



TRIGEMINAL NEURALGIA: AN OVERVIEW OF LITERATURE WITH EMPHASIS ON MEDICAL MANAGEMENT

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ABSTRACT

Pain is a complex human psycho-physiological experience. Neuralgic pain is produced by a change in neurological structure or function rather than by the excitation of pain receptors that causes nociceptive pain. Neuralgic pain follows the path of a nerve that may give rise to the sensation of tooth pain which often is a diagnostic dilemma for dentist. Trigeminal neuralgia is a disorder of the trigeminal nerve that causes episodes of unilateral intense, stabbing, electric shock like pain in the areas of the face supplied by trigeminal nerve-lips, eyes, nose, scalp, forehead, upper and lower jaw. TN is not fatal, but is universally considered to be one of the most painful afflictions known. An early and accurate diagnosis is mandatory, as therapeutic interventions can reduce or eliminate pain attacks. Treatment of this debilitating condition may be varied, ranging from medical management to surgical interventions. This article deals about the etio-pathogenesis, clinical characteristics, diagnosis and treatment strategies for trigeminal neuralgia.

KEYWORDS: Facial pain, Trigeminal neuralgia, Carbamazepine.

INTRODUCTION

Historical Background

Areataeus of Cappadocia was the first to describe trigeminal neuralgia, as early as the first century A.D.¹ Jujani, an Arab physician, mentioned unilateral facial pain and suggested the cause of pain as proximity of the artery to the nerve.² The condition was later discussed by Johannes Bausch in 1672.³ John Locke in 1677 gave the first complete description of TN.² Term “tic douloureux” was used by Nicolas Andre in 1756.³ In 1773, John Fothergill gave a full and accurate description of TN.³ TN has also been called Fothergill’s disease, however, the terminology is no longer in use now. Pujol, Chapman and Tiffany, in the 18th and 19th century differentiated TN from other common facial pain conditions, such as toothache. Oppenheim, in the 20th century, described an association between multiple sclerosis and TN, and familial incidence was noted by Patrick.⁴

Epidemiology

TN usually affects patients during middle and old age. There seems to be a predominance of women with TN.⁵ In the United States, the reported incidence per 100,000 inhabitants per year is 2.7 for men and 5.0 for women.⁵ No known racial or ethnic risk factors exist. Patients with multiple sclerosis may develop trigeminal neuralgia as a secondary symptom. However, this occurrence is relatively rare, involving only approximately 1% of patients with multiple sclerosis.⁶

Diagnostic Criteria

TN is defined by the International Association for the study of Pain (IASP) as “a sudden, usually unilateral, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve”.⁵ International Headache Society (IHS) defined TN as “painful unilateral affliction of the face, characterized by brief electric shock like pain limited to the distribution of one or more divisions of the trigeminal nerve. Pain is commonly evoked by trivial stimuli including washing, shaving, smoking, talking, and brushing the teeth, but may also occur spontaneously. The pain is abrupt in onset and termination and may remit for varying periods”.⁷ IHS described a criteria for the diagnosis of classical and symptomatic TN.⁸

Classical TN	Symptomatic TN
A. Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes, affecting one or more divisions of the trigeminal nerve and fulfilling criteria B and C.	A. Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes, with or without persistence of aching between paroxysms, affecting one or more divisions of the trigeminal nerve and fulfilling criteria B and C.
B. Pain has at least one of the following characteristics: 1.Intense, sharp, superficial or stabbing. 2.Precipitated from trigger areas or by trigger factors.	B. Pain has at least one of the following characteristics: 1.Intense, sharp, superficial or stabbing. 2.Precipitated from trigger areas or by trigger factors.
C. Attacks are stereotyped in the individual patient.	C. Attacks are stereotyped in the individual patient.
D. There is no clinically evident neurological deficit.	D. A causative lesion, other than vascular compression has been demonstrated by special investigations and/or posterior fossa exploration.
E. Not attributed to another disorder.	

