



## Trigeminal Neuralgia: Issues of Pathogenesis and Treatment (Review)

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**ABSTRACT:** The neurostomatological syndromes are common syndromes among neurological diseases, and their diagnosis and treatment are relevant due to the variety of clinical manifestations and intensity of pain paroxysms. Trigeminal neuralgia is the most common type of prosopalgia. Due to the frequent occurrence of the disease and the very high intensity of pain paroxysms, the difficulty of diagnosis and difficulties in treatment, it is of great scientific and practical importance. Modern methods of treatment of trigeminal neuralgia are conservative, surgical and physiotherapeutic methods, which are prescribed depending on the type of neuralgia. The article provides information about the pathogenesis of trigeminal neuralgia, diagnostic methods and modern treatment methods.

**KEYWORDS:** trigeminal neuralgia, pathogenesis, treatment issues, neurological diseases, causes, fundamental aspects, diagnostic method, permanent cure, intense pain, symptoms, painful affection, acupuncture, neurostomatological syndromes, conservative method, surgical method, physiotherapeutic method.

Trigeminal neuralgia, which is defined as the periodic occurrence of intense pain in a specific location of the trigeminal nerve's innervation, was recognized as a distinct medical condition over 200 years ago. Although a significant amount of time has elapsed, there are still several fundamental aspects of the causes, development, symptoms, and treatment of this disease that necessitate additional comprehensive investigation and research. There is evidence in the literature that the issue of this medical condition was documented during the age of Hippocrates. Hua Tuo, an Ancient Chinese healer during the Han Dynasty, was among the earliest to document trigeminal neuralgia. He attempted to treat a high-ranking imperial official suffering from this condition using acupuncture. Although the pain was temporarily relieved, the treatment did not provide a permanent cure. As a result, Hua Tuo was executed. The initial documentation of this illness in Western literature is credited to the Venetian physician Massa (1550), who provided an account of his examination of a 45-year-old patient experiencing recurring intense pain in the lower right jaw. In the 18th century, Aibge (1756) described paroxysmal symptoms associated with trigeminal neuralgia—a condition characterized by intense pain that occurs during activities such as chewing, talking, and coughing. In 1781, the British physician John Fothergill recognized trigeminal neuralgia as a distinct form of illness in his work “Of a painful affection of the face”, and since then it has been commonly referred to as “The disease of Fothergill”.

The incidence of trigeminal neuralgia is relatively high, with a rate of 30–50 cases per 100,000 individuals. Trigeminal neuralgia has an incidence rate of 2–4 cases per 100,000 individuals, as reported by the World Health Organization (WHO). As per the research conducted by V.E. Grechko et al. in Russia, the incidence rate is 5 instances per 100,000 individuals annually. The reference is from the work of E.V. Balyazina published in 2012. The disorder is most prevalent in women over the age of 40. The authors De Toledo IP, Conti Reus J, Fernandes M, Porporatti AL, Peres MA, Takaschima A, Linhares MN, Guerra E, De Luca Canto G. obtained similar data in their studies, which also showed that older women over 40 years old had the highest prevalence of NTN. Typically, the maxillary and mandibular branches of the trigeminal nerve were predominantly affected in this pathological process. Trigeminal neuralgia primarily affects women over the age of 40 and is defined by the abrupt appearance of paroxysmal pain resembling an electric shock in the innervation area of one or more branches of the trigeminal nerve. The pain typically occurs unilaterally and manifests spontaneously or with minimal stimulation of trigger points in the facial region, such as during tooth cleaning, washing, or biting. The duration of a painful attack ranges from a few seconds to 1–2 minutes. Typically, pain is localized to the right side. The primary manifestation of trigeminal neuralgia is severe lancinating pain. Trigeminal neuralgia (TN) is the predominant and widely recognized form of prosopalgia. In recent decades, there has been extensive discussion over the cause and development of this disease. Multiple researchers hold varying perspectives on the origin of this illness. According to Sicard (1925),



