

Aetiology and Pathogenesis of Trigeminal Neuralgia: a Comprehensive Review

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ABSTRACT

Objectives: The aim of present paper was to discuss issues related to trigeminal neuralgia with strong emphasis on the aetiology and pathogenesis of this problem.

Material and Methods: An electronic search of 5 databases (1965 - Oct 2012) and a hand search of peer-reviewed journals for relevant articles were performed. In addition, experience acquired from treating 3263 patients in the Department of Maxillofacial Surgery, Lithuanian University of Health Sciences, were also summarized.

Results: Generally, aetiological factors can be classified into 3 most popular theories that were based on: 1) Related to other disease, 2) Direct injury to the trigeminal nerve, and 3) Propagates the polyetiologic origin of the disease. In addition, two pathogenesis mechanisms of trigeminal neuralgia were proposed. First: the peripheral pathogenetic mechanism that is often induced by progressive dystrophy around the peripheral branches of the trigeminal nerve. Second, central pathogenetic mechanism which often triggered by peripheral pathogen that causes long-lasting afferent impulsion and the formation of a stable pathologic paroxysmal type irritation focus on the central nerve system (CNS).

Conclusions: Patients with susceptible trigeminal neuralgia should be examined carefully by specialists who have expertise in assessing and diagnosing of possible pathological processes and be able to eliminate the contributing factors so the trigeminal neuralgia can be properly managed.

Keywords: trigeminal neuralgia; trigeminal ganglion; trigeminal nerve; trigeminal nuclei.

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INTRODUCTION

Trigeminal neuralgia (TN) is one of the most common diseases of cranial nerves. Furthermore, it is the most frequently diagnosed form of facial pain with a prevalence of 4 per 100,000 in the general population [1]. This condition has been known since ancient times, having been described by Arateus in the first century A.D. [2]. John Locke, in 1677 identified the major clinical features of TN [3]. French physician Nicolaus Andre in 1756 gave the name “*tic douloureux*” because of the facial spasms that would accompany the attacks [4]. English physician John Fothergill in 1773 defined the major clinical features of TN [5]. Since that time TN has been investigated extensively by scientists and clinicians from different fields: pathophysiologicals, neuromorphologists, dentists, neurologists, neurosurgeons, oculists, and psychiatrists. Unfortunately many problems associated with TN remain unresolved.

MATERIAL AND METHODS

This article reviewed the literature related to the etiologies and pathogenesis of TN. Due to enormous literature available it is impossible to review and cite all papers, hence we cited literature when appropriate. In addition, we have added our experience/views acquired from treating 3263 patients in the Department of Maxillofacial Surgery, Lithuanian University of Health Sciences.

Aetiology of trigeminal neuralgia (TN)

There are many different opinions concerning TN aetiology, however some of them are controversial and suffer from a lack of objective evidence. Such are aetiologic theories as endogenous and exogenous

intoxication [6], temporomandibular joint pathology [7-9] and high position of the petrous pyramid apex of the temporal bone [10].

Currently, there are three most popular TN aetiologic theories. First theory is based on diseases-related, second is direct trauma to the nerve and the third theory propagates the polyetiologic origin of the disease (Table 1). In reality, for most patients with TN, there is no identifiable cause [11].

Because patients suffering from TN often have vascular diseases such as atherosclerosis, arterial hypertonia, some authors suggested vascular theory of TN aetiology. They found morphological and functional disturbance in blood vessels supplying the peripheral [12] and central [13,14] part of trigeminal nerve system (TNS). However, there is no evidence that supports direct relation of blood vessels pathology to TN. Smoliar [15] investigated blood vessels supplying trigeminal nerve for a large number of cadavers who died because of cardiovascular disease. Although, clear morphological changes were noted in the blood vessels but no TN was diagnosed. That’s why we prefer to support the concept [16,17] that organic or functional changes of blood vessels supplying TNS can not be the primary cause of TN, however, they can make influence on pathogenesis of the disease.

