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ACCOMMODATION TO DIAGNOSIS OF TRIGEMINAL NEURALGIA

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SUMMARY – Trigeminal neuralgia is one of the most common causes of facial pain. It implies short lasting episodes of unilateral electric shock-like pain with abrupt onset and termination, in the distribution of one or more divisions of the trigeminal nerve that are triggered by innocuous stimuli. Most cases of trigeminal neuralgia are caused by compression of the trigeminal nerve root. Depending on the etiology, trigeminal neuralgia can be classified as classic trigeminal neuralgia or painful trigeminal neuropathy. It may be precipitated by some actions at trigger zones. The diagnosis of trigeminal neuralgia is based on diagnostic criteria for classic trigeminal neuralgia, neuroimaging and electrophysiologic trigeminal reflex testing. Treatment of classic trigeminal neuralgia for most patients is pharmacological therapy, while surgical approach is reserved for patients that are refractory to medical therapy and in cases of painful trigeminal neuropathy.

Key words: *Trigeminal neuralgia – therapy; Trigemnial neuralgia – surgery; Central nervous system – vascular malformations; Blinking; Carbamazepine*

Introduction

Trigeminal neuralgia (TN) is one of the most common causes of facial pain, with the annual incidence of 4 to 13 *per* 100 000 people and increasing gradually with age[1,2]. It is one of the most frequent neuralgias in the elderly population, with the male to female ratio 1:1.7[3]. Trigeminal nerve starts at the midlateral surface of the pons, and its sensory ganglion (gasserian ganglion) resides in Meckel's cave in the floor of the middle cranial fossa. It brings sensory supply to the face and the sensory and motor supply to the muscles of mastication. It divides into three main branches, ophthalmic, maxillary and mandibular. TN is characterized by recurrent short lasting episodes of unilateral electric shock-like pain with abrupt onset and termination, in the distribution of one or more divisions of the trigeminal nerve that are triggered by innocuous stimuli[4].

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Etiology and Pathogenesis

Most TN cases are caused by compression of the trigeminal nerve root, usually within a few millimeters of entry into the pons[5]. Compression can be caused by an aberrant loop of an artery or vein (80 to 90 percent of cases)[5-7], or vestibular schwannoma (acoustic neuroma), meningeoma, epidermoid or other cyst, or rarely a saccular aneurysm or arteriovenous malformation[8-14]. Idiopathic TN or TN caused by vascular compression is considered classic TN, and other causes of TN *via* compression are classified as painful trigeminal neuropathy. The mechanism by which compression of the nerve leads to symptoms appears to be related to demyelination in a circumscribed area around the compression[15,16]. The mechanism by which demyelination results in the symptoms of TN is not entirely clear. It is also possible that there is a role of the central pain mechanisms. Demyelination of one or more of the trigeminal nerve nuclei may also be caused by multiple sclerosis or other structural lesions of the brainstem, although vascular compression has also been noted in these patients[17].

Classification of Trigeminal Neuralgia

The International Classification of Headache Disorders, 3rd edition (ICHD-3) classifies TN into two categories: classic TN that encompasses idiopathic TN and TN caused by neurovascular compression, and painful trigeminal neuropathy caused by many other conditions mentioned before[4]. Painful trigeminal neuropathy encompasses painful trigeminal neuropathy attributed to acute herpes zoster, postherpetic trigeminal neuropathy, painful posttraumatic trigeminal neuropathy, painful trigeminal neuropathy attributed to multiple sclerosis plaque, painful trigeminal neuropathy attributed to space-occupying lesion and painful trigeminal neuropathy attributed to other disorder[4].

Clinical Presentation of Trigeminal Neuralgia

Trigeminal neuralgia is clinically defined by paroxysmal, stereotyped attacks of usually intense, sharp, superficial or stabbing pain in the distribution of one or more branches of the trigeminal nerve[4]. The pain of TN tends to occur in paroxysms and is immediately maximal in intensity. The pain is often described as unilateral repetitive electric, shock-like or stabbing, lasting from one to several seconds. A refractory period of several minutes during which a paroxysm cannot be provoked is common. Some patients with long-lasting TN may have continuous dull pain that is present between paroxysms of pain. TN does not awake patients. Facial muscle spasms can sometimes accompany the pain. Trigger zones in the distribution of the affected nerve may be present and are often located near the midline. Triggers include lightly touching these zones, chewing, talking, brushing teeth, cold air, smiling, and/or grimacing. TN can also be precipitated by dental procedures and 'pretrigeminal neuralgia', which is dull, continuous, aching pain in the jaw evolving eventually into TN. It is suspected to have a dental origin and unnecessary dental procedures have been performed in many cases[18]. Episodes of TN may last for weeks or months, followed by pain-free intervals. Recurrence is common, and some patients may have concomitant persistent background facial pain. Generally, the condition tends to decrease in severity and frequency of pain exacerbations.

