

# The aspects of aetiology and peripheral pathogenetic mechanism of trigeminal neuralgia

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The article presents the results of a study of 2963 patients with trigeminal neuralgia. Morphological investigation has shown that the peripheral pathogenetic mechanism of neuralgia includes a progressive dystrophy of the peripheral branches of the trigeminal nerve which determines a long-lasting continuous afferent impulse transmitting and forming a central pathogenetic mechanism – a pathologic paroxysmal excitation focus in the central nervous system. One of the causes of such process is compression of branches of the trigeminal nerve. In one third of the studied patients, this process was revealed in the narrowed infraorbital canal (causing compression of the 2nd branch of the trigeminal nerve) and in the mandibular canal (resulting in compression of the 3rd branch of the trigeminal nerve). The blood flow velocity in the arteries located in the narrowed canals was less than half the velocity determined in the contralateral arteries located in the un narrowed canals.

The next cause of the progressive dystrophy is immune response taking place in them, during which degranulation of mast cells occurs and histamine is released. The narrowing of the canals and local inflammation are caused by inflammatory disorders in the ear, nose and larynx, and other maxillofacial regions.

**Key words:** trigeminal neuralgia – aetiology and pathogenesis

## INTRODUCTION

Trigeminal neuralgia as a single disorder was described by N. André in 1756 (13). Since that time it has been investigated by various researchers, such as dental medicine specialists, neurologists, neurosurgeons, otorhinolaryngologists, in several countries. However, some problems concerning the disorder still remain unsolved. Discussions are being carried out on the main aspects of aetiology, pathogenesis, diagnosis and treatment of this neuralgia (2–9, 13, 14, 17).

The aim of this study was to investigate the morphological state of peripheral branches of the trigeminal nerve in different stages of neuralgia and to

determine the causal agents influencing the development of this disorder, and basing on the obtained data to construct an aetiological and pathogenetic conception of trigeminal neuralgia.

## MATERIAL AND METHODS

During the period 1973–2003 we treated 2963 patients in the Department of Maxillofacial Surgery of Kaunas University of Medicine. Most of the patients were women and individuals over 45 years of age (Table 1). Most of them suffered from the second-branch (37.7%) or third-branch (29.2%) trigeminal neuralgia. The duration of the disorder ranged from several days up to 20 and more years. In 43.2% of cases the patients had suffered for more than 3 years.

All patients had paroxysms of acute pain during the periods of recrudescence of neuralgia in the distribution of sensory divisions of the trigeminal nerve, correspondingly radiating to the skin of the face

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Table 1. Distribution of patients according to sex and age

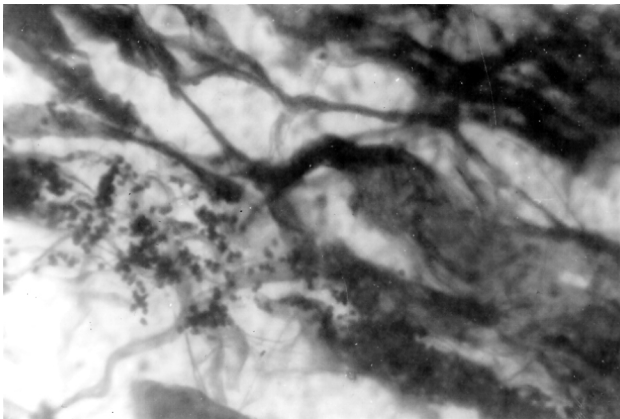
Patients	Sex		Age (years)				Total
	Men	Women	Under 45	45-59	60-75	> 75	
Number	1 235	1 728	136	1 081	1 428	318	2 963
%	41.7	58.3	4.6	36.5	48.2	10.7	100.0

Table 2. Maxillofacial and otorhinolaryngological disorders in trigeminal neuralgia patients

