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# New insight into trigeminal neuralgia

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**Abstract** Trigeminal neuralgia is universally considered the neuropathic facial pain most and best known in medical practice. We propose a short review on trigeminal neuralgia reporting its main clinical aspects, unsolved problems and highlighting differential diagnosis between classical and symptomatic trigeminal neuralgia.

**Key words** Trigeminal nerve • Trigeminal neuralgia • Pain mechanisms

## Introduction

The International Association for the Study of Pain (IASP) defines trigeminal neuralgia (TN) as "a sudden, usually unilateral, brief stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve".

Trigeminal neuralgia may have no apparent cause (idiopathic, essential or classic TN) or be secondary to multiple sclerosis (MS) or benign compressions in the posterior fossa (symptomatic TN). Because the debate about the possible causes of so-called "idiopathic" TN is still open, we believe that the labels and definitions proposed by the International Headache Society (IHS) are the most appropriate: classic TN (with no apparent cause other than vascular compressions) (CTN) and symptomatic TN (pain indistinguishable from that of classical TN but caused by a demonstrable structural lesion other than vascular compressions) (STN) [1–3].

## Clinical aspects

### Sex and side differences

Whereas CTN is more common in women than in men (female-to-male ratio 3:2), there is no sex difference in STN patients [2, 3].

Mean onset age is significantly higher in CTN (63 years) than STN (51 years) [2, 3]. But the "50-year-lower-limit", i.e. the historical notion that patients with an onset age lower than 50 years have symptomatic TN, seems to be hardly tenable [2, 3]. Several patients with CTN did not respect this rule [3]; naturally the proportion is far higher

in the STN group, having an onset age lower than 50 years. A "40-year-lower-limit" is probably a more reliable discriminant [3].

The right-left ratio is 1.5 in CTN and reached 2.4 in STN. Why tumours and demyelinating plaques able to induce TN should be far more frequent on the right side, it is hard to explain [3].

### Symptoms

TN symptoms are unmistakable and usually TN is recognisable by patient history alone. Pain distribution is unilateral (bilateral TN may sometimes occur in MS) and follows the sensory distribution of the trigeminal divisions. Pain, usually referred to as stabbing or electric-shock-like, is brief and paroxysmal, lasting a few seconds, with no pain between paroxysms. Pain may be provoked by stimulating cutaneous or mucous trigeminal territories (trigger zones), regardless of the distribution of the perceived pain. Gently touching the face, washing, shaving, talking, brushing the teeth, chewing, swallowing or even a slight breeze, but never thermal or painful stimuli, can trigger the paroxysms. Adjunctive signs may occur during paroxysms. Pain may provoke brief muscle spasms of the facial muscles, thus producing the tic. Lacrimation is unusual, rhinorrhoea very rare.

With the standard clinical examination no sensory deficits can usually be detected either in CTN or STN, with few exceptions. Usually, when the disease damages a large number of nerve fibres, thus producing hypoaesthesia, patients report, rather than the typical paroxysmal attacks of trigeminal neuralgia, dysaesthesias, or constant pain. There are indeed some reports of sensory changes in TN, but these changes can only be detected with quantitative sensory testing (QST) and as mean differences at group level [4].

## Pathophysiology

### Aetiology

Symptomatic TN can be related to slowly growing tumours, such as cholesteatomas, meningiomas or neurinomas of the eighth nerve, which compress the trigeminal nerve root near the dorsal root entry zone [2, 3]. MS is typically associated with TN (2%–4% of patients with TN) [5]. Neurophysiological, neuroimaging and pathological studies indicate that the demyelinating plaque that provokes TN affects the intrapontine presynaptic primary afferents near the root entry zone [2, 3].

