12.6 per 100,000 to 27 per 100,000. Women are more likely to have TN [3]. According to the National Institute of Neurological Disorders and Stroke, 12 persons per 100,000 individuals are affected each year.

Classification:

TN is classified into two categories. 1. Traditional TN (CTN) 2. TN with symptoms (STN)

CTN is caused by the trigeminal nerve being compressed by a blood vessel. Multiple sclerosis (MS), space-occupying lesions, and neuropathy have been the most leading triggers of STN. The table shows the differences across CTN and STN.

Sr. No.	Features	CTN	STN
01	Sensory loss	Absence of sensory loss	Presence of sensory loss
02	Cause	Neurovascular compression	Vestibular schwannoma, multiple sclerosis, meningioma
03	Associated symptoms	There are no significant symptoms linked with 7th and 8th nerve palsy.	7th and 8th nerve palsy might cause significant symptoms.
04	Pain	During paroxysms, the patient is pain-free.	A persistent ache in the intervals between paroxysms

Table 1. Difference across CTN and STN

CTN is an idiopathic episodic pain that lasts a few seconds and has no sensory loss or interictal numbness, as well as no major accompanying symptoms with 7th and 8th nerve palsy. STN is caused by underlying pathology and is characterised by chronic pain between paroxysms, sensory loss, and interictal numbness on pathological evaluation [4].

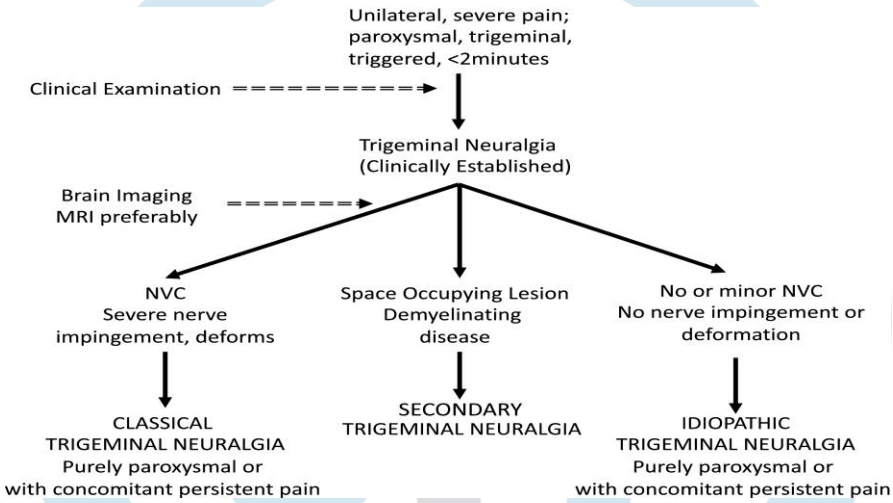

Fig. 2. Diagrammatic Presentation of classification of Trigeminal nerve

Clinical Features:

Shooting, stabbing, acute, electric shock-like pain are the most common clinical characteristics of TN. Light touch causes pain; it could be caused by intraoral or extra-oral stimuli [5]. The following are major triggering factors:

- Facial cleansing
- Teeth brushing
- Shaving
- Vibrations from walking when applying makeup
- Hair on the cheeks that is falling off
- Because of the cold breeze

Patients express briefly the sharpness of the pain, as well as its quickness and severity, when they first experience TN pain [6]. From patient narratives, the following are some descriptions of pain in Tennessee:

- A ache that feels like an electric jolt
- Sparks are flying off the live wire,
- Shooting jolts of energy directly into the raw materials.

The pain associated with the TN illness is chronic and debilitating, reducing one's quality of life.