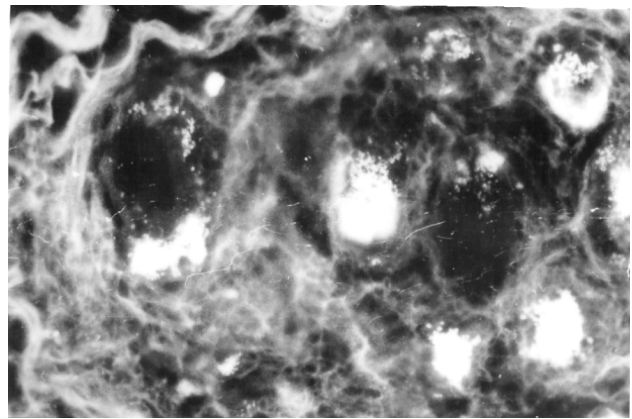
Name of the disorder	Patients	
	n	%
Dental and periodontal disorders	2889	97.5
Odontogenic sinusitis	827	27.9
Rhinogenic sinusitis	184	6.2
Sialadenitis	124	4.2
Stomatitis	124	4.2
Trauma to the face and jaws	121	4.1
Embedded teeth	113	3.8
Chronic tonsillitis	38	1.3

and the oral mucous membrane, and set off by touching trigger points or activity (e.g., chewing). The dental, maxillofacial and otorhinolaryngological disorders supposed to directly cause trigeminal neuralgia are listed in Table 2. The following were common diseases that could influence the development of trigeminal neuralgia in the studied patients: atherosclerosis (in 28.3% of patients), arterial hypertension and atherosclerosis (in 12.8%), multiple sclerosis (0.2%).

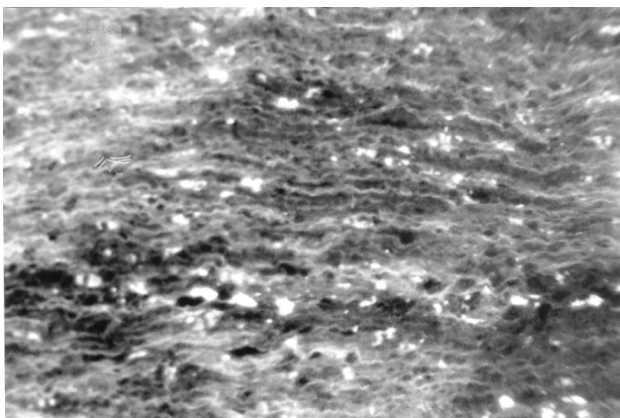
In order to diagnose trigeminal neuralgia, reveal the cause of its development, evaluate the course of the illness and apply a purposeful management, we performed, besides routine clinical tests, also the following special investigations: X-ray examination of



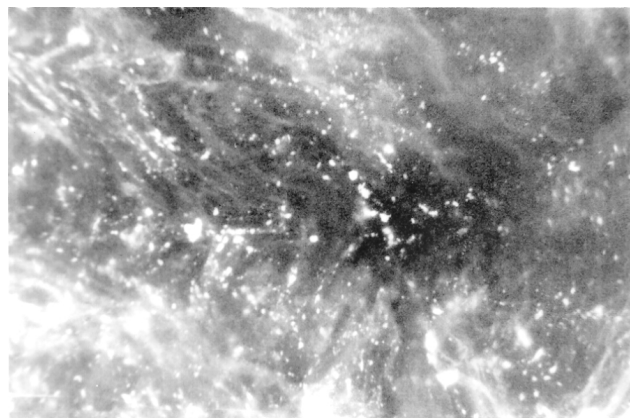
**Fig. 1.** Morphologic state of the coverings of an affected branch of the compromised nerve in an acute period of trigeminal neuralgia; van Gieson's staining; magnification  $\times 320$



**Fig. 2.** Fluorescent photomicrograph of an affected peripheral branch of the compromised nerve in an acute stage of trigeminal neuralgia. Mast cell degranulation. Magnification  $\times 300$