Trigeminal Neuralgia Diagnosis and Differential Diagnosis

The initial diagnosis of TN is based on the characteristic clinical features. Then, search for secondary causes usually takes place. Younger patients and patients with trigeminal sensory loss or bilateral involvement are probably at a higher risk of painful trigeminal neuropathy, but the absence of any of these clinical features does not rule it out. Hypoesthesia or hypoalgesia in the affected trigeminal region always indicates axonal damage and therefore trigeminal neuropathy, while hyperalgesia in the painful region should not immediately lead to the diagnosis of trigeminal neuropathy because it may reflect increased attention to the painful side[4].

The ICHD-3 diagnostic criteria for classic TN from The International Classification of Headache Disorders comprise the following[4]:

A) At least three attacks of unilateral facial pain fulfilling criteria B and C
B) Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
C) Pain has at least three of the following four characteristics:
   - recurring in paroxysmal attacks lasting from a fraction of a second to two minutes
   - severe intensity
   - electric shock-like, shooting, stabbing or sharp in quality
   - at least three attacks precipitated by innocuous stimuli to the affected side of the face (some attacks may be, or appear to be, spontaneous)
D) No clinically evident neurologic deficit
E) Not better accounted for by another ICHD-3 diagnosis

Neuroimaging and trigeminal reflex testing are considered useful for distinguishing patients with classic TN from those with painful trigeminal neuropathy[19]. Neuroimaging with head computed tomography (CT) or magnetic resonance imaging (MRI) may be useful for identifying patients that have a structural lesion as the cause of painful trigeminal neuropathy[19,20]. High-resolution brain MRI and magnetic resonance angiography (MRA) may be useful to identify vascular compression as the etiology of classic TN. Brain MRI

is recommended to rule out causative structural brain lesions in patients with trigeminal sensory loss, patients with bilateral symptoms and patients under the age of 40.

Electrophysiologic trigeminal reflex testing (blink reflex and the masseter inhibitory reflex) is probably useful for distinguishing classic TN from painful trigeminal neuropathy. These tests are usually normal in patients with classic TN. Five studies underline the accuracy of trigeminal reflex testing in the evaluation of TN[19]. One of them was a prospective report[21], whereas the other four studies were retrospective[22-25]. Based on high sensitivity and specificity from these studies, the AAN/EFNS have concluded that abnormal trigeminal reflexes are associated with an increased risk of painful trigeminal neuropathy. In contrast, testing with trigeminal evoked potentials is not useful for making this distinction, as it has been underlined in four studies[19].

The differential diagnosis of classic TN includes short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), clustertic syndrome, jabs and jolts syndrome, and other painful facial neuralgias.

Therapy of Trigeminal Neuralgia

In most patients, the initial treatment of classic TN is pharmacological therapy. Surgical approach is reserved for patients that are refractory to medical therapy. In cases of painful trigeminal neuropathy, no medications have been established as effective but treatment of the underlying condition is recommended. In addition, it is reasonable to treat the pain associated with painful trigeminal neuropathy using the same medications that are employed for classic TN.