White and Sweet⁹ proposed a diagnostic criteria for TN. The criteria includes 5 major features-

1.Paroxysmal pain-Paroxysmal attacks of pain are the key feature, and invariably the presenting complaint. TN has an electric shock like pain, sudden in onset and often severe in intensity, resulting in facial grimace.TN patients are typically symptom free between attacks. A patient who experiences significant dull pain between attacks doesnot fit TN diagnostic criteria.

2.Pain provoked by light touch to the face. (Trigger zones)- A TN “trigger zone” is an area of facial skin or oral mucosa where low intensity mechanical stimulation (light touch, an air puff, or even hair bending can elicit typical facial pain. TN trigger zones are few millimeters in size and seen exclusively in the peri-oral regions.¹⁰

3.Pain confined to the trigeminal nerve distribution-Pain paroxysms in TN are confined to the sensory distribution of the trigeminal nerve one one side. The lancinating pain attacks occur most frequently in the third trigeminal division and radiate along the mandible. Less often, pain occurs in the second division or in both divisions. Rarely, first division pain occurs.^{11,12}

Characteristically, pain attacks are stereotyped i.e each attack has a similar quality, location, and intensity.

4. Pain is unilateral. Right side of the face is more commonly involved than the left side. This could be attributed to the narrower foramina (Rotundum and Ovale) on the right side.^{11,12}

5. Normal clinical sensory examination.

Etiopathogenesis

The underlying neurophysiologic mechanisms of TN are not understood.¹³ The preferred theory of causation is vascular compression of the trigeminal root adjacent to the pons.^{14,15,16}

The nerve impingement in the trigeminal root entry zone is often accompanied by a demyelination.¹⁷ It is believed that these alterations promote ectopic firing from the injured nerve fibers as well as allow transmission of painful impulses.¹⁸ There are various evidences which support the theory of nerve compression. (a) Imaging modalities (MRI) during posterior fossa surgery for TN have revealed close approximation of a blood vessel with the nerve root.¹⁹

(b) Most patients got long term pain relief after elimination of compression.²⁰ (c) Intra-operative recordings showed immediate improvement in nerve conduction following decompression and the patients wake up from the operation pain free.²¹ (d) Sensory functions recover following decompression (although recovery is slower than in nerve conduction).²² Current theory also includes the possibility that TN is a symptom of a central nerve disease characterized by a failure of central inhibitory mechanisms.^{23,24} Other authors regard TN as a symptom of a primarily vascular disease of the trigeminovascular system. This system is characterized by a functional interplay between a sensory trigeminal plexus and blood vessels localized in the pia and dura mater.²⁵ Also, damage to the myelin sheath can cause trigeminal pain. This type of damage typically occurs in connection with multiple sclerosis.²⁶

Diagnosis

A detailed history is very important for the diagnosis. Physical examination includes neurologic examination and the finding of typical trigger zones verifies the diagnosis of trigeminal neuralgia. Imaging is carried out to rule out other causes of compression of trigeminal nerve such as mass lesions, or vascular malformations. Imaging modalities includes MRI: 3 dimensional constructive interface in steady state (3-D-CISS) showed the proximity between trigeminal nerve and the region of neuralgic manifestation.²⁷

Differential Diagnosis

The list of disease which should be considered in the differential diagnosis is long. However, some of the lesions which should not be ignored are specific and non specific facial pains, TMJ disorders, dental disorders, vascular migraine, cluster headache, chronic paroxysmal hemicranias, cracked tooth syndrome, post herpetic neuralgia and giant cell arteritis.²⁸

Treatment

There is indeed a gamut of medical and surgical treatment modalities available for trigeminal neuralgia. As per AANEFNS (American Academy of Neurology- European Federation of Neurological Societies) guidelines²⁹, medical therapy is started and surgical options are considered only if there is failure to respond to medical therapy. Other treatment modalities include TENS, Acupuncture and psychological methods.