**Fig. 3.** Fluorescent photomicrograph of an affected peripheral branch of the compromised nerve in the remission period of trigeminal neuralgia. Granules of mast cells. Magnification  $\times 300$



**Fig. 4.** Immunofluorescent photomicrograph of an affected peripheral branch of the compromised nerve in the remission period of trigeminal neuralgia. Small immune complexes. Magnification  $\times 300$

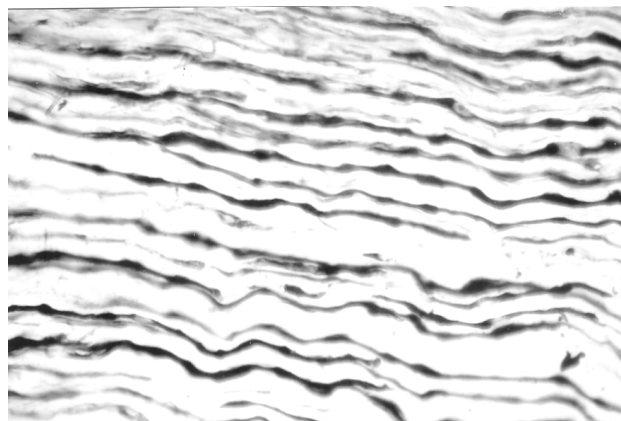
the infraorbital and mandibular canals, blood flow velocity assessment in the infraorbital and inferior alveolar arteries by Doppler ultrasonography, determining the levels of histamine in venous blood and saliva. The resected trigeminal nerve branches were studied by the neuromorphological, neurohistochemical and immunofluorescent methods.

## RESULTS

We have detected by morphological methods certain inflammatory or dystrophic structural alterations in the sheaths of the peripheral branches of the trigeminal nerves taken from the patients who had not been treated by destructive methods (injections of alcohol) prior to the surgical operation. During the acute period of neuralgia, the sheaths of peripheral branches of the trigeminal nerve showed signs of acute inflammatory alterations: swollen, hyperaemic epineurium, infiltrated with blood elements and homogenized collagen fibres with widened interspaces (Fig. 1). In the remission period, proliferative-reparative processes predominated in the connective tissue of the nerve trunks. Macrophages and newly developed connective tissue were found in the inflammatory focus. Examination under a fluorescence microscope of the nerve trunks resected during the acute period of neuralgia revealed many yellowish green fluorescent mast cells and their granules (Fig. 2). 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 (Fig. 3). For elucidation of the nature of inflammation, histologic specimens treated with a fluorescein-labelled antiserum (Anti-Human-C<sub>3</sub> fluorescein-konjugiert-Magdeburg) were examined under a fluorescence microscope. In the nerve trunks with many degranulating mast cells we observed conglomerates of immune complexes of various size, whereas in the trunks with only mast cell granules there was a large number of small immune complexes (Fig. 4).

The morphologic alterations in the fibres of peripheral branches of the trigeminal nerve depended on the duration and stage of the illness. There were only some morphologic signs of early lesion in the axis cylinders of the thick and middle-thick nerve fibres. These fibres had some nodular thickened parts or were evenly swollen. Their myelin sheath was swollen, and Schmidt-Lantermann incisures were widened. These morphologic alterations in the nerve fibres are characteristic of second-stage dystrophy. Almost all the nerve trunks contained some thin, even, slightly silver-stained regenerating nerve fibres surrounded by proliferating and hypertrophied Schwann cells (Fig. 5).