As already anticipated, many investigators refute the term idiopathic TN because they support the view that, when no lesion affecting the trigeminal system can be demonstrated, TN is constantly related to a vascular compression of the trigeminal nerve root by tortuous or aberrant vessels (so-called neurovascular conflict). Microsurgical interventions in the posterior fossa have shown that the compressing vessel is most often the superior cerebellar artery (about 75% of cases); a vein may contribute to compression in about 10% of patients [6]. Further support for this view comes from MRI studies reporting frequent contact between vessels and the trigeminal root.

Nevertheless, other investigators do not support this view, because autopsy findings seem to demonstrate that a vascular compression cannot be the main factor: vascular compression of the trigeminal nerve root is often found (7%–12%) during standard autopsy of patients with no history of TN, and the neurovascular contact often occurs precisely near the root entry zone [7].

### Pain mechanisms

Because the symptoms of classical and symptomatic TN are identical, and the latter is always secondary to an extra-axial or intra-axial lesion near the root entry zone, also in classical TN the primary site of damage is thought to be peripheral, near the root entry zone. Possibly because the nerve fibres change their myelination (from Schwann cells to oligodendroglia) in this site, this area may represent a *locus minoris resistentiae* [8].

Demyelination of the primary afferents, whether produced by MS or chronic compression exerted by a blood vessel or a benign tumour, increases the susceptibility of the nerve fibres to ectopic excitation, ephaptic transmission and high-frequency discharges [9]. Ephaptic transmission between large myelinated, non-nociceptive afferents and nociceptive afferents may explain how innocuous stimuli can trigger the painful paroxysms [10]. That the most frequent trigger zones are perioral would be explained by the large number of afferents innervating this area. This theory entails demyelination of and ectopic activity in Aδ nociceptive afferents. But paroxysmal bursts of ectopic activity arising from large-diameter, non-nociceptive afferents may induce a secondary central dysfunction: a repeated, abnormally high-frequency activity in tactile afferents projecting to WDR neurons in the spinal trigeminal nucleus may change their excitability and induce a persistent derangement that provokes high-frequency signals from WDR neurons and thus pain [11]. Several works supporting this hypothesis have been reported [12]. The

perioral location of the trigger point would in this case be explained by the large representation of the perioral region in the spinal trigeminal nucleus, which makes it the most likely source of paroxysmal activity [12]. In summary, the primary cause of TN must necessarily affect the peripheral afferents, but the pathophysiological mechanism may or may not secondarily involve the brainstem neurons.

## Neurophysiological diagnostic test

According to the recommendations of the International Federation of Clinical Neurophysiology and the European Federation of Neurological Societies [13, 14], the neurophysiologic recording of trigeminal reflexes represents the most useful and reliable test in the laboratory diagnosis of trigeminal pains.

The trigeminal reflexes consist of a series of reflex responses (R1 and R2 components of the blink reflex after electrical stimulation of the ophthalmic division, SP1 and SP2 components of the masseter inhibitory reflex after electrical stimulation of the maxillary or mandibular division, and the jaw jerk to chin taps) that assess function of the trigeminal afferents from all trigeminal territories, as well as the trigeminal central circuits in the midbrain, pons and medulla [13].

Trigeminal reflex testing represents the best tool to differentiate CTN and STN [3]. In the majority of patients with CTN, all reflexes are normal [2, 3, 15]. The short-latency, oligosynaptic reflexes (R1, SP1 and JJ) are more sensitive than the long-latency, polysynaptic reflexes (R2 and SP2) in detecting abnormalities in STN; this finding is supported by several studies [2, 3, 15]. The high sensitivity of the short-latency, Aβ-fibre-mediated reflexes is explained by a great stability and small normal range on one side, and by the greater susceptibility of large-myelinated fibres to compression and demyelination [3].

Because clinical data are by all means insufficient and because the high cost of MRI may limit its use in all patients with TN, trigeminal reflex testing may be used as a reliable screening in all patients with TN. Naturally, the finding of any reflex abnormality or clinical data that are not straightforwardly in favour of CTN by all means require MRI examination.

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