Some authors have suggested the importance of multiple sclerosis in TN aetiology [17-26]. However, others have disputed this link because TN is reported to occur only in 0.9% to 4.5% of patients that had multiple sclerosis [27-29]. Conversely, 1.7% to 15% of patients diagnosed with TN had developed of multiple sclerosis [1,27,28,30,31]. This is further supported by Rusthon and Olfason [27], who examined 3880 patients with multiple sclerosis and 1735 patients with TN and found only 35 patients had both diseases. In patients with both TN and multiple sclerosis, TN is the first symptom of multiple sclerosis in 9% - 14% patients [29,30]. After treatment of 3263 patients with diagnosed TN in our department, we found that 46 (1.4%) of patients suffered from rheumatism,

Table 1. Three most popular theories of trigeminal neuralgia aetiology

Diseases related	Direct injury to the trigeminal nerve		Polyetiologic origin
	Peripheral part of TNS	Central part of TNS	
Vascular diseases, multiple sclerosis, diabetes mellitus, rheumatism and others.	<p>“Allergic hypothesis” due to odontogenic inflammatory diseases, otolaryngological pathology, getting cold and others.</p> <p>“Compression syndrome hypothesis” due to the narrowing of the osseous canals, trauma.</p>	<p>“Neurovascular compression hypothesis” at the root entry zone due to arteriovenous malformation, vestibular schwannomas, meningiomas, epidermoid cysts, tuberculomas, various other cysts and tumours, aneurysm, vessels aggregation and occlusion due to arachnoiditis and others.</p>	All possible aetiological factors that can affect TNS and evoke demyelination and dystrophy.

TNS = trigeminal nerve system.

only 7 (0.23%) from multiple sclerosis and 7 (0.23%) from malaria. Therefore, there is insufficient evidence to support that multiple sclerosis can be a primary cause of TN.

Urban et al. [32] investigated the frequency of subclinical trigeminal and facial nerve involvement in 40 patients with diabetes mellitus (DM) and without clinical signs of cranial nerve lesions. Sixty percent of the patients had distal symmetric sensory polyneuropathy that was confirmed by nerve conduction studies. An electrophysiological study indicated that DM could often affect trigeminal nerve function. Finestone et al. [33] reported that among a series of 40 patients with TN, 19 patients (48%) had DM. Collis et al. [34] reviewed 30 patients with typical TN and found elevated blood sugar (using glucose tolerance tests) in 10 patients. Consequently, DM can be a causative factor for TN.

One of the local aetiological TN factors discussed in the literature is the history of odontogenic inflammatory diseases. Some authors declare that a variety of odontogenic inflammatory diseases can be a cause of TN development [35-39]. In contrast, Kerr [16] deny the odontogenic origin of TN.

There seem to be a consensus between different authors concerning the importance of the otolaryngological pathology in TN aetiology. Chronic inflammation of maxillary sinuses and other ear, nose and throat (ENT) inflammatory disorders can be a direct cause of TN development [40-43]. Consequently, 89.5% of our treated patients suffered from inflammatory diseases in the maxillofacial region or had history of inflammatory disorders of ear, nose and throat region. Most of them suffered from chronic maxillary sinusitis, periodontitis, periostitis, phlegmone, and dental cysts.

Some authors suggest that the cause of the TN can be related to the compression syndrome, and the most popular is neurovascular compression hypothesis [44-56]. Neurovascular compression at the root entry zone can be evoked by an arteriovenous malformation [57-60]. A wide range of other compressive lesions can also cause TN. These include vestibular schwannomas [61,62],