E.K. Sepp (1941), and other researchers, trigeminal neuralgia is caused by the constriction of the bone openings through which the branches of the trigeminal nerve travel. Several contemporary authors, including Liu, Pengfei PhD, MD; Zhong, Wenxiang PhD, MD; Liao, Chenlong PhD, MD; Liu, Ming MD; Zhang, Wenchuan PhD, MD, have the same viewpoint. Their study indicates that primary trigeminal neuralgia can arise without any neurovascular conflict. The researchers analyzed a group of 21 patients diagnosed with TN, in whom no neurovascular conflict was identified during surgical procedures, together with a control group of 30 healthy individuals. The authors argue that, alongside neurovascular conflict, the constricted foramen ovale of the skull may operate as a causative component for NTN in certain patients. According to authors Leriche (1937) and L.G. Erokhin (1966), the trigeminal nerve is more prone to being affected by low temperatures, which may be the reason for trigeminal neuralgia when the face is excessively cooled. Based on the conclusion of research of L.Y. Livshits, it was observed that 70% of patients with TN on the affected side had an elevated position of the temporal bone pyramid. This elevation has the potential to irritate the root of the TN. Later, it was discovered that in individuals without health issues, the right trigeminal depression at the top of the pyramid-shaped temporal bone is somewhat elevated compared to the left one. Domestic literature suggests that stenosis of the mandibular canal on the side of pain, as identified by radiography, is a likely cause of neuralgia of the third branch of the trigeminal nerve. Nevertheless, despite the implementation of surgical interventions targeting the enlargement of the mandibular canal, there persists a significant recurrence incidence of the disease. Based on the findings of G.K. Jamakochina's research in 1968, TNT can be triggered by factors such as drunkenness, infection, facial and head injuries, hypertension and atherosclerosis, metabolic problems, and allergic reactions. Several domestic authors believe that the beginning of the disease could be linked to dental conditions, specifically odontogenic non-tuberculous mycobacteria (NTM) infections. Typically, this refers to a distressing removal of teeth that results in harm to the nerves in the socket, the presence of leftover tooth roots in the sockets, shards of bone, or localized inflammatory conditions such as pulpitis or osteomyelitis. It is important to mention that the pain associated with odontogenic NTN is of moderate intensity and persists for a lengthy duration, without the presence of trigger zones. The idea of "odontogenic NTN" is not present in foreign literature.

In 1934, the American neurosurgeon W. Dandy discovered that in 60% of trigeminal neuralgia cases, the root cause is a conflict between the cranial nerve (CTN) and nearby blood vessels in the cerebellum (namely, the superior cerebellar artery, posterior inferior cerebellar artery, and anterior inferior cerebellar artery). In 1956, W. Gardner and V. Miclos were the pioneers of a surgical procedure known as decompression of the TN root. They also provided a detailed description of the compression of the trigeminal nerve root by the cerebellar arteries. The notion of vascular compression of the CTN as a source of paroxysmal facial pain was established. Subsequently, P. Jannetta substantiated this notion with a significant number of triumphant microvascular decompression (MVD) surgeries on the trigeminal nerve root.

Several contemporary researchers hold a consensus on this matter. Based on the authors' observations, classical trigeminal neuralgia is caused by a neurovascular conflict between the artery and the nerve root. This conflict arises due to the shortening of the arachnoid strings. Inflammatory processes such as otitis, sinusitis, and carious teeth can lead to the formation of rough arachnoid adhesions. Nociceptive stimulation of the pulsatile artery in patients with a proximal arterial loop to the nerve root results in demyelination of the trigeminal nerve root. Over time, atherosclerosis causes these processes to become more severe, resulting in thickening of the arterial walls and the formation of arachnoid threads. However, currently, the idea of symptomatic trigeminal neuralgia caused by tumors in the cerebellopontine angle, arachnoid cysts, saccular aneurysms, multiple sclerosis, Arnold-Chiari syndrome, and other conditions is still maintained.

The authors Love S., Hilton D.A., and Coakham H.B. conducted research that revealed the presence of demyelination in the area where the CTN is compressed by the vessel. This information is supported by sources. It merely recorded the specific location where the CTN made contact with the neighboring vessel. Consequently, the authors started to regard neurovascular conflict as the fundamental cause of the pathophysiology of NTN. Subsequently, at the location of the neurovascular conflict, ephapses (artificial synapses) were discovered, which are instances of a short circuit that irritates the afferent fibers. This phenomenon stimulates the abnormal creation and transmission of spontaneous impulses in a non-adjacent manner. Following the MVD operation, the neurovascular conflict is resolved, leading to the complete disappearance of all symptoms associated with NTN. This is achieved by separating the demyelinated fibers from the pulsing artery, which stops the transmission of spontaneous ephaptic impulses. Other writers, such as Balyazina E.V., Stepanchenko A.V., Broggi G., Ferroli P., Franzini A., also agree that the pathophysiology of NTN is based on the neurovascular conflict and the resulting ectopic focus with ephaptic propagation of spontaneous nerve impulses.