Etiology:

The following are the three most radical theories about TN aetiology:

1. Disease-related: vascular disorders, diabetes, multiple sclerosis, and other conditions.
2. Direct injury to the trigeminal nerve
   - Schwannomas, tuberculomas, neurovascular compression, aneurysms, and meningiomas affect the central section of the trigeminal nerve system.
   - The peripheral section of the trigeminal nerve system: the "allergic theory" related to odontogenic inflammatory pathology, getting chilly, and the "compression syndrome hypothesis" due to osseous canal constriction.
3. Polyetiologic origin: other such aetiological factors affecting the trigeminal nerve system [7].

Pathophysiology:
Due to the availability of multiple etiologic variables, the pharmacotherapy of TN is extremely complex. Neuralgia is caused by nerve compression, which causes focal demyelination of the nerve, resulting in ectopic production of spontaneous nerve impulses and pain episodes. Painful stimuli activated the primary and secondary somatosensory cortices, thalamus, anterior cingulate cortex, hippocampus, premotor/motor cortex prefrontal areas, spinal trigeminal nucleus, putamen, and insula in TN patients, while non-painful stimulation of the trigger zone activated all except for three of these structures (brain stem, spinal trigeminal nucleus, anterior cingulated cortex) [8, 9].

Diagnosis:
The patient's historical record is the most important tool for diagnosing CTN. Neuroimaging approaches have been used to diagnose STN [3, 10].
Neuroimaging and neurophysiological studies are utilized to determine the origin of STN and to distinguish symptomatic from typical TN in patients with STN.

Neuroimaging techniques:
Neuroimaging techniques, such as MRI and MRA (magnetic resonance angiography), have been used to diagnose the problem of TN and rule out other probable reasons of face discomfort. Trigeminal neuralgia vascular compression is identified and determined using MRIs. These procedures aid a clinician in locating the neurovascular loop's location and identifying any secondary causes. Changes in brain activity linked with stimulation of the cutaneous trigger zone can be identified with functional MRI in patients with Trigeminal neuralgia.

Neurophysiology tests:
Neurophysiology tests are helpful in detecting lesions by recording abnormal trigeminal nerve evoked potentials, abnormal trigeminal reflexes, and trigeminal sensory impairments, as well as bilateral involvement [11,12].

Treatments:
The treatment of TN varies from patient to patient, depending on the patient's age and general health.
The following are TN treatments:

1. Medical supervision
- Treatment for epilepsy using anti-epileptic drugs
- Non anti-epileptic medication therapy

2. Surgical intervention
- Techniques used in the peripheral
- At the level of the gasserain ganglion, a percutaneous procedure is performed.
- Surgery using a gamma knife
- Decompression of the microvessels

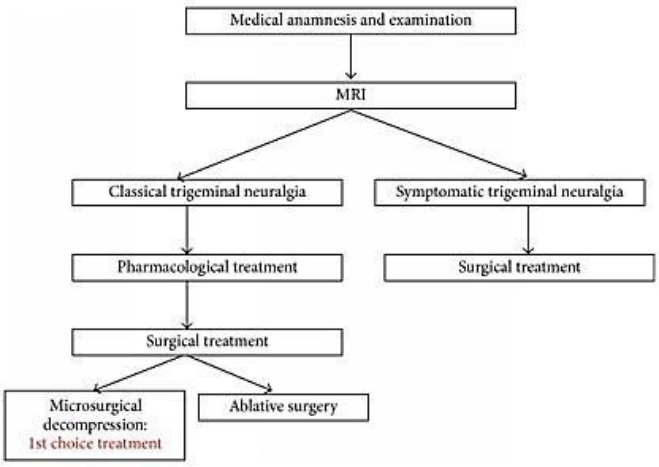

Fig. 3. Diagnostic and therapeutic management of patients suffering from Trigeminal neuralgia [12]

1. Medical Supervision:
The drugs used to treat TN work by acting on voltage sodium channels and GABA receptors. Antiepileptic (AED) medicines are effective in treating TN. The gold standard medicine for TN is carbamazepine (CBZ), which has been approved by the Food and Drug

