World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

IDIOPATHIC TRIGEMINAL NEURALGIA AND ITS PHARMACOLOGICAL MANAGEMENT – A CASE REPORT AND SHORT REVIEW

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Article Received on 20/05/2018 **Article Revised on 10/06/2018** **Article Accepted on 01/07/2018**

ABSTRACT

Trigeminal neuralgia is a craniofacial pain which is also known as tic douloreux presents with multiple episodes of sharp, severe, lancinating, "electric shock - like" pain. The International Association for the Study of Pain (IASP) defines classical idiopathic trigeminal neuralgia (TN) as "a sudden, usually unilateral, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve." Idiopathic trigeminal neuralgia is the most common type of facial pain neuralgia. The pain typically occurs in the distribution of one of the branches of the trigeminal nerve (cranial nerve V), usually unilaterally.

KEYWORDS: Trigeminal neuralgia, Tic douloreux, International Association for the Study of Pain (IASP), Idiopathic trigeminal neuralgia, Trigeminal nerve, fifth cranial nerve.

INTRODUCTION

Trigeminal neuralgia is also known as Tic douloureux, trifacial neuralgia and fothergill's disease. It is the most common of the cranial neuralgias which affects individuals >50 years of age. It is classified as Classic trigeminal neuralgia & Symptomatic trigeminal neuralgia. Maxillary and mandibular divisions of the trigeminal nerve are more commonly affected than the ophthalmic division. It exhibits a trigger zone which upon stimulation causes a paroxysm of pain.[1]

In 1934 Dandy first proposed that vascular compression of the trigeminal nerve was a cause of trigeminal neuralgia (TN). However, he also pointed out that vascular contact occasionally occurs without the production of trigeminal neuralgia and that trigeminal neuralgia can occur in the absence of contact.[2] Compression of the trigeminal nerve by a blood vessel at or near the root entry zone [2,3,4] is still thought to be the most common cause for trigeminal neuralgia. Devor's "ignition theory" of TN relies on a focus of hyperactivity in the retrogasserian root, consistent with a focus of demyelination within the nerve possibly caused by vascular compression. The theory states that "nerve injury results in hyperexcitabilty of injured afferents, which results in after discharges large enough to result in non-nociceptive signal being perceived as pain. This leads to wind-up and both peripheral and central sensitization."[5] Other etiologies such as multiple sclerosis,[6] central or peripheral demyelination,[7,8] root injury, and tumors may be associated with TN.[9]

Vascular compression of the trigeminal nerve is also known to occur in patients who do not have TN, and TN is known to occur in patients who have no vascular compression. In 1989, Adams questioned the role of "microvascular compression" in the surgical treatment of TN, reviewing all the evidence at the time.[10]

It present with episodes of intense shooting, stabbing pain that lasts for a few seconds and then completely disappears. Pain is electric shock–like quality and is unilateral. Light touch on a "trigger zone" present on the skin or mucosa provokes the pain episode. Shaving, showering, eating, speaking, or even exposure to wind provokes the pain episode and patients often protect the trigger zone with their hand or an article of clothing. A frozen or mask like face is seen due to involuntary contortion of the face on the affected side. Intraoral trigger zones can confuse the diagnosis. Just after an attack, there is a refractory period during which touching the trigger zone will not precipitate pain. The number of attacks may range from one or two per day to several per minute. In case of severe trigeminal neuralgia, the patients are disabled by attacks that are triggered by speaking or other mouth movements Trigger zone of ophthalmic branch is present on the Supraorbital ridge. Maxillary branch involvement causes pain on touching the skin of the upper lip, ala nasi or cheek or on the maxillary gingiva. Mandibular branch if involved presents with pain on touching the lower lip, teeth or gingiva of the mandible and tongue.[11]

Diagnosis is chiefly by careful history taking and clinical examination. History of shooting pain is precipitated by touching a trigger zone, examination should reveal a shooting pain. Diagnostic local anesthetic blocks are highly useful. A routine cranial nerve examination will be normal in the case idiopathic TN, but sensory and/or motor changes are altered in the case of underlying tumors or other CNS pathology. Electrophysiologic testing of trigeminal reflexes provides an accurate diagnosis. MRI (brain) is always advised to rule out tumors, multiple sclerosis, and vascular malformations. Magnetic resonance angiography can also be used to visualize vascular abnormalities. Initial therapy is with anticonvulsant drugs such as carbamazepine. Surgically managed with peripheral neurectomy, cryosurgery, radiofrequency thermocoagulation, balloon compression**,** glycerol rhizotomy, microvascular decompression and gamma knife radiosurgery.[12]In this case report we present a 70-year-old female patient who reported to the Clinic with a complaint of sharp, shooting and episodic pain in her right side preauricular region.