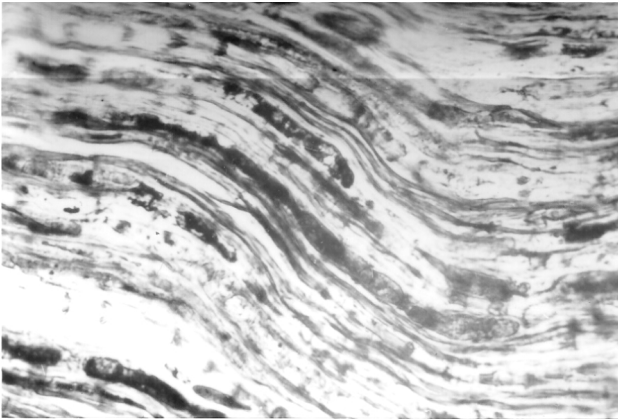
During the acute period of neuralgia, the nerve fibres were damaged more severely. Most of them



**Fig. 5.** Part of thick nerve fibres with nodular thickenings in an affected peripheral branch of the compromised nerve taken during an acute period of trigeminal neuralgia from a patient with a more than three-year-long history of the disorder. Bielschowsky-Gross silver impregnation; magnification  $\times 240$

were unevenly swollen, vacuolated, disintegrated into fragments (Fig. 6). Some of the fibres were demyelinated or their myelin sheath was swollen, Schmidt-Lantermann incisures were widened (Fig. 7). The latter alterations were characteristic of the third-stage dystrophy. During the acute stage of the illness, the morphologically detectable regenerating fibres were absent. During the acute stage of a long-term (of more than three-year duration) illness, fibres with signs of third-stage dystrophy predominated in the nerve trunks. During transition of the illness to remission, the number of fibres with signs of dystrophy decreased while the number of regenerating fibres increased. However, not all the damaged fibres recovered. Part of the disintegrated cells was resorbed and replaced by proliferating connective tissue. The longer duration of the illness, the more regenerating nerve fibres with various size thickened ends, called the growth cones (Fig. 8), were found in the nerve trunks. The regeneration of the nerve fibres may be interfered by proliferating connective tissue replacing the disintegrated and resorbed nerve trunk fibres. With every exacerbation of neuralgia, dystrophic alterations in the peripheral branches of the trigeminal nerve progressed, the amount of connective tissue in them increased, and thus the conditions for regeneration of the nerve fibres worsened. In patients with long-term neuralgia, the number of nerve fibres in the peripheral branches of the trigeminal nerve was smaller than in the analogous structures of patients with a short duration of the illness, and interfibril spaces were wider in them (Fig. 9). These alterations indicate that part of the nerve fibres were resorbed.

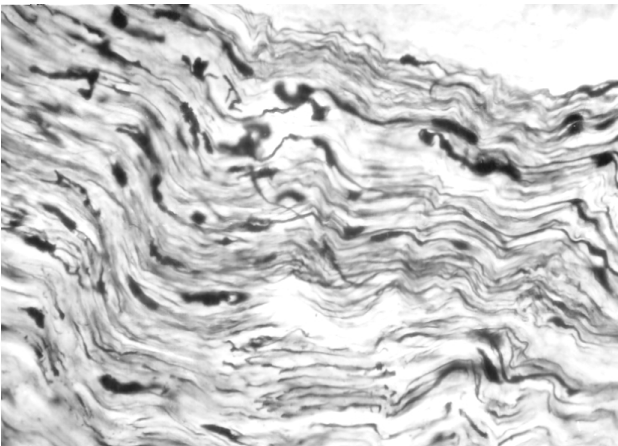
On analysing the X-ray films of the maxillary and mandibular canals, we determined that 29.2% of patients with trigeminal neuralgia had a narrowed infraorbital canal transmitting the branches of the tri-



**Fig. 6.** Vacuolisation and disintegration of nerve fibres in an affected peripheral branch of the compromised nerve taken during an acute period of trigeminal neuralgia from a patient with a more than three-year-long history of the disorder. Bielschowsky–Gross silver impregnation; magnification  $\times 240$