Administration (FDA). Gabapentin, Oxcarbazepine (OXC), Lamotrigine, Phenytoin, and non-epileptic medicines like Botulinum toxin A and Baclofen are some of the other AEDs used to treat TN [13, 14, 15, 16].
Detail regarding medications is explained in the table. (Table 2 & Table 3)

Sr. No.	Drug	Mechanism of Action	Dosage range	Side effects
01	Lamotrigine	Stabilizes presynaptic neuronal membranes and inhibits glutamate release by binding sodium channels selectively.	200 – 400 mg (daily)	If the dose is increased rapidly, rashes are common.
02	Carbamazepine	Sodium channel blockers, such as carbamazepine, are used to treat seizures. It binds to voltage-gated sodium channels in their inactive state, which prevents action potential firing from being repeated and sustained.	300 – 1000 mg (daily)	Ataxia, dose-related effects, sedation
03	Gabapentin	Gabapentin inhibits calcium entrance into neurons via binding to N-type calcium channels.	900 – 2000 mg (daily)	Ataxia, sedation
04	Oxcarbazepine	Oxcarbazepine works by blocking voltage-sensitive sodium channels, causing hyper-excited neural membranes to stabilize, and repeated neuronal firing to be suppressed and synaptic impulse propagation to be reduced.	300 – 1200 mg (daily)	hypovolemic hyponatremia

Table 2. Pharmacology of anti - epileptic drugs

Sr. No.	Drug	Mechanism of Action	Dosage range	Side effects
01	Botulinum toxin A (BTA)	The neurotransmitter Ach, as well as other neurotransmitters, is inhibited by BTX-A. The release of these neurotransmitters from nociceptive nerve terminals can be inhibited, resulting in pain alleviation.	0.5 mg human albumin + 0.9 mg sodium chloride in 2 mL saline solution	Blurred vision, dry mouth
02	Baclofen	Baclofen is a GABA analogue that activates $GABA_B$ receptors and hence inhibits excitatory neurotransmission.	50 – 80 mg (daily)	Drowsiness, motor incoordination, behavior effects

Table 3. Pharmacology of non anti - epileptic drugs

2. Surgical intervention:

There is just one treatment for relieving trigeminal nerve compression. There has been microvascular decompression. Other surgical treatments, on the other hand, try to decrease sensory input.
The surgical procedures are focused on three key areas:

- Peripheral At some trigger points, a Gasserian ganglion appears.
- Level of the Gasserian ganglion
- The root interior zone's posterior fossa

Microvascular decompression (MVD):

It is a partially invasive and non-destructive surgery for TN. This surgical technique is advised for people who are younger and have a longer life expectancy. In MVD, a post-auricular craniotomy is performed to identify the vessel compressing the trigeminal nerve, which is then relocated out of direct contact with the nerve [17, 18].

Gamma knife radiosurgery:

Radiosurgery using a gamma knife is an adjuvant treatment. Radiation is utilized in this therapy to inhibit the transmission of excessive sensory information that causes pain episodes [19]. The pain alleviation lasts for three years. This method is the most acceptable because it is the least painful and has no negative consequences [20]. Pain alleviation took a few months following the treatment as well. In normal neuralgia with specific nerve distribution pain, a better outcome occurs.

Percutaneous procedures at the level of Gasserian Ganglion:
Under general anesthesia, a cannula is inserted into the foramen ovale of the trigeminal ganglion, and the ganglion is subsequently lesioned using heat, mechanical compression, or glycerol injection with a balloon. After glycerol injection, pain alleviation lasts for 5 years [21, 22].

Peripheral techniques:
Neurectomies, peripheral acupuncture, radiofrequency thermocoagulations, cryotherapy, and a range of injections such as alcohol, phenol, and streptomycin are all used to repair peripheral nerves. The pain alleviation lasts for ten months [1, 21].

Conclusion:
TN is a rare disease, but the terrible and debilitating pain it causes can have a significant influence on a patient's quality of life. Medical treatment for TN is ineffective due to a lack of understanding of the exact pathophysiology. Different neurological disorders can have symptoms that are similar to it, thus a diagnosis is necessary before starting treatment. The FDA has approved CBZ as the only treatment option for TN. When a patient's medical treatment isn't working, surgical operations are performed.