CASE REPORT

A 70-year-old female patient reported to the clinic with a chief complaint of pain in relation to the right side of the face in front of the ear. History revealed sharp shock like pain. Pain is intermittent and aggravates on mastication and other functions. Paroxysmal attacks of pain. Pain is electric shock like and pricking. Pain is unilateral. Refractory period is present.

On inspection, involuntary twitching of muscles was not evident. She braced and guarded the right side of the face during the period of attack. On palpation tenderness was present in the temporal region (Figure 1) and a trigger zone (Figure 2) was present in the maxillary alveolar ridge on the buccal aspect of 14,15,16 & 17 tooth region.

Figure 1: Patient pointing out the region of tenderness (Temporal region).

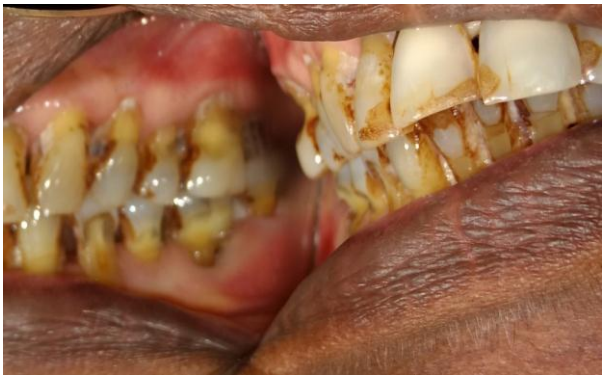

Figure 2: Trigger zone in relation to the gingiva on the buccal aspect of 14,15,16 & 17.

Based on the history and clinical findings a provisional diagnosis of trigeminal neuralgia – Maxillary division – right side was considered and the patient was subjected to an MRI (Figure 3) of the brain which revealed multiple chronic focal lacunar infarcts in the pons.

Hypoplastic/Absent A1 segment of the right anterior cerebral artery and no sign of any vascular compression on the cisternal segment of the trigeminal nerve on either side.

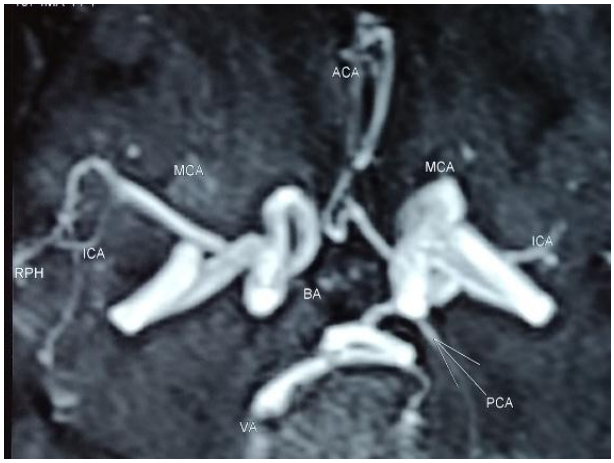

Figure 3: MRI of brain showing no evidence of vascular compression on the trigeminal nerve.

Based on history, clinical features and the impression of the MRI a final diagnosis idiopathic trigeminal neuralgia – Maxillary division – right side was established. The patient was prescribed carbamazepine 200 mg twice daily for a period of 2 weeks. The patient reported back for a review after 2 weeks and did not give a history of pain during the past 2 weeks and did not reveal any sign of sensitization of nerve leading to a neuralgic pain episode during palpation of the trigger zone. She is presently under follow-up and has not complained of recurrence of painful episodes.