meningiomas [63-66], epidermoid cysts [67-70], tuberculomas [71-72] and various other cysts and tumours [66,67,70,73-77]. TN can be evoked also by presence of aneurysm [78,79], vessels aggregation and occlusion due to arachnoiditis [80]. Compression of the trigeminal nerve root may be mediated by the tumour itself, by an interposed blood vessel or by distortion of the contents of the posterior fossa with displacement of the nerve root against a blood vessel or the skull base. On the other hand, many patients with TN do not have a culprit vessel [81]. In several reported cases, the neuralgia was contralateral to the side of the mass lesion [63,74,75]. Furthermore, there is some evidence contrary to the neurovascular compression hypothesis. For example, in two studies on cadavers without TN, neurovascular contact was observed in 13 - 32% of cadavers with neurovascular compression ranging from 8 to 10% [45,82]. Similarly, in one MRI study that examined 170 trigeminal nerves in 85 non-TN patients, 79 nerves (46%) had some point of contact with a vascular structure, 24 (14%) had cisternae contact, 52 (30%) had contact at the root entry zone, and remaining 3 (2%) had an actual deformity of the root entry zone [84]. On the contrary, in non-TN patients, vascular contact with trigeminal nerve occurred only in 7% [84] and 8% [85] of cases. Although the vascular compression theory is popular, it cannot account for all phenomena associated with the TN [86].

As early as 1925, Sicard [87] proposed a hypothesis according to which TN may develop due to the narrowing of the osseous canals transmitting the corresponding nerve branches. We analyzed the maxillary (n = 359) and mandibular (n = 239) canals using the orthopantomograms in patients suffering from TN. The analysis revealed that 29.2% of patients had a narrowed infraorbital canal (Figure 1) and 31.4% mandibular canal (Figure 2) transmitting the branches of the affected side of trigeminal nerve. Doppler ultrasound examination indicated reduced blood flow

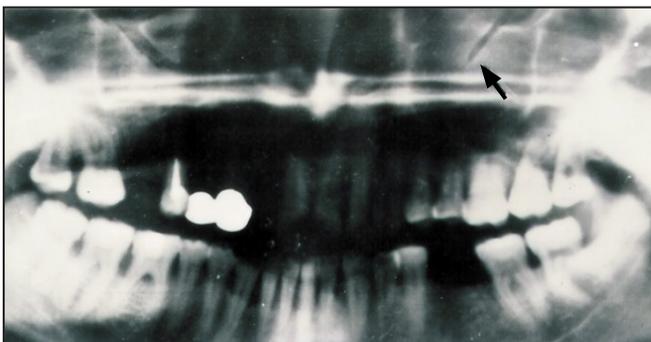


Figure 1. An orthopantomograph of a patient with infraorbital neuralgia: a narrowed left infraorbital canal (arrow).



Figure 2. An orthopantomograph of a patient with a third-branch trigeminal neuralgia: a narrowed left mandibular canal in the region of a second molar.

velocity in the infraorbital (asymmetry coefficient = 2.23) and inferior alveolar (asymmetry coefficient = 2.33) arteries on the affected side in comparison with intact side arteries, confirmed radiological findings and presence of compression mechanism.

“Allergic hypothesis” of TN aetiology has also been proposed [88-91]. However, there is only indirect evidence that supports allergy might cause TN. This is often due to unexpected and irregular rise of the clinical symptoms, remissions and recurrences, sensitive to the provocative endogenous and exogenous factors, and finally the increased serum levels of histamine. We noted that under the influence of various damaging factors, such as getting cold, tonsillitis, chronic rhinitis, maxillary sinusitis, and chronic inflammation existed in the maxillofacial region can trigger local immune response. As a result, the amount of IgE secretion increases. The degranulating mast cells release biologically active substances, such as histamine, serotonin and others, into the intercellular space. Hence, histamine release and accumulation in the trigeminal nerve during a local allergic reaction plays an important role in the pathogenesis of neuralgia [92]. Furthermore, this process is confirmed by the data of our morphologic trigeminal nerve examination and histamine levels in peripheral blood and saliva investigations [92]. Thus, microscopic immuno luminescent investigation of peripheral part of trigeminal nerve rhizotomy specimens from the TN patients revealed many degranulating mast cells and conglomerates of immune complexes of various sizes (Figure 3A). During remission, mast cells were absent in the resected nerve trunks. Many disorderly scattered granules of different size and their accumulations were found in the internal and external epineurium of the trunks (Figure 3B). At the same time we have determined an increase of histamine level in the blood and saliva during the acute period of TN. Consequently the levels of histamine in blood were:

$3.879 \pm 0.342 \mu\text{mol/l}$ (mean \pm standard deviation) and saliva $4.554 \pm 0.513 \mu\text{mol/l}$ were statistically significantly higher ($P < 0.05$) when compared to the healthy individuals where the histamine level in the blood was $0.558 \pm 0.063 \mu\text{mol/l}$ and in saliva $0.522 \pm 0.001 \mu\text{mol/l}$. Moreover, the concentration of histamine level in the saliva of the TN patients was significantly higher ($P < 0.001$) than in their blood. This fact indicates that histamine is released locally for those patients.

