

Pathophysiology of Trigeminal Neuralgia

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Neuropathic pain results from abnormal or inappropriate neural activity and frequently occurs in the absence of obvious organic pathology. Neuropathic pain thought to arise from aberrant regeneration or conduction following injury to the nervous system.

Trigeminal neuralgia (TN) is a sudden and usually unilateral severe brief stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve. It is an excruciating, short-lasting (<2 minutes), unilateral facial pain that may be spontaneous or triggered by gentle, innocuous stimuli.

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 (Evidence of neurovascular compression as causative for trigeminal neuralgia: (1) An aberrant loop of artery, or less commonly vein, is found to be compressing the root entry zone of the trigeminal nerve in 80% to 90% of patients at surgery. (2) The trigeminal nerve is demyelinated next to the compressing vessel. (3) Eliminating the compression by surgery provides long-term relief in most patients. (4) Intraoperative assessments report immediate improvement in trigeminal conduction on decompression. (5) Sensory function recovers after decompression. (6) Other causes, such as compression by tumors or the demyelinating plaques of multiple sclerosis, produce similar lesions of the root entry zone of the trigeminal nerve (Bennetto?L et al.: Trigeminal neuralgia and its management. BMJ 2007;334:201-205))

The plaques of demyelination lead to hyperexcitability of injured afferents, which results in after discharges large enough to result in a non-nociceptive signal being perceived as pain (Bennetto L et al.: Trigeminal neuralgia and its management. BMJ 2007;334:201-205). One theory to explain TN is the one proposed by Devor et al., called the "ignition theory", which can be explained by follows (Devor M, Amir R, Rappaport ZH: Pathophysiology of trigeminal neuralgia: the ignition hypothesis.?Clin J Pain 2002;18:4-13). The triggering of pain in TN may follow innocuous stimuli, a phenomenon that is probably explained by postinjury changes in neuronal function. After nerve injury, there are an increased proportion of A-beta fibers with subthreshold oscillations that ultimately generate ectopic discharges. These produce a transient depolarization and cross-excitation in neighboring passive C-neurons in the same ganglion. Insofar as the subsequent spread of impulses is concerned, it is that the close apposition of demyelinated axons in regions of vascular compression should facilitate the ephaptic transmission of nerve impulses. Ephaptic cross-talk between fibers mediating light touch and those involved in the generation of pain may account for the precipitation of attacks of neuralgia by light tactile stimulation of facial trigger zones (Love S, Coakham HB: Trigeminal neuralgia: pathology and pathogenesis. Brain 2001 Dec;124(Pt 12):2347-60). An objection that has been raised to a central role for demyelination in the development of trigeminal neuralgia relates to the rapid clinical and electrophysiological recovery that usually occurs after surgical decompression of the affected nerve (Leandri M, Eldridge P, Miles J. Recovery of nerve conduction following microvascular decompression for trigeminal neuralgia. Neurology 1998 Dec;51(6):1641-6).

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a sudden and usually unilateral severe brief stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve.

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Etiology

1. **Compression of the trigeminal nerve root**, usually within a few millimeters of entry into the pons, i.e. the root entry zone.
2. **Primary demyelinating disorder.**
3. **Infiltration of nerve root, gasserian ganglion or nerve** by a tumor or amyloid
4. **Non-demyelinating lesions of the pons or medulla** - small infarcts or angiomas in the pons or medulla.
5. **Undetermined.**

1. Compression of the trigeminal nerve root

Aberrant loop of artery or vein.

Saccular aneurysm or AVM.

Vestibular schwannomas.

Meningiomas.

Epidermoid cysts.

Various other cyst and tumors.

Evidence of neurovascular compression as causative for trigeminal neuralgia:

(Bennetto L, Patel NK, Fuller G. BMJ. 2007;334:201-205)

- 1) An aberrant loop of artery, or less commonly vein, is found to be compressing the root entry zone of the trigeminal nerve in 80% to 90% of patients at surgery.
- 2) The trigeminal nerve is demyelinated next to the compressing vessel.
- 3) Eliminating the compression by surgery provides long-term relief in most patients.