DISCUSSION

As early as 1934 Dandy pointed out that vascular contact occasionally occurs without the production of TN and that TN may be present in the absence of contact.[2]In

1982, Adams et al. reported "our failure to be convinced by vascular compression as a cause for the majority of our patients' pain."[10]

Hamlyn, in 1992, noted that an explanation for TN cases in which no vessel was found in contact with the trigeminal nerve at operation was needed and that it should be possible to identify those cases preoperatively.[13] In 2009, Miller et al. stated that "trigeminal NVC occurs in asymptomatic patients but is more severe and more proximal in patients with TN."[14] While vascular compression of the trigeminal nerve by a blood vessel at or near the root entry zone,[2,6,15] remains the primary pathology of TN, there remains an unexplained subset of cases of TN without clear NVC. Improvements in surgical approaches and advances in imaging technology have only reinforced this discrepancy.[16,21] Trigeminal neuralgia recurrence rates after an initially successful MVD have been reported as ranging from 6% to 41%. [22-25] In a study it has previously demonstrated that 17% of the general population manifests NVC of the trigeminal nerve.[35] If, as has been estimated, the incidence of TN in the population is 1: 10,000 (0.01%),[32] then 99.94% of individuals with trigeminal NVC do not have TN. Given these statistics, and the present evidence that TN can both occur and recur without NVC, the hypothesis that TN is caused by neurovascular conflict must be challenged.[26]

The diagnosis of trigeminal neuralgia (TN) critically depends on a patient's description of pathognomonic pain attacks.[27] Unequivocal definition of the characteristic features of TN is therefore mandatory. Etiology of trigeminal neuralgia is varied and numerous authors have proposed plenty of theories to support their hypothesis. Vascular compression of the cisternal segment of the trigeminal nerve is the most accepted theory and some patients do not present with any clinically or imaging based evident etiological factor. They are classified as idiopathic trigeminal neuralgia. Vascular compression of the trigeminal nerve is also known to occur in patients who do not have TN, and TN is known to occur in patients who have no vascular compression.

In 2009, Miller et al.,[14] evaluated neurovascular compression (NVC) in patients with and without TN and concluded that trigeminal NVC occurred in asymptomatic patients but was more severe and more proximal in patients with TN. A review of the literature reveals that a wide range (4%–89%) of TN patients has no demonstrable vascular contact. TN patients often experience a recurrence after an initially successful surgical procedure.[16-18]

Surgical alternatives after recurrence include repeat exploration for recurrent vascular compression and microvascular decompression (MVD), internal neurolysis, or radiofrequency lesioning. Other alternatives for recurrent TN include partial or complete sensory rhizotomy, balloon rhizotomy, glycerol injections, and radiosurgery. Most experienced surgeons tend to favor less destructive approaches since anesthesia dolorosa (deafferentation pain) is a known, and feared, complication of application of destructive procedures to the trigeminal nerve.

A recent study by Giorgio cruccu et al, have defined and classified trigeminal neuralgia one that integrates an evaluation of diagnostic certainty based on criteria equivalent to those applied for neuropathic pain in general given by Treede et al. According to the study trigeminal neuralgia is defined as an orofacial pain restricted to one or more divisions of the trigeminal nerve. With the exception of TN caused by multiple sclerosis, the pain affects one side of the face. It is abrupt in onset and typically lasts only a few seconds (2 minutes at maximum). Patients may report their pain as arising spontaneously but these pain paroxysms can always be triggered by innocuous mechanical stimuli or movements. Patients usually do not experience pain between paroxysms. If they report of continuous pain, in the same distribution and in the same periods as the paroxysmal pain, they are understood to have TN with continuous pain. It has been classified in 3 etiologic categories. Idiopathic TN occurs without apparent cause. Classical TN is caused by vascular compression of the trigeminal nerve root. Secondary TN is the result of a neurologic disease, e.g., a tumor of the cerebellopontine angle or multiple sclerosis. Either phenotype (with purely paroxysmal pain or with additional continuous pain) may occur with any of the 3 categories.[28]

A huge variety of pharmacological and surgical treatments are available for TN. The practice parameters and guidelines published in 2008 from the American Academy of Neurology (AAN), and the European Federation of Neurological Societies (EFNS)[29,30] recommend starting treatment with drugs in patients with classic TN. Surgical procedures should be reserved for patients who are refractory to medical therapy or when drugs are causing unacceptable adverse effects. There are few studies directly comparing medical and surgical treatments.