Jia and Li [93], explored the non-invasive methods to treat TN and as a result they also proposed a new hypothesis on the pathogenesis of TN - bioresonance. The bioresonance hypothesis states when the vibration frequency of a structure surrounding the trigeminal nerve becomes close to its natural frequency, the resonance of the trigeminal nerve occurs. The bioresonance can damage trigeminal nerve fibers and lead to the abnormal transmission of the impulse, which may finally result in facial pain.

Devor et al. [94] raised the ignition hypothesis of TN that is based on recent advances in the understanding of abnormal electrical behavior in injured sensory neurons and the findings from histopathologic observations obtained from patients with TN, who are undergoing microvascular decompression surgery. According to this hypothesis, TN results from specific abnormalities of trigeminal afferent neurons in the trigeminal root or ganglion. Injury renders axons and axotomized somata hyperexcitable. The hyperexcitable afferents, in turn, give rise to pain paroxysms as a result of synchronized after discharge activity. Nonetheless, more evidences are needed to further verify this hypothesis.

Pathogenesis and pathomorphology

Pathogenesis of TN is one of the most complicated, unclear and extensively debated topics in medicine. Many theories and hypotheses concerning peripheral

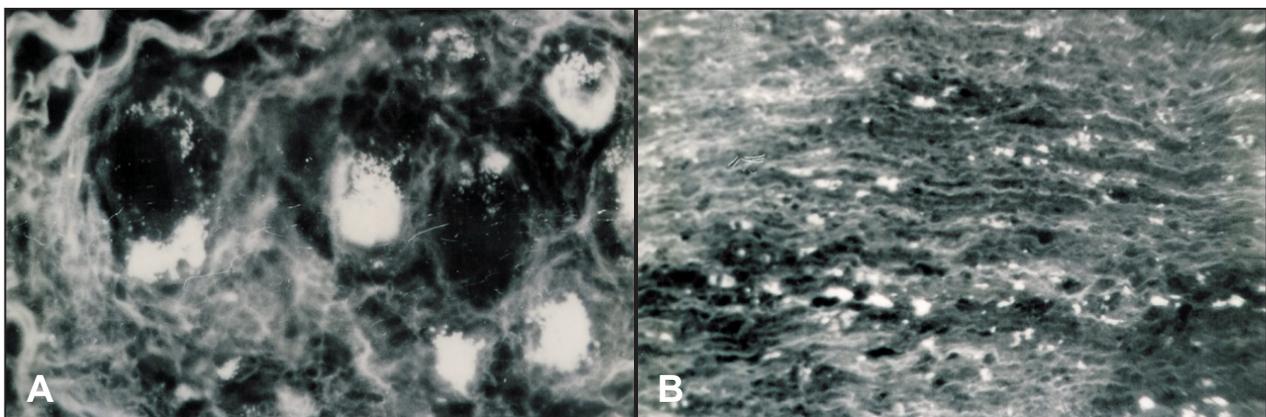


Figure 3. Fluorescent photomicrograph of an affected peripheral branch of the compromised nerve: A = Acute stage of TN. Mast cell degranulation. Magnification x300. B = Remission period of TN. Granules of mast cells. Magnification x300.