Carbamazepine

Since its introduction in TN therapy more than 30 years ago,³⁰ the anticonvulsant carbamazepine (Tegretol) is

considered to be the drug of choice for the initial and long-term management of TN. Among all pharmacologic agents used for this purpose, it shows the greatest effectiveness.³¹ Carbamazepine is a tricyclic imipramine first synthesized in 1961 and introduced for treatment of trigeminal neuralgia by Blom.³⁰ The mechanism of action may be related to its ability to block voltage sensitive sodium channels which result in stabilization of the hyperexcitable trigeminal neural membranes.³² Dosage used may range from 100 mg to 1200 mg per day, and most patients respond to 200 to 800 mg per day in two- three divided doses.

However, adverse reactions are common. Typical complaints during the initial phase of carbamazepine therapy are transient and dose-dependent. They include drowsiness, dizziness, confusion, vertigo, nausea, and vomiting. Hepatotoxic and hematologic side effects, including agranulocytosis, aplastic anemia, leukopenia, or pancytopenia, may develop. Complete hematologic and liver function evaluation is recommended before and during the therapy and should include a complete blood cell count (CBC), serum ion concentration, serum ionized calcium concentration, liver function tests, and plasma carbamazepine concentration. The patient should have regular monitoring blood tests. The laboratory tests should be monthly during the first year and quarterly thereafter. Additional adverse drug reactions to carbamazepine can occur. Possible gastrointestinal manifestations are abdominal pain, diarrhea, constipation, anorexia, stomatitis, glossitis, and dryness of the mouth and pharynx. Potential skin manifestations include pruritus and erythematous rashes, urticaria, and photosensitivity. Other adverse reactions may affect the nervous system (blurred or double vision or nystagmus), the cardiovascular system (aggravation of hypertension), the respiratory system (pulmonary hypersensitivity), the genitourinary system (oliguria), and the musculoskeletal system (arthralgia and myalgia). Drug interactions with erythromycin may occur, the antibiotic erythromycin increases the plasma levels resulting in toxicity of carbamazepine.³³

Oxycarbazepine

Oxycarbazepine is a keto analogue of carbamazepine which has a better toxicity profile. It may be a useful alternative in patients who do not tolerate carbamazepine.^{34,35} Oxycarbazepine was associated with substantially fewer adverse events than carbamazepine; in particular, there were fewer incidences of vertigo, dizziness, ataxia and fatigue. Tolerability was reported as 'good' to 'excellent' by 62% of patients receiving oxycarbazepine, compared with 48% of patients receiving carbamazepine.³⁶

Baclofen

Baclofen (Lioresal), a muscle relaxant and antispastic used for the treatment of signs and symptoms associated with multiple sclerosis was introduced for the therapy of TN in 1984.³⁷ It is prescribed if monotherapy with carbamazepine has failed. Baclofen can be used alone or in combination with carbamazepine or phenytoin, respectively.³⁸ Initial dose is 5 mg tid for three days and the dose may be increased to 10 to 20 mg / day every 3 days, and the maximum tolerated dose is 50 to 60 mg / day.³⁹ Typical adverse effects of baclofen include drowsiness, dizziness, weakness, fatigue, and nausea. Abrupt discontinuation of baclofen can cause severe withdrawal symptoms (hallucinations and seizures).⁴⁰ Nevertheless, baclofen has the strongest evidence for efficacy of trigeminal neuralgia after carbamazepine.⁴¹ Patients with multiple sclerosis and trigeminal neuralgia derive special

benefit with baclofen as the drug can target the symptoms of both the disease conditions.⁴²

Phenytoin

Phenytoin (Dilantin) is an antiepileptic agent that has been used for TN management for a long time. It was first reported in the literature 30 years ago.⁴³ Long-term success can be achieved in only 25% of the cases when phenytoin is used alone. Therefore phenytoin is often prescribed in combination with baclofen.³⁸ The more common possible adverse effects of phenytoin include ataxia, slurred speech, decreased coordination, and nausea. Initially given at a dose of 100 mg twice or thrice daily, and gradually increasing the dose as required to a maximum daily dose of 800 mg. Many patients gained benefit within one to two days.⁴⁴