Different medication has been considered for treatment of TN. Based on the level of evidence; carbamazepine and oxcarbazepine should be offered as a first line for pain control.[29] There is limited evidence for efficacy of different AEDS to treat TN; other medications such as Baclofen and Botulinum Toxin A seem promising treatment for this disorder.[29]

First-line therapy - According to current evidence- based treatment guidelines published in 2008 from the AAN and EFNS,[30] carbamazepine is established as effective (level A) and oxcarbazepine is probably effective (level B) for controlling pain in classic TN. These guidelines recommend carbamazepine (200-1200 mg/d) and

oxcarbazepine (600-1800 mg/d) as a first-line therapy for classic TN.

Carbamazepine inhibits voltage-gated sodium channels, as a result reducing the excitability of neural membranes. Carbamazepine has also been shown to potentiate gamma aminobutyric acid (GABA) receptors made up of alpha1, beta2, and gamma2 subunits. This may be relevant to its efficacy in neuropathic pain.[31] In newly diagnosed cases of TN, the usual starting dose is 100 to 200 mg twice daily. The daily dose should be increased by 100 mg every other day until sufficient pain relief is attained or until intolerable side effects prevent further upward titration. The typical total maintenance dose is 300-800 mg/d, given in 2-3 divided doses. The maximum suggested total dose is 1200 mg/d. With appropriate dose adjustments, pain can be controlled in around 75% of patients.[32,33] The dose may be tapered once pain is controlled, since remission may occur. Extended release carbamazepine is useful as a night dose in patients with pain attacks during sleep, as drug levels do not fall. This not only keeps patients pain free during sleep, but may reduce side effects, as high serum peaks are not achieved.[34,35] Common side effects include sedation, dizziness, nausea, vomiting, diplopia, memory problems, ataxia, elevation of hepatic enzymes, and hyponatremia, which may contraindicate it for elderly patients. Potentially serious but uncommon side effects are carbamazepine-induced leucopenia, aplastic anemia, allergic rash, systemic lupus erythematosus, hepatotoxicity, and Stevens-Johnson syndrome (SJS). It is advisable to order complete blood count, serum sodium, and liver function tests within several weeks after starting therapy to detect any complications quickly.[36,37]

Oxcarbazepine is a keto-analogue of carbamazepine that is rapidly converted into its pharmacologically active 10-monohydroxy metabolite. The keto derivative of carbamazepine does not pass through the liver cytochrome system, resulting in an improved side effect profile and fewer drug interactions than with carbamazepine.[38-40] Oxcarbazepine is an acceptable alternative to carbamazepine, which may have provided pain relief but has caused unacceptable adverse effects. Better tolerability can also be considered an advantage over carbamazepine. Oxcarbazepine can be started at 150 mg twice daily. The dose can be increased as tolerated in 300 mg increments every third day until pain relief occurs. Maintenance doses range between 300-600 mg twice daily.[34] The maximum suggested total dose is 1800 mg/d. The risk of allergic cross reactivity between carbamazepine and oxcarbazepine is around 25%, so oxcarbazepine is best avoided when carbamazepine allergy is evident.[36]

Second-line therapy - Second-line treatment is based on very little evidence. Three drugs are included in this class - lamotrigine, baclofen, and pimozide. Each drug has been studied in single trials,[41-43] and per AAN/EFNS guidelines, are possibly effective for controlling pain in patients with classic TN.

The initial dose of lamotrigine is 25 mg twice daily, and can be increased gradually to a maintenance dose of 200-400 mg/d in 2 divided doses.[15] The dosage required for adequate pain relief varied widely from 100-400 mg/d.[35] Common side effects are sleepiness, dizziness, headache, vertigo, and ataxia. Some (7-10%) of patients report a skin rash during the first 1-2 months of treatment that most often resolves with continued therapy.[36] Stevens-Johnson syndrome can occur in one in 10,000 patients taking lamotrigine.[44] Such adverse reactions can be prevented by slower titration of the drug.