and central pathogenetic mechanisms existed today. At the beginning TN was characterized as functional disease because there was no evidence of organic (morphologic) changes in trigeminal nerve. However, more than 40 years ago, Kerr [16] examined histologically the rhizotomy specimens from the TN patients and found morphological nerve changes existed typical for interstitial neuritis, neural fibers demyelization, and perineural and endoneural sclerosis. For many years, the most popular theory of peripheral mechanism of the disease was “short connection” theory proposed by Dott in 1951 [103]. According to this theory, TN attack starts from demyelinated axons interconnection, spontaneous activity and ectopic impulses generation. Later published data addressing morphological changes occurred not only in peripheral branches but also in central structures of trigeminal nerve [95-98]. Central mechanisms theory assumes that TN starts due to thalamus [99], nuclei of trigeminal nerve [100], encephalic trunk or cerebral cortex injury [101,102]. However, there is a lack of objective evidence supporting the theories of central and peripheral TN pathogenetic mechanism. Furthermore, such theories are not clarifying symptoms and clinical course of the disease. More works in this area are needed.

Williams [104] was first to describe TN attack as multineuronal reflex, which involves the following structures: trigeminal and facial nerves systems, formation reticularis, diencephalon nucleus and cortex of the brain. Some researchers [101,105] have indicated that afferent physiologic stimulation of trigeminal nerve receptors can induce paroxysmal excitation focus on central structures that generates efferent impulses to the peripheries. However two main questions remain unanswered: what structures are generating long prethreshold impulses from peripheries? And what central structures of the trigeminal nerve are responding by paroxysmal type discharge?

The morphological data obtained from rhizotomy specimens collected from the 212 TN patients [89] was designed to answer the first question and to explain the peripheral pathology mechanism of the TN. The dystrophy of neural fibers is prevalent in the acute period of neuralgia. In contrast, proliferation and reparation is starting in subacute period: number of neural fibers with signs of dystrophy is decreasing and fibers with signs of regeneration increasing (Figure 4A). Connective tissue is replacing destroyed neural fibers. Consequently the conditions for nerve regeneration are worsening after each exacerbation of the disease (Figure 4B). These include but not limited to sclerotic changes of the nerve, hypoxia due to insufficient blood supply is developing and metabolic products are accumulating. Peripheral nerve branches are first affected by dystrophic changes. Nerve dystrophy is developing retrogradially and finally all peripheral branches of trigeminal nerve system are involved. This is often referred to “vicious cycle”. Because the functional and anatomical connectivity between neural fibers of main trigeminal nerve branches and their surrounding sheaths and blood vessels, when one get affected, it affects the others too and vice versa. With progressing of the disease, the dystrophy is developing not only in peripheral branch of trigeminal nerve but also in intracranial nerve part. Injury of “vicious circle” and dystrophy of the TNS can be evoked by mentioned above different aetiological factors.

It was demonstrated that allergic-immune reaction of trigeminal nerve peripheral branches with expressed mast cells degranulation could be other cause of the TNS dystrophy. Biologically active agents like histamine, serotonin, heparin, bradikinin, and others are migrating into intracellular spaces during mast cells degranulation [106-107]. Mast cells degranulation evokes local immediate hyperergic reaction [108-109]. This reaction starts when immunoglobulines,