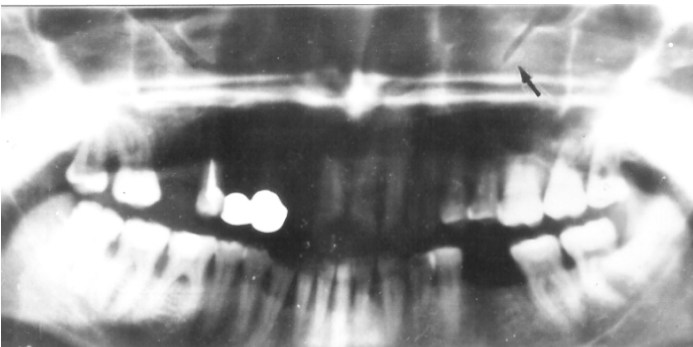
**Fig. 7.** Demyelination of nerve fibres in an affected peripheral branch of the compromised nerve taken during an acute period of trigeminal neuralgia. Marchi's staining; magnification  $\times 142$



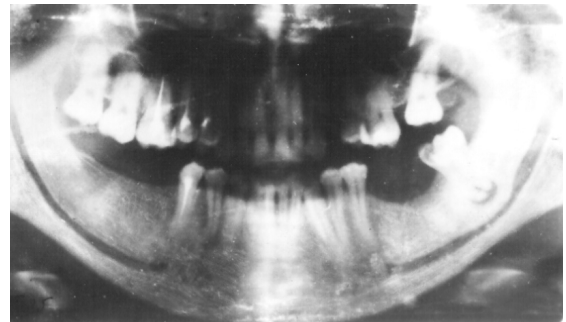
**Fig. 8.** Pathologic regeneration shown in a specimen of an affected peripheral branch of the compromised nerve taken during a remission period of trigeminal neuralgia. Bielschowsky–Gross silver impregnation; magnification  $\times 150$



**Fig. 9.** Increased amount of connective tissue and decreased number of nerve fibres in an affected peripheral branch of the compromised nerve taken from a patient with a more than ten-year-long history of trigeminal neuralgia. Silver impregnation; magnification  $\times 75$



**Fig. 10.** Orthopantomograph of patient with infraorbital neuralgia. A narrowed left infraorbital canal



**Fig. 11.** Orthopantomograph of patient with third-branch trigeminal neuralgia. A narrowed left mandibular canal in the region of a molar tooth

geminal nerve. The infraorbital canal of patients with the second-branch neuralgia was significantly narrower in the affected side of the face than the canal in the intact side. Its lumen was narrowed by the evenly thickened walls of the canal (Fig. 10). In so-

me patients with the third-branch trigeminal nerve neuralgia, the mandibular canal was narrowed along its whole length; in others, there was a local narrowing of the canal, most often near the molar teeth, rarer at the mental foramen.

It was determined by Doppler ultrasound examination that during remission of the second-branch trigeminal neuralgia the mean blood flow velocity in the unnarrowed infraorbital arteries on the affected side was  $0.37 \pm 0.05$  m/s, whereas in the analogous contralateral arteries  $0.35 \pm 0.04$  m/s; asymmetry coefficient, 1.02. In the patients with a narrowed canal on the affected side, the mean blood flow velocity in the infraorbital arteries was  $0.17 \pm 0.03$  m/s, whereas in the contralateral arteries on the intact side it was  $0.38 \pm 0.02$  m/s; asymmetry coefficient, 2.23. In the patients with the third-branch trigeminal neuralgia whose mandibular canals were symmetrical, the mean blood flow velocity in the inferior alveolar artery on the affected side was  $0.33 \pm 0.04$  m/s, whereas in the contralateral analogous arteries it reached  $0.34 \pm 0.02$  m/s; asymmetry coefficient, 1.03. In the patients with asymmetrical canals, the mean blood flow velocity in the inferior alveolar artery on the affected side (in the narrowed canal) was  $0.15 \pm 0.04$  m/s, whereas in the contralateral artery on the intact side it was  $0.35 \pm 0.03$  m/s; asymmetry coefficient, 2.33.