Baclofen, a skeletal muscle relaxant, is a GABA analogue that activates GABAB receptors and thus depresses excitatory neurotransmission.[36] It is effective in controlling pain in TN at a dose of 60-80 mg/d. Baclofen can be used alone or in combination with carbamazepine.[37] The initial dose is 10 mg/d for 3 days, which can be increased to 10-20 /d every 3 days if needed. The maximum tolerated dose is 60-80 mg/d, administered 3-4 times per day.[37] If baclofen is an add-on therapy with carbamazepine, it is advisable to reduce the dose of carbamazepine to 500 mg/d to maintain a putative synergistic effect.[36] Typical side effects of baclofen include drowsiness, dizziness, weakness, fatigue, nausea, hypotension, and constipation. Abrupt discontinuation of baclofen can cause withdrawal symptoms (hallucinations and seizures).[44] Patients with MS and trigeminal neuralgia obtain additional benefits with baclofen because it is a muscle relaxant.[39] To date, baclofen has the strongest evidence for efficacy in the treatment of TN after carbamazepine.[44]

Pimozide, a dopamine receptor antagonist, is used mainly in the management of Tourette syndrome. Pimozide, at a dose of 2-12 mg/d in TN treatment, is seldom used clinically because it has multiple potential serious side effects, including, arrhythmias, acute extrapyramidal symptoms, and Parkinsonism.

Third-line therapy - The newer AEDs tested within the past few years are gabapentin, pregabalin, topiramate, and levetiracetam.[34]

Gabapentin, a GABA receptor agonist, acts primarily on presynaptic calcium channels of neurons to inhibit the release of excitatory neurotransmitters. Treatment can be started at a dose of 300 mg/d, and may be gradually increased by 300 mg every 2-3 days as tolerated. For maximum efficacy, the dose can be increased to 1800 mg/d.[15, 44] Gabapentin has many advantages, including faster titration, no known drug interactions, no known idiosyncratic skin reactions, and a favorable side-effect profile, with mild somnolence, dizziness, headache, confusion, nausea, and ankle edema. Hyperlipidemia is an important side effect to watch for with gabapentin therapy.[39]

Pregabalin is an analog of GABA, structurally related to gabapentin. It acts by interacting with the alpha-2-delta (α2-δ) subunit of voltage-gated calcium channels.[45] Although a potentially useful drug for neuropathic pain in some patients, evidence is scant in TN. Side effects are similar to other AEDs but less marked; most common are dizziness and sleepiness.[45]

The exact mechanism of action of topiramate is unknown. However, its pain-modulating effect might be related to its property of blockage of the voltage-gated sodium channel and an augmentation of GABA activity by binding to a non-benzodiazepine site on the GABA receptor. The most frequently registered side effects of topiramate were dizziness, somnolence, cognitive impairment, and weight loss.[37]

Levetiracetam is a newer AED that has been tried in TN. The exact mechanism by which it acts is unknown, but it is thought to target high- voltage, N-type calcium channels as well as the synaptic vesicle protein 2A (SV2A); by this, it impedes impulse conduction across synapses.[45] Its evidence in TN is scant. The effective dose range of levetiracetam in TN is 1000-4000 mg/d. Levetiracetam has advantages, including no need for routine blood tests, less drugs interactions,[11] the absence of auto-induction effect, nasopharyngitis, sleepiness, headaches, and irritability are side effects when starting levetiracetam.[39]

Botulinum toxin A (BTX-A) has been thoroughly studied as a potential tool in the treatment of several pain syndromes, such as migraine, tension headache, occipital, and postherpetic neuralgias. The BTX-A's mechanism of analgesic effect is still unclear, but it is postulated it causes local release of anti-nociceptive neuropeptides such as substance P, glutamate, and calcitonin-gene related peptide, inhibiting central and possibly peripheral sensitization. The most commonly used dose of BTX-A was 20-75U, however, patients also showed significant reduction in intensity of pain at lower doses (6-9U). Based on this available limited evidence, BTX-A seems promising treatment of TN.[46-48]

A number of other drugs have been tried in treating TN, showing limited benefit such as phenytoin and intravenous phenytoin, fosphenytoin, clonazepam, valproic acid, misoprostol, tocainide, topical capsaicin cream, intranasal lidocaine, tizanidine, sumatriptan, and amitriptyline.[49-53]

CONCLUSION

Trigeminal neuralgia can present with various etiological factors and most times as an idiopathic pain condition. Absence of a definable etiological factor does not rule out the possibility of trigeminal neuralgia. A sound knowledge of various neuralgias of the head and neck and their associated factors will guide the clinician in arriving at a proper diagnosis which will lead to a proper care and cure of the neuralgic pain.

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