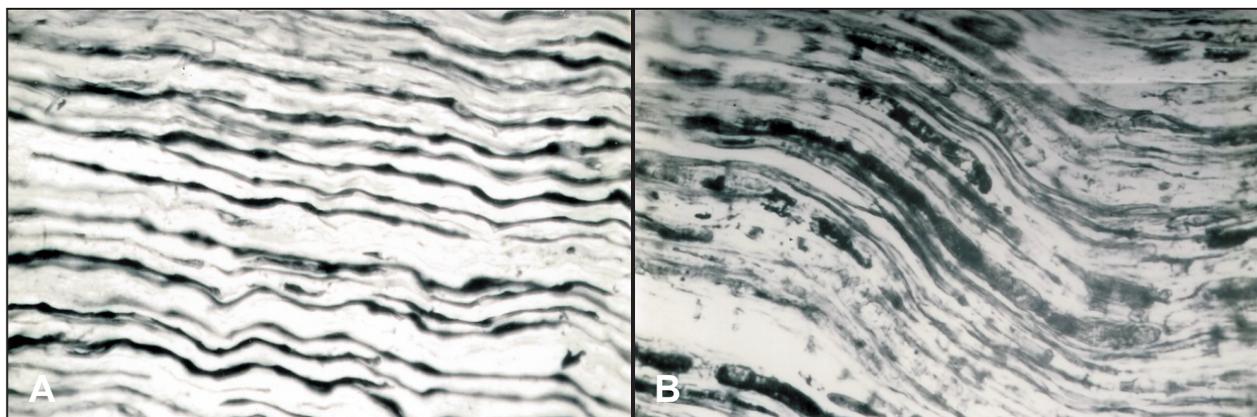


Figure 4. Illustrated an affected peripheral branch of the compromised trigeminal nerve. This sample was taken during an acute period of trigeminal neuralgia from a patient with at least three-year-long history of the TN (Bielschowsky-Gross silver impregnation; magnification x240): A = Part of thick nerve fibers with nodular thickenings; B = Vacuolisation and disintegration of nerve fibers.

mainly IgE, are fixing to specific receptors of mast cells [110-111]. Cells producing IgE are localized in lymphoid tissue, ears, nose, oral cavity and upper respiratory tract mucous membrane [112]. In presence of some diseases, concentration of IgE is increasing considerably, for example in case of ear, nose and throat inflammatory disease it increases 3 times and in nasal polyps 5 - 6 times [113]. Therefore, the amount of IgE-antibodies is increasing when individual is suffering from inflammatory diseases noted in the maxillofacial region (e.g., face, nose, maxillary sinus, tonsil etc) as it was shown in case of TN (Figures 5 and 6).

Furthermore, histamine level increases significantly ($P < 0.05$) in acute TN period [114]. Histamine is an active regulator of neural structures functional activity including pain reaction mediation [115]. It has been shown that TNS is chemoreceptor trigger zone of histamine [89]. This may explain why histamine released during immediate local immune reaction and accumulated in trigeminal nerve during TN pathogenesis. Neurovascular bundles of trigeminal nerve are localized in osseous canals. Hence, edema of peripheral nerves evoked by immune inflammation often results in manifestation of "tunnel syndrome". It means that the osseous canals will become narrower to compress the nerve that can lead to TN.

What we have discussed here are examples to illustrate that peripheral mechanism of TN pathogenesis. This theory is based on dystrophy of progressing TNS, which evokes long-lasting prethreshold afferent pathologic impulsion. Studies have shown that ectopic impulses can arise from demyelinated axons [116,117]. However, this hypothesis is not in coincidence with clinical signs of short paroxysms. Maybe, there are other pathologic mechanisms of TN, which might evoke pain paroxysms. Karlov [118] proposed the "Central pathogenesis theory" since TNS conjunction to the central structure is capable to exert inhibitory action upon the segmental and suprasegmental formations. This inhibitory action is capable to form a stable irritation focus of paroxysmal type located in the CNS. This central pathogenesis theory was confirmed further by Smith and McDonald [117]. They proved experimentally that demyelination could be the source of ectopic impulses that evokes functional disturbances and pain dominant focus formation in the segmental apparatus of brain stem and in suprasegmental brain centers. Thus, progressive dystrophy in the TNS stimulates the central pathogenesis mechanism of neuralgia. Undoubtedly, there should be appropriate conditions in the body for these pathogenetic mechanisms to manifest. Atherosclerosis and other age related alterations weaken the state of the neurohumoral barrier complex, on which the reliability of adaptive and compensatory reactions depends. Therefore, more

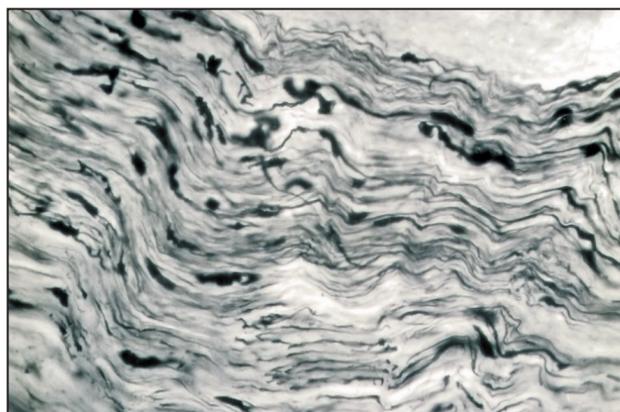


Figure 5. Pathologic regeneration shown in a specimen of an affected peripheral branch of the compromised nerve taken during a remission period of TN (Bielschowsky-Gross silver impregnation; magnification x150).