The works of Ustyujantsev N.E., Chetvernykh V.A., and Balandina I.A. (2006) discuss the involvement of demyelination in the zone of neurovascular conflict. According to their research, the presence of core myelin in the first part of the trigeminal nerve root is a feature that influences the development of trigeminal neuralgia. This central myelin is more susceptible to demyelination compared to the myelin of peripheral nerves.

Based on the research conducted by V.A. Karlov (2002) and other authors (Puzin M.N., 2006, Woda A., 2005), the compression of the trigeminal nerve in the peripheral region causes a disruption in the flow of afferent impulses. This disruption leads to the development of a paroxysmal type algogenic system in the central structures.

Foreign scholars have put up a contemporary perspective on the pathophysiology of NTN, suggesting the bioresonance hypothesis as an explanation. The core of this idea posits that trigeminal resonance occurs when the vibration frequency of the surrounding structures aligns with the frequency of the trigeminal nerve. Bioresonance adversely affects the trigeminal nerve fibers, resulting in the interruption of impulse transmission, finally causing facial pain. The authors propose that by adhering to the bioresonance concept, novel non-invasive approaches for the treatment or potential eradication of TN can be devised.

The trigeminal nerve system disease is characterized by episodes of intense and agonizing shooting pain in the region innervated by one of the branches of the trigeminal nerve. As the condition advances, a sudden and intense episode of pain can spread from one area of the nerve supply of the branches of the trigeminal nerve to the areas of the nerve supply of its other branches. During an attack, individuals may experience vegetative symptoms such as excessive tearing, runny nose, excessive sweating, and increased blood flow to certain areas of the body. During an excruciating episode, individuals refrain from vocalizing or shedding tears, instead experiencing a state of immobility. Occasionally, patients experience a distressing facial expression known as a “pain tic”, during which they forcefully apply pressure to the painful area of their face with their hands. Even gentle contact with the face can elicit a subsequent episode of pain. The attack typically lasts for a brief period, ranging from a few seconds to 1–2 minutes. Occasionally, patients assert that they experience “persistent pain” and frequently deceive the doctor. However, by conducting a thorough interrogation of the patient, it is feasible to ascertain the existence of brief periods of relief between episodes. NTN is distinguished by the existence of trigger zones located on the facial skin and within the mouth cavity. Even minimal irritation of these zones can induce a distressing paroxysm of pain. Trigger zones are commonly seen on the wing of the nose, the inner corner of the eye, the nasolabial fold, and the chin. Painful attacks are triggered by activities such as cleaning, talking, eating, brushing teeth, shaving, or merely moving the lower jaw. Trigger zones may cease to exist with long-lasting remission of the condition. During intense pain episodes, there may be involuntary contractions of the facial muscles, although the occurrence of this symptom is quite uncommon thanks to the use of anticonvulsant medications.

Status neuralgicus is the most severe form of trigeminal neuralgia. In this scenario, the assault becomes protracted. Nevertheless, by conducting thorough inquiries with the patient, it is feasible to determine the sporadic nature of the pain, which bears resemblance to electric shocks, as well as the existence of intervals between each painful episode. This is a sequence of assaults characterized by a remarkably brief interictal interval, in which one attack commences before the previous one has a chance to fully develop. It is imperative to establish “trigger” zones on the patient’s face following the cessation of the neuralgic state. During the interval between attacks, individuals experience behavioral responses that are influenced by the anxiety of the trigeminal neuralgia attacks recurring. Trigeminal neuralgia is categorized into primary (idiopathic, classical) and secondary (symptomatic) forms. Recent research has confirmed that the primary etiology of classical trigeminal neuralgia (TN) is a neurovascular conflict resulting from the compression of the TN root by a pathologically twisted loop of the superior cerebellar artery at the point where the nerve root enters the brainstem. This compression accounts for over 80% of TN cases. Symptomatic trigeminal neuralgia is a condition characterized by neuralgia that is not caused by vascular compression, but rather by other degenerative processes. This could potentially indicate the initiation of a demyelinating disorder, such as multiple sclerosis. NTN can be caused by various factors such as tumors located in the trunk, base of the skull, or cerebellopontine angle, as well as trauma, inflammatory lesions in the paranasal sinuses or temporomandibular joint, and traumatic tooth extraction. Carbamazepine (finlepsin), initially suggested by S. Blom in 1963, is currently the most efficacious medication for managing trigeminal neuralgia. The therapeutic efficacy of carbamazepine stems from its ability to inhibit sodium channels in hyperactive neurons, as well as reduce the impact of excitatory neurotransmitters and enhance inhibitory GABAergic processes. Consequently, it effectively hinders the propagation of pain signals. Extended administration of this medication leads to a reduction in its efficacy, and based on certain observations, pain worsens, hence requiring an escalation in dosage. Prolonged administration of high doses of carbamazepine may result in adverse effects such as nausea,