Evidence of neurovascular compression as causative for trigeminal neuralgia (cont'):

- 4) Intraoperative assessments report immediate improvement in trigeminal conduction on decompression.
- 5) Sensory function recovers after decompression.
- 6) Other causes, such as compression by tumors or the demyelinating plaques of multiple sclerosis, produce similar lesions of the root entry zone of the trigeminal nerve.

2. Primary demyelinating disorders

Multiple sclerosis. – a plaque of demyelination encompasses the root entry zone of the trigeminal nerve in the pons.

Charcot-Marie-Tooth disease.

3. Infiltrative disorders of the trigeminal nerve root, gasserian ganglion and nerve

Carcinomatous deposits within the nerve root, gasserian ganglion and nerve.

Trigeminal amyloidomas.

4. Non-demyelinating lesions of the pons or medulla

Small infarction or angioma in the brainstem.

5. Familial trigeminal neuralgia

Charcot-Marie-Tooth disease.

Autosomal dominant hypertension and brachydactyly.

Pathology

Compression of the trigeminal nerve root

Hilton et al. (1994) observed focal loss of myelin and close apposition of demyelinated axons.

There were few residual oligodendrocytes and no inflammatory cells.

Immunoelectron microscopy for GFAP revealed that astrocyte processes were largely confined to the periphery of the lesion.

Love et al. (1998) observed a circumscribed zone of chronic demyelination immediately beneath the region of indentation.

Compression of the trigeminal nerve root (cont')

Love et al. (2001) have demonstrated demyelination in several further trigeminal rhizotomy specimens from patients with vascular compression of the nerve root.

Foci of apposition of demyelinated axons and a paucity of glial and inflammatory cells have been relatively consistent ultrastructural features in these biopsies.

Pathophysiology

Hyperactivity or abnormal discharges arising from the gasserian ganglion, the "injured" nerve root and the trigeminal nucleus within the brainstem.

(Moller, 1991; Burchiel, 1993; Pagni 1993; Rappaport and Devor, 1994; Moulin 1998)

There is a good experimental evidence that ectopic impulses can arise from demyelinated axons.

(Rasminsky, 1978; Smith and McDonald, 1980, 1982)

Smith and McDonald demonstrated that

many experimentally demyelinated nerve fibers in the dorsal spinal white matter of the cat were spontaneously active discharging either in small bursts or steadily.

Small deformation of the spinal cord in the region of demyelination not only increased the level of activity in fibers already discharging, but also transiently induced activity in fibers that had previously been electrically silent.

An objection that has been raised to a central role for demyelination in the development of trigeminal neuralgia relates to the rapid clinical and electrophysiological recovery that usually occurs after surgical decompression of the affected nerve.

(Leandri M, Eldridge P, Miles J. Neurology 1998 Dec;51(6):1641-6)

- 1) The rapid relief of clinical symptoms probably reflects the cessation of the ectopic generation of impulses and of their ephaptic spread to adjacent fibers.
- 2) The recovery of conduction probably reflects rapid reversal of conduction block in relatively large-calibre, fast-conducting fibers that are not demyelinated.

Ephaptic cross-talk between fibers mediating light touch and those involved in the generation of pain may account for the precipitation of attacks of neuralgia by light tactile stimulation of facial trigger zones.

(Love S, Coakham HB. Brain 2001 Dec;124(Pt 12):2347-60)

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“Ignition theory”

The triggering of pain in TN may follow innocuous stimuli, a phenomenon that is probably explained by postinjury changes in neuronal function.

After nerve injury, there are an increased proportion of A-beta fibers with subthreshold oscillations that ultimately generate ectopic discharges.

“Ignition theory” (cont’)

These produce a transient depolarization and cross-excitation in neighboring passive C-neurons in the same ganglion.

The close apposition of demyelinated axons in regions of vascular compression should facilitate the ephaptic transmission of nerve impulses.

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(Bennetto L et al. BMJ 2007; 334:201-205)

Causes of TN

1. Demyelination coming from compression of the 5th N by an artery or vein at the root entry zone
2. Demyelination of the junctional area between central & peripheral myelin at root entry zone
3. Ephaptic transmission from large A fibers to nociceptive A δ & C fibers