We have determined an increase of histamine in the blood and saliva during the acute period of trigeminal neuralgia. In the healthy individuals (control group), histamine level in the blood was  $0.558 \pm 0.063$   $\mu\text{mol/l}$  and in saliva  $0.522 \pm 0.001$   $\mu\text{mol/l}$ , whereas in patients during the acute period of neuralgia the levels of histamine in blood ( $3.879 \pm 0.342$   $\mu\text{mol/l}$ ) and saliva ( $4.554 \pm 0.513$   $\mu\text{mol/l}$ ) were statistically higher than in the analogous fluids of healthy persons. Moreover, the concentration of histamine in the saliva of the neuralgia patients was significantly higher than in their blood.

## DISCUSSION

Morphological investigation of the resected peripheral branches of the trigeminal nerve removed from the trigeminal neuralgia patients has convincingly shown that their morphological state mainly depended on the stage and duration of the illness. During the acute period of the illness, disintegration and demyelination of the nerve fibres takes place, whereas during remission, partial restoration of these structural elements occurs. One of the causes of progressive dystrophy of the peripheral branches of the trigeminal nerve may be their compression due to the narrow bone canals. As early as 1925, Sicard, and later (in 1941) Sepp and Krol (13) proposed a hypothesis according to which trigeminal neuralgia may develop due to the narrowing of the osseous canals transmitting the corresponding nerve branches. This assumption has been convincingly confirmed by the data of our X-ray examinations in approximately one third of the patients with the second- or third-branch trigeminal neuralgia: the infraorbital or mandibular canals were narrowed on

the affected side of the face. We suppose that the walls of the canals thicken and the lumina becomes narrowed due to secondary hyperostosis caused by local chronic inflammation. Most of the patients with a narrow infraorbital canal suffered from chronic maxillary sinusitis; the rest, from other facial and maxillary inflammatory illnesses such as periodontitis, periostitis, phlegmon, etc. The narrowed mandibular canals most often are located near dental cysts, the periodontium is damaged by the inflammatory process or in the place of teeth extracted because of chronic periodontitis. A question arises whether the narrowed canals always result in a compression of the neurovascular bundle. A reply to this question may be found in the data of our Dopplerographic examinations: we found that the blood flow velocity in the narrowed canals was half the velocity established in the normal lumen canals. Recently, the role of the compression factor in the development of trigeminal neuralgia has been also confirmed by many other investigators who point out that neuralgia develops due to compression exerted upon the intracranial part of the trigeminal nerve by anomalous brain vessels, their aneurysms, brain tumours, etc. (1, 3, 4, 11, 12, 16). Joffroy et al. (6) call it "a neurovascular conflict" when an artery has an offending contact with the trigeminal nerve root, which results in local demyelination and ectopic triggering of neural discharges.

Another frequent cause of progressive dystrophy in the peripheral branches of the trigeminal nerve is allergic inflammatory reaction manifesting itself in the mast cell degranulation when antibodies, most often of the immunoglobulin E class, attach to the specific receptors on the surface of mast cells (5). Cells synthesizing IgE are present in the lymphoid tissue, in the mucous membranes of the eye, nose, oral cavity, upper respiratory tract (10). In some disorders, the concentration of IgE may increase greatly: in inflammatory diseases of the otorhinolaryngological organs, trebly; in nasal polyps, five to six times (3, 5).

Thus, under the influence of various damaging factors, such as cooling injury to the face, tonsillitis, chronic rhinitis, paranasal sinusitis, and chronic inflammation of other organs in the region of face and jaws, the amount of IgE and antibody complexes that may attach to the mast cell and result in local immune response during which degranulation of the cells is increased. The degranulating mast cells release biologically active substances as histamine, serotonin and others into the intercellular space. This process is confirmed also by the data of our morphologic and histamine investigations. The fact that we have determined a significantly higher concentration of histamine in saliva than in blood shows the existence of a local histamine source, which is conditioned by the local immune reaction in the peripheral trigeminal nerve branches. Histamine actively participates in the regulation of functional activity of various neural structures.

res as a mediator of pain reactions (15). Therefore, undoubtedly, histamine which is released during a local allergic reaction and is accumulated in the trigeminal nerve plays an important role in the pathogenesis of neuralgia.

