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ROLE OF CARBAMAZEPINE AND GABAPENTINE IN THE TREATMENT OF TRIGEMINAL NEURALGIA

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Abstract

Classical trigeminal neuralgia (TN) is a rare neuropathic pain. The pain, also known as "tic douloureux", is paroxystic and very severe. It can be triggered by a light coetaneous stimulus on a much localized spot on the face (so called "trigger zone"). The patient can sometimes benefit from long remissions without any treatment. With the exception of multiple sclerosis and of uncommon cases of posterior fossa tumors or other lesions impinging on the trigeminal nerve, ganglion or root, trigeminal neuralgia is considered as "idiopathic". Both medical and surgical modalities exist in the treatment of patients with TN. Carbamazepine still remains as the gold standard drug in terms of efficacy in TN. Several other drugs can be used as alternatives for TN such as oxcarbazepine, baclofen, lamotrigine, levetiracetam, gabapentin, valproate, botulinum toxin A injection.

KEY WORDS: Trigeminal Neuralgia, tic Douloureux, Carbamezapine, Gabapentine,Idiopathic

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INTRODUCTION

Trigeminal Neuralgia (TN), a neuropathic pain syndrome, is defined by the International Association for the Study of Pain (ISAP) as "a sudden and usually unilateral severe brief stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve[1]." It is an excruciating, short-lasting (<2 minutes), unilateral facial pain that may be spontaneous or triggered by gentle, innocuous stimuli and separated by pain-free intervals of varying duration.

Trigeminal Neuralgia is classified as follows:

Classic (also known as primary or idiopathic) and

Symptomatic (or secondary) - Due to intrinsic brainstem pathology with trigeminal nerve, nuclei, or tract involvement (e.g., multiple sclerosis or lacunars infarction), or due to extrinsic cerebellopontine angle pathology (e.g., neoplasm or vascular lesions). Most TN patients (>85%) have classic TN. Diagnosis in typical cases is often straightforward; however, most TN patients suffer from misdiagnosis[2].

Etiology and pathogenesis

Considerable progress has been made in elucidating the etiology of TN. In most patients with classic TN, the pain is generated because of compression of the trigeminal nerve most commonly at the root entry zone by an artery or vein. The plaques of demyelination lead to hyper excitability of injured afferents, which results in after discharges large enough to result in a nonnociceptive signal being perceived as pain[3]. One theory to explain TN is the

one proposed by Devor and colleagues[4], called the ignition theory, which can be explained as follows. The triggering of pain in TN may follow innocuous stimuli, a phenomenon that is probably explained by post injury changes in neuronal function. After nerve injury, there are an increased proportion of A-beta fibers with sub threshold oscillations that ultimately generate ectopic discharges[5]. These produce a transient depolarization in neighboring passive C neurons in the same ganglion[6].

These findings favor a mechanism whereby afferent nociceptors could be stimulated by activity in injured low-threshold mechanoreceptors. It is likely that both central and peripheral changes occur, which would explain why not all patients with a treated compression of the nerve get permanent relief. There are likely other factors involved given the rarity of the disease, and there are reports of genetic and familial forms[7].

Epidemiology

Few data are available. Incidence rate of TN is about 3 to 5 cases/year/100.000 persons[8,9]. Prevalence has been estimated at 107.5 men and 200.2 women/1 million population[10]. Risk factors have been investigated: multiple sclerosis is well known but additional risk factors are not confirmed[11].

Clinical features

These include paroxysmal attacks of pain, characterized by intense, sharp, superficial, or stabbing precipitated from trigger areas or by trigger factors, similar attacks in a patient, absence of neurological findings, and absence of other demonstrable cause. However, these criteria have not been validated[12]. The most problematic feature of the diagnostic criteria is a requirement for absence of sensory deficit in the absence of prior surgical intervention history. There is abundant evidence that subtle clinically detectable sensory deficits are present in the setting of typical TN as well as evidence that electrophysiological abnormalities may antedate detectable sensory loss on examination[13]. There are other forms of TN that most frequently have been called atypical trigeminal neuralgia and trigeminal neuropathy. Because there are no long-term cohort studies, it is not possible to determine whether these atypical forms are in fact the same condition but further on in the natural history or whether they may represent a distinct condition.

The timing of the attacks and remission periods, as well as the character of the pain, are the distinguishing features for classic TN. Many patients with increased pain severity during the day and only one third of patients will report nocturnal pain resulting in awakening. Patients with atypical TN often describe a burning, dull, aching after pain that is persistent with a completely pain-free interval. Quality of life in TN can be severely impaired. Because the attacks are usually spontaneous and provoked when eating or talking, this reduces the ability to relax and enjoy social activity. Depression is common, and suicides have been reported. Although on routine examination most patients have no sensory deficit, existing minor sensory deficits may be very subtle and may increase in frequency with chronicity of the syndrome. Abnormalities in neurophysiologic testing may identify subclinical deficits[14]. Patients may exhibit tactile trigger areas within the trigeminal distribution, which will precipitate an attack when stimulated. There are no autonomic features.