Lamotrigine

Lamotrigine is a phenyltriazine derivative developed for the treatment of partial and generalized tonic clonic seizures. It acts as a voltage sensitive sodium channel and stabilizes neural membranes.⁴⁵ Initial dose is 25 mg twice daily and it can be increased gradually to a maintenance dose of 200-400mg/day in two divided doses. Fewer side effects are encountered, the most common being sleepiness, dizziness, headache, vertigo and rash. Steven-Johnson syndrome can occur in 1 in 10,000 patients taking the drug. This reaction, which is more common at the advent of therapy can be prevented to a certain extent by taking care not to escalate the dose too rapidly.⁴⁶

Gabapentin

Gabapentin, an anti epileptic drug has shown adequate efficacy alone and in combination with local injections of ropivacaine used to block trigger points in TN.⁴⁷ Treatment should be started at a dose of 900 mg/day (300 mg/d on day 1, 600 mg/d on day 2, and 900 mg/d on day 3). The dose can also be increased to a maximum of 1800 mg/d for greater efficacy. Some patients may be requiring up to 3600 mg/d.⁴⁸ However the effective dose should be individualized based on response and tolerability. Hyperlipidemia is one of the important side effects known to occur while other side effects such as dizziness, coordination problems, infections, nausea, vomiting are usually self limiting within ten days of initiation of therapy.

Pregabalin

Pregabalin is a GABA analogue structurally related to gabapentin which modifies the synaptic or non synaptic release of GABA. Pregabalin interact with the $\alpha 2\delta$ subunit of voltage-gated calcium channels by increasing the brain concentration and rate of synthesis of gamma aminobutyric acid.⁴⁹ Pregabalin (150-600 mg/day) proved to be effective in reducing TN pain by over 50% in 74% of patients.⁵⁰

Topiramate

Topiramate, a newer antiepileptic drug acts by sodium channel blockade, enhancing GABA activity by binding to a non-benzodiazepine site on GABAA receptors, and selectively blocking AMPA/kainite glutamate receptors. Topiramate (100-400 mg/day) was effective in 75% of patients in a very small sample of only eight patients.⁵¹ Dizziness, sedation, cognitive impairment, fatigue, nausea, blurred vision and weight loss are the common side effects.

Miscellaneous Drugs

Other drugs that have been suggested for the treatment of TN are the anticonvulsants clonazepam⁵² and sodium valproate,⁵³ and the antipsychotic drug pimozide.⁵⁴ The efficacy of these drugs remains unclear.

Clonazepam, given in the dose of 4-8 mg / day, is the drug of choice in patients in whom carbamazepine is contraindicated.

Botulinum toxin has been found to effective in the treatment of several pain syndromes such as migraine and occipital neuralgia. Injection of botulinum toxin causes inhibition of acetylcholine release in nerve endings causing relaxation of muscles and pain relief. Another hypothesis is that botulinum stops secretion of some nociceptive neuropeptides which prevent pain sensation.⁵⁵

Other drugs which can be used in TN include topical capsaicin, lidocaine, amitriptyline, sumatriptan, and intranasal lidocaine.

Surgical Treatment

Surgical treatment is considered in cases refractory to pharmacological therapy. Various surgical procedures that are currently practiced are:

1. Microvascular decompression.
2. Ablative procedures:
 - Percutaneous radiofrequency thermal rhizotomy
 - Glycerol rhizolysis
 - Balloon compression of trigeminal ganglion.
3. Gamma knife radiosurgery
4. Other procedures-neurectomy, cryotherapy, and alcohol injections.

CONCLUSION

Trigeminal neuralgia is a common neuropathic pain characterized by paroxysmal pain, along the distribution of trigeminal nerve. Diagnosis is made clinically by characteristic signs and symptoms. Anticonvulsants form the mainstay of treatment and surgery is considered when medicinal therapy fails. Dentists should be aware of this common facial pain entity and should make accurate and early diagnosis of this debilitating entity.

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