Due to inflammatory swelling of the trigeminal nerve branches, the canals transmitting them become relatively too narrow, and in this way the mechanism of the nerve branch compression becomes involved in the pathogenetic chain of trigeminal neuralgia.

The presented examples show that the essence of the peripheral mechanism of neuralgia is progressive dystrophy of the trigeminal nerve which predetermines a long-lasting preterminal afferent pathological impulsion. The trigeminal nerve system conjuncting the central structures capable to exert inhibitory action upon the segmental and suprasegmental formations is able to form a stable irritation focus of paroxysmal type in the CNS, whilst a chronic irritation focus exists in the periphery (8). Thus, progressive dystrophy in the trigeminal nerve system stimulates the central pathogenetic 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 favourable conditions develop for the formation of the pathogenetic mechanisms of trigeminal neuralgia in the elderly and in old individuals affected by an aetiological factor.

## CONCLUSIONS

1. The peripheral pathogenetic mechanism of trigeminal neuralgia is induced by progressive dystrophy in the peripheral branches of the trigeminal nerve which predetermines long-lasting afferent impulsion and the formation of a central pathogenetic mechanism (a stable pathologic paroxysmal type irritation focus in the CNS).

2. The dystrophy in peripheral branches of the trigeminal nerve results in their compression in the narrowed bone canals transmitting them and their inflammatory processes manifesting by mast cell degranulation.

3. The narrowing of the bone canals transmitting the peripheral trigeminal nerve branches and the inflammatory processes can result in dental, otorhinolaryngological disorders and other illnesses of the facial and maxillary region, which can be considered to be the direct causes of trigeminal neuralgia, whereas atherosclerosis and arterial hypertension are the predisposing factors.

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## TRIŠAKIO NERVO NEURALGIJOS ETIOLOGIJOS IR PERIFERINIŲ PATOGENETINIŲ MECHANIZMŲ ASPEKTAI

Santrauka

Điame straipsnyje pateikiami 2 963 pacientų, sergančių trišakio nervo neuralgija, tyrimo rezultatai. Mūsų atlikti morfologiniai tyrimai rodo, kad periferinis patogenezės mechanizmas apima progresuojančią periferinių trišakio nervo šakų distrofiją. Šis centrinis patogenezės mechanizmas apibrė-

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biomas kaip ilgai trunkantis ácentrinis impulsas, kuris patologinio paroksizminio tipo þidiná formuoja centrinėje nervø sistemoje. Viena iš ðio proceso prieþasėiø yra triðakio nervo ðakø kompresija. Vienam treðdaliui mûsø tirtø pacientø ðis procesas pasireiðkė susiaurėjusiam paakiduobiniam kanale (sukeldamas II triðakio nervo ðakos kompresijà) ir apatinio þandikaulio kanale (sukeldamas III triðakio nervo ðakos kompresijà).

Kraujo tekėjimo greitis arterijose, esanëiose ðalia susiaurėjusio kanalø, buvo perpus mažesnis negu kolateralinëse arterijose, išsidėsëiusiose platesniuose kanaluose.

Kita ðios progresuojanëios distrofijos prieþastis yra nervø imuninis atsakas, kai vyksta kamieniniø lãsteliø degranuliacija ir išsiskiria histaminas. Kanalø susiaurėjimà ir vietinà uþdegimà sukelia uþdegiminiai reiškiniai ausyse, nosyje, gerklose ir kitose veido þandikaulio srityse.

**Raktaþodþiai:** triðakio nervo neuralgija, etiologija, patogenezė