In patients with classic TN, carbamazepine is recommended as the initial, first-line therapy (grade 1A). Side effects (drowsiness, dizziness, nausea and vomiting) can appear but are generally manageable, particularly if low doses are prescribed initially with gradual titration. Carbamazepine-induced leukopenia is not uncommon, but it is usually benign. Aplastic anemia is a rare adverse effect, as well as Stevens-Johnson syndrome and/or toxic epidermal necrolysis, especially in Asian patients. The usual carbamazepine starting dose is 100 to 200 mg twice daily. The dose can be increased gradually in increments of 200 mg daily. The typical total maintenance dose is 600 to 800 mg daily, given in two divided doses in the form of tablets and extended release capsules, or four divided doses in the form of oral suspension. The maximum suggested total dose is 1200 mg daily. For patients who do not respond to or tolerate carbamazepine, oxcarbazepine is recommended (grade 1B). It can be started at a total dose of 600 mg daily, given in two divided doses. The dose can be increased in 300-mg increments every third day to a total dose of 1200 to 1800 mg daily. For patients who are refractory to or intolerant of carbamazepine and oxcarbazepine, switching to treatment with baclofen (grade 2C) or lamotrigine as add-on therapy is recommended. In patients who are not taking other anticonvulsants, lamotrigine is typically started at 25 mg daily for the first two weeks, and then increased to 50 mg daily for the next two weeks. The dose is then titrated, increasing by 50 mg daily every one to two weeks. The suggested total dose of 400 mg daily is given in two divided doses. For patients taking an anticonvulsant drug that induces hepatic enzymes (carbamazepine, phenytoin or primidone), the initial dose of lamotrigine is 50 mg once daily, titrating upward to 100 mg once daily at the third week, 200 mg once daily at the fifth week, 300 mg once daily at the sixth week, and 400 mg once daily at the seventh week. For patients taking valproate, the initial dose of lamotrigine is 12.5 to 25 mg every other day, with increases of 25 mg every two weeks to a maximum of 400 mg *per* day. For patients with TN that are refractory to the first- and second-line therapy, an ample of other medications with limited evidence of benefit may be considered. Botulinum toxin injections may be beneficial for patients with medically refractory TN, although data are limited[26]. A systematic review and practice parameter published in 2008 by the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) has concluded that carbamazepine is effective for controlling pain in patients with classic TN, oxcarbazepine is probably effective, and baclofen, lamotrigine and pimozide are possibly effective[19]. There are limited data and uncertain effectiveness regarding other drugs that have been used for TN, including clonazepam, gabapentin, phenytoin, tocainide, tizanidine and valproate. They have shown some evidence of efficacy for TN in small, generally lower-quality controlled trials. The choice among these agents is driven by patient preference, side effect pro-

file, cost, and physician familiarity. Although there are no controlled data regarding the efficacy of opioids in TN specifically, some specialists use opiates in patients with acute exacerbations of pain lasting for days to weeks. Opiates may help make the pain endurable while more effective long-term treatments work out. Their experience suggests partial analgesia with central side effects when these drugs are used alone, as high doses are usually required. Opiates seem to be more effective at lower doses in combination with other neuropathic analgesics.

In patients with TN refractory to medical therapy, it is reasonable to discuss options for surgical therapy using microvascular decompression or ablative procedures (rhizotomy with radiofrequency thermocoagulation, mechanical balloon compression, or chemical (glycerol) injection, radiosurgery, peripheral neurectomy and nerve block). Microvascular decompression is invasive, although the overall mortality and complication rates are low. Ablative procedures are less invasive, but recurrence may be more common. Although surgical therapy for TN is generally well-tolerated, one of the worse complications is painful posttraumatic trigeminal neuropathy (anesthesia dolorosa), a condition characterized by persistent, painful anesthesia or hypesthesia in the denervated region[4]. Few surgical treatments for TN have been studied in controlled trials, and most evidence comes from observational studies[27]. It is considered that microvascular decompression, rhizotomy, and gamma knife radiosurgery are possibly effective in the treatment of TN[19]. Evidence for peripheral neurectomy was considered negative or inconclusive. Indirect comparisons of the findings from different surgical studies suggest that microvascular decompression has a longer duration of pain control than other surgical interventions for TN. The decision to have surgery and the choice among surgical options will be influenced by individual circumstances including patient preference, side effect profile of the techniques available, and expertise of the local center.

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Sažetak

TRIGEMINALNA NEURALGIJA

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Trigeminalna neuralgija jedan je od najčešćih uzroka boli u području lica. Definicija trigeminalne neuralgije podrazumijeva kratkotrajne epizode jednostrane boli nalik elektroškovima s iznenadnim početkom i završetkom u distribuciji jedne ili više grana trigeminalnog živca, a potaknute bezopasnim poticajem. U većini slučajeva trigeminalna neuralgija uzrokovana je pritiskom na korijen trigeminalnog živca. Ovisno o etiologiji, trigeminalna se neuralgija klasificira kao klasična trigeminalna neuralgija odnosno kao bolna trigeminalna neuropatija. Moguće ju je izazvati određenim aktivnostima u području zona okidanja. Dijagnoza trigeminalne neuralgije postavlja se na osnovi dijagnostičkih kriterija, slikovnih prikaza struktura središnjega živčanog sustava te elektrofizioloških testiranja trigeminalnih refleksa. Liječenje klasične trigeminalne neuralgije za većinu bolesnika je farmakološke naravi, dok je operativni pristup rezerviran za bolesnike refraktorne na medikamentnu terapiju te bolesnike s bolnom trigeminalnom neuropatijom.

Ključne riječi: *Trigeminalna neuralgija – terapija; Trigeminalna neuralgija – kirurgija; Središnji živčani sustav – vaskularne anomalije; Refleks treptanja; Karbamazepin*