Diagnosis

The diagnosis of trigeminal neuralgia should be considered in all patients with unilateral facial pain. Accurate and prompt diagnosis is important because the pain of trigeminal neuralgia can be severe. Other diagnoses must also be considered, particularly in patients with atypical features of the disease or “red flags” in the history or physical examination. In addition, it is important to distinguish classical from symptomatic trigeminal neuralgia for the purpose of treatment. Symptomatic trigeminal neuralgia is always secondary to another disorder, and treatment should focus on the underlying condition[15].

Differential diagnosis

The list of differential diagnosis is very long. However, some of the lesions which should not be ignored are

- Specific and non specific facial pains
- Dental disorders

- Temporomandibular joint disorders
- Vascular migraine
- Cluster headache
- Chronic paroxysmal hemicranias
- post herpetic neuralgia
- Cracked tooth syndrome and
- Giant cell arteritis[16].

Treatment

Carbamezapine

Carbamazepine is a tricyclic imipramine first synthesized in 1961 and introduced for treatment of trigeminal neuralgia by Blom[17]. The four placebo controlled studies totaling 147 patients provide good evidence for the efficacy of carbamazepine[18] and the number needed to treat (NNT) to achieve a 50% reduction in pain is less than two (1.7[19], 1.8[20]). Not only are the intensity of attacks reduced, but the frequency is also lowered[18]. Carbamazepine has still retained its position as the initial drug of choice for trigeminal neuralgia despite the entry of several new drugs for this condition over the last few decades. This is because of the robust evidence of its efficacy in RCTs (randomized controlled trials) among patients with trigeminal neuralgia[21]. The mechanism may relate to its ability to block voltage sensitive sodium channels which result in stabilization of the hyper excitable trigeminal neural membranes[22]. A much lower dose (300-800 mg/day) than the conventional antiepileptic dosage is sufficient in alleviating the pain of trigeminal neuralgia. The efficacy at the start of therapy may be even as high as 80% but only 70% obtain complete relief. Common side effects include drowsiness, diplopia, ataxia and hyponatremia. The uncommon but serious adverse effects include allergic rash, myelosuppression, hepatotoxicity, lymphadenopathy, systemic lupus erythematosus, Steven-Johnson syndrome and aplastic anemia. The prevalence of aplastic anemia is 1 in 200,000 patients although mild leukopenia may be seen during early stages of therapy (10%). Skin rashes are more common in the Asian population. Adverse effects require discontinuation in 5-20% of patients. After commencing therapy it is prudent to monitor the complete blood count, serum sodium and liver function test within a few weeks of therapy to detect any adverse reactions. Drug interactions with carbamazepine are a potential problem as the drug has the capacity to induce hepatic drug metabolizing enzymes. Oxcarbazepine 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[23, 24]. In double blind RCTs there was a reduction in the number of attacks (88% of patients showed atleast 50% reduction or more) and the global pain assessment scores were equally good for both oxcarbazepine and carbamazepine[25].

Mechanism of action

Carbamazepine slows the recovery rate of voltage – gated sodium channels, modulates activated calcium channel activity, and activates descending inhibitory modulation system.

Dosage

The dose of carbamezapine is 200 to 1200 mg in two divided doses[26].

Common adverse effects

- Nausea
- Drowsiness
- Dizziness
- Fatigue
- Memory problems
- Diplopia
- Liver dysfunction
- Nystagmus
- Hematosuppression(rare)

Gabapentin

Gabapentin, an antiepileptic drug has shown promise in relieving some forms of neuropathic pain. In a retrospective study, involving 194 cases of trigeminal neuralgia, with paroxysmal facial pain resistant to previous surgical interventions or treatment with multiple medications, 92 patients received a trial of gabapentin, and of this 43 patients reported decline in facial pain. The benefit obtained was complete in 16, nearly complete in 9, moderate in 12 and partial in 6 patients. Onset of pain relief was found to occur during the first 1 to 3 weeks of therapy. In these patients, gabapentin was found to be effective at a daily dose range of 100 to 2400 mg per day in three divided doses with a mean dose 930 mg/day. During a mean follow-up time of 8 months, pain relief was found to continue in two third of

patients[27]. From the studies done so far, it appears that 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[28]. 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.

Mechanism of action

Unknown but possibly includes blockage of voltage gated calcium channels by binding to α_2/delta subunit

Dosage

The dose of gabapentin is 1200 to 3600mg daily in 3 to 4 divided doses[26].

Common adverse effects

- Somnolence
- Fatigue
- Dizziness
- Ataxia
- Nystagmus
- Tremor

Prognosis

Untreated, TN becomes gradually more severe with fewer remission periods, but the rate at which this occurs is unpredictable. Spontaneous remission periods of up to 6 months are common, yet the syndrome remains predominantly progressive in nature. Up to 44% of patients when followed for up to 16 years will fail to get complete pain relief with medical therapy[29].

CONCLUSION

Trigeminal neuralgia is a common neuropathic pain characterized by paroxysmal pain, along the distribution of trigeminal nerve. Although trigeminal neuralgia is a rare disorder with a high degree of morbidity a myriad of medical and surgical options do exist to alleviate the patient's symptoms. Carbamazepine has clearly surpassed other drugs in terms of strength of evidence and experience in this condition. Surgical options may be considered for patients who do not respond to medical management. The majority of patients tolerated Carbamazepine however; other medications may be tried if Carbamazepine is unsuccessful or provides only partial relief. Gabapentin is multimodal perioperative drug has efficacy in the treatment of neuropathic pain.

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