sleepiness, ataxia, headache, and dizziness. Presently, gabapentin (Neurontin) is extensively utilized both internationally and domestically. This medication, akin to carbamazepine, functions as an anticonvulsant and exerts an analgesic impact, comparable to GABAergic drugs. Hence, gabapentin demonstrates efficacy in managing neuropathic pain in individuals, encompassing both paroxysmal and non-paroxysmal trigeminal prosopalgia. The recommended daily dosage of gabapentin can vary from 300 to 1500 mg, with a minimum frequency of administration of three times per day. It is also feasible to administer higher doses (the maximum daily dosage is 3600 mg). Subsequently, the dosage ought to be systematically decreased. Abrupt cessation of the medication can trigger a worsening of the pain syndrome. In contrast to carbamazepine, this medication can be taken for an extended period of time due to its high tolerability and few occurrence of side effects.

Several authors argue that in the case of trigeminal neuralgia originating from the periphery, the treatment strategy should incorporate nonsteroidal anti-inflammatory medications (NSAIDs) and non-narcotic analgesics.

As stated by M.N. Puzina (2013), solely administering pain relief medication without implementing treatment to enhance the anatomical and functional condition of the nerve fiber would ultimately result in a decline in the patient's well-being and the development of sensory and vegetative-trophic diseases. Therefore, apart from anticonvulsants, antidepressants, and NSAIDs, it is imperative to administer neurotrophic and neurometabolic medications, along with antioxidants and antihypoxants.

During the 1960s to 1980s, when traditional treatment procedures proved to be futile, the technique of alcoholization of a specific branch of the trigeminal nerve was commonly employed. The concept of alcoholization of nerves was initially introduced by Schlosser in 1903 (C. Schlosser, 1903). In 1909, V.I. Razumovsky pioneered the use of alcoholization of the Gasserian ganglion as a therapeutic method for trigeminal neuralgia. The technique relies on the ability of concentrated alcohol solutions to induce coagulation in biological tissue. Alcohol use leads to a condition called aseptic necrosis, characterized by the formation of scar tissue. Nerve tissue loss results in chemical denervation of a specific region. Presently, this strategy is rarely employed. To execute this procedure, employ a solution consisting of 80% ethyl alcohol and 20% novocaine, diluted in a ratio of 1:4. Preliminary conduction anesthesia is recommended, as the administration of local anesthetic to the nerves diminishes the impact of alcohol. The remedy is administered into the egress sites of the agonizing division of the trigeminal nerve. Following successful alcoholization, the painful attacks diminish within a few hours, although in certain instances they may not completely resolve until 10–12 days later. The length of the effects of alcoholization typically lasts approximately one year, while there are occasionally shorter durations ranging from 3 to 6 months. Although this operation is highly unpleasant, the majority of patients consented to have it as a result of the excruciating TN attacks they had.

If conservative therapy proves to be ineffective, surgical treatment techniques are employed. Presently, the trigeminal nerve undergoes several surgical procedures, including high-frequency selective rhizotomy, retrogasserian rhizotomy with glycerol, balloon microcompression, microvascular decompression of the trigeminal nerve root, open or stereotactic trigeminal nucleotomectomy, and epidural neurostimulation of the motor cortex. Two often used and highly efficient procedures are high-frequency selective rhizotomy and microvascular decompression of the trigeminal nerve root. Other surgical techniques have not gained popularity due to their exorbitant cost, requirement for specialized equipment, and inferior effectiveness when compared to the aforementioned methods.

The surgical procedure known as microvascular decompression of the trigeminal nerve root, pioneered by P. Jannetta in 1977, is now widely practiced. This procedure is quite efficient. Nevertheless, MVD can be quite distressing, resulting in brain stem infarction in approximately 1.5–3% of patients. Furthermore, it should be noted that neurovascular conflict does not always serve as the underlying cause of NTN. A highly efficient surgical technique is high-frequency selective rhizotomy of the trigeminal nerve, with a success rate of 92%. Nevertheless, the therapeutic efficacy after a duration of 5 years is observed in only 57.7% of patients. However, this procedure remains prevalent due to its minimal occurrence of significant problems.

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