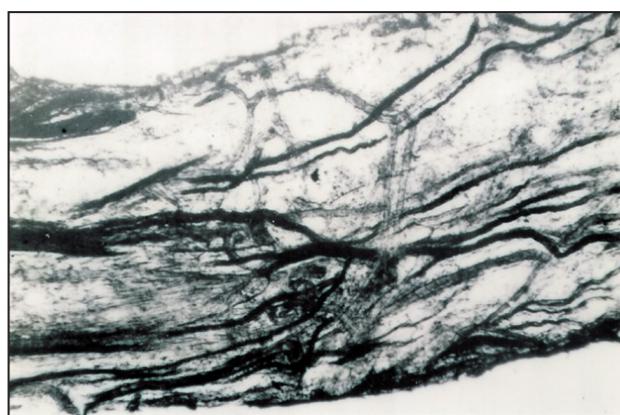


Figure 6. Increased amount of connective tissue and decreased number of nerve fibers in an affected peripheral branch of the compromised nerve. The sample was taken from a patient with a more than ten-year-long history of TN (Silver impregnation; magnification x75).

favorable conditions develop for the formation of the pathogenetic mechanisms of TN in the elderly and in older individuals affected by the local aetiologic factors. We support mechanism of TN where a long-lasting afferent pathologic impulsion from periphery is forming "focus" or "generator" in CNS which is independent of afferent impulsion. Impulses from trigger zones are passing to the main neurons of "generator" and activating them. "Generator" is activating reticulate, mesencephalon structures, limbic nuclei, limbic system, and brain cortex and finally pathologic algogenic system is forming. Figure 7 describes the two most common mechanisms of TN.

CONCLUSIONS

The peripheral pathogenetic mechanism of trigeminal neuralgia is induced by progressive dystrophy in the peripheral branches of the trigeminal nerve

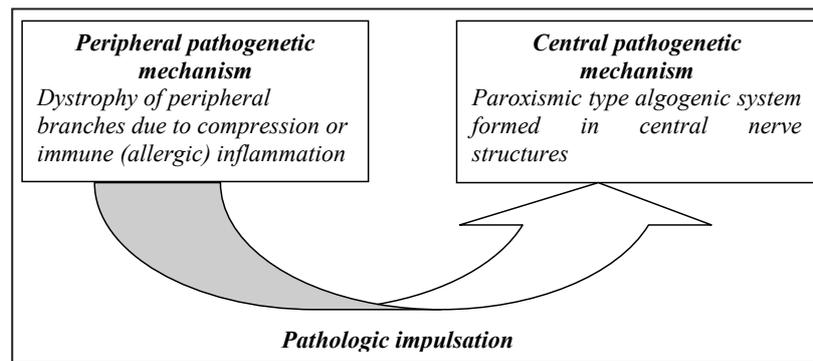


Figure 7. Pathogenetic scheme of TN.

which can be evoked by the compression syndrome (neurovascular compression due to neoplasms, narrowed bone canals and others) or allergic-immune reaction (mast cell degranulation and histamine release). This predetermines long-lasting afferent impulsion and the formation of a central pathogenetic mechanism (a stable pathologic paroxysmal type irritation focus in the central nerve system). Patients with suspicious trigeminal neuralgia should be examined carefully by specialists who have expertise in assessing and diagnosing of possible pathological processes

and be able to eliminate the contributing factors so the trigeminal neuralgia can be properly managed.

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The authors report no conflicts of interest related to this study.

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