References:
[1]. Joanna M Zatrzewska, Roddy Mc Millan, Trigeminal neuralgia: the diagnosis and management of this excruciating and poorly understood facial pain;2011,87: 410-416
[2]. Rudolph M. Krafft, MD-trigeminal neuralgia,2008,77(9):1125-32
[3]. Nicola Montano et.al, advances in the diagnosis and treatment of trigeminal neuralgia,2015:11(289-299)
[4]. Majeed MH, Arroj S, Khokhar M, et,al(December 18,2019) Trigeminal neuralgia:A clinical review for the general physician, cureus 10(12):3750 doi: 10.7759/cureus.3750
[5]. Limonadi FM , McCartney S, Burchiel KJ: design of an artificial neural network for diagnosis of facial pain syndromes
[6]. Zatrzewska JM, Patsalos PM, long-term cohort study comparing medical (Oxcarbazepine) and surgical management of intractable neuralgia pain 2002,95:259-66
[7]. Gintautus Sabalys, Gintaras Juodzbalys, and Hom-Lay Wang: Aetiology and pathogenesis of trigeminal neuralgia: A comprehensive review 2103,jan pmid:24422020
[8]. Love .S,Coakham HB: trigeminal neuralgia pathology and pathogenesis: Brian 2001,124:2347-2360
[9]. Svensson E.: Pain mechanisms in myogenous temporo-mandibular disorders, pain forum 1997; 6:158-165
[10]. Luke Bennetto, Nikunj K Patel, Geraint fuller, trigeminal neuralgia and its management: jan 2007, vol:334(201-205)
[11]. Headache classification of the international headache society(HIS): the international classification of the headache disorders ,3rd edition(beta version).cephalagia 2013,33:629-808
[12] Pihut, M., Szuta, M., Ferendiuk, E., & Zeńczak-Więckiewicz, D. (2014). Differential Diagnostics of Pain in the Course of Trigeminal Neuralgia and Temporomandibular Joint Dysfunction. BioMed Research International, 2014, 1–7. doi:10.1155/2014/563786
[13]. Cruccu G, Gronseth G, Alkne.J, et.al, AANEFNS guidelines on trigeminal neuralgia management. Eur J neurol 2008;15:1013-28
[14]. Gronseth G, Cruccu G, Alksne J et.al: practice parameter; the diagnosis evaluation and treatment of trigeminal neuralgia(an evidence –based review): report of the quality standards subcommittee of the American academy of neurology and European federation of neurological societies: neurology 2008,71:1183-90
[15]. Ulku Turk Boru, MD, Arda Duman MD and Mustafa Tasdemir MD – Botulinum toxin in the treatment of trigeminal neuralgia ,2017 sep
[16]. Robert A Egan, MD et.al; Trigeminal neuralgia treatment and management 2019; july-11
[17]. Barbor.M, MVD bests gamma knife for pain in trigeminal neuralgia. October 22 2015.
[18]. Pollock BE, Ecker RD, A prospective costeffectiveness study of trigeminal neuralgia surgery.Clin S pain 2005 jul-aug 21(4):317-322
[19]. Gorgulho A. Radiation mechanism of pain control in classical trigeminal neuralgia.surg. neurol int.2012; 3(suppl 1): 517-25
[20]. Deinsberger R, Tid strand J , Linac radiosurgery as a tool in neurosurgery. Neurosurg rev 2005 apr.28(2):79-88
[21]. Yad Ram Yadav, Yadav Nishtha, Trigeminal neuralgia2017,oct-dec 12(4): 585-597
[22]. Bender.M, Pradilla G,Batra S, See A, Bhutiani N, James et.al, Effectiveness of repeat glycerol rhizotomy in treating recurrent Trigeminal Neuralgia Neurosurgery, 2017:70:1125-32