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Immunohistochemical analysis of the arterial supply and mast cells of the trigeminal ganglion

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Abstract: The aim of this study was to quantify the distribution of microvessels and mast cells in all three parts of the trigeminal ganglion (TG). Statistical analyses were applied to investigate possible micromorphological regional differences in their density. Five serially sectioned human TGs were prepared for CD34 and mast cell tryptase immunostaining. The following quantifications were performed in microscopic fields of three parts of the TG: microvessel density (MVD), mast cell density (MCD) and ganglionic cell count. The density of CD34-positive microvessels was not significantly different in any of the three observed parts of the TG. The distribution of neurons showed no significant statistical difference in three parts of the TG. There was no difference in the density of tryptase-positive mast cells within the TG, but there was an abundant presence of mast cells in the periganglionic dural and subdural tissues, a finding hitherto not reported. We can say that there is a homogenous vascular pattern within the TG which excludes local predominance in pathogenesis of trigeminal neuralgia. Second, and more important, the finding of peri-trigeminal mast cells indicates their important role in migraine pain and confirms their degranulation as the main therapeutic goal for this condition.

Keywords: immunohistochemical analysis; mast cells; microvessels; neurons; trigeminal ganglion

INTRODUCTION

The trigeminal nerve roots emerge from the ventrolateral surface of the pons and form the trigeminal nerve (TN). The nerve extends to the dural entrance into Meckel's cave where it joins the trigeminal ganglion (TG). The intracranial part of the TN is located in the cerebellopontine cistern, composed of the small motor portion (root) and the large sensory portion (root). This cisternal segment of TN is continuous with the plexal segment. The trigeminal (semilunar) ganglion is located distal to the network of the plexal part of the TN, and sends off three divisions of the TN, the ophthalmic nerve (V1), the maxillary nerve (V2), and the mandibular nerve (V3) [1].

The average cisternal portions of the TN range from 10.2-20.4 mm (mean, 14.01 mm) in length [2]. The trigeminal root entry zone (TREZ) is the most proximal central myelin root portion of the TN, covered with pia mater extending from the pontine surface. The extent of the central myelin sheath of the TREZ is shorter in the motor part of the nerve than in the sensory part and occupies an average of the initial 4.91 mm of the sensory root (from 3.1 to 10 mm) and 0.77 mm of the motor root (from 0.5 to 1 mm) [2,3].

The TREZ is an anatomical landmark of great clinical importance, showing increased sensitivity to mechanical compression and a feeble blood supply that can lead to trigeminal neuralgia. This transition zone between central and peripheral myelin forms an apex described as the glial dome, surrounded by an outer mantle of astrocytes. This zone in which glial cells end and Schwann cells begin is known as the Obersteiner-Redlich zone. It has a sufficient blood supply because of the significant metabolic

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requirements of the highly concentrated transitional nodes of Ranvier [4-7].

Previous studies [2,8] have described the blood supply of the TN and TG, the different origins and the external distribution of the trigeminal branches. What remains unknown is the precise internal vascular pattern of TG microcirculation [9]. The TG lies beyond the blood-brain barrier, but the arrangement of satellite glial cells (SGC) covering cell bodies of TG neurons is unique. SGC are in close contact, lying between trigeminal neurons and microvessels, and they represent the blood-nerve tissue barrier of the peripheral nervous system [10]. The distribution of intraganglionar microvessels is of crucial importance for the functional capabilities of the neural network of the TG. Irregularities in the intraganglionar blood supply can lead to changes in neurons, with dysfunction as a final result. Such a scenario generates hyperexcitability of the trigeminal cell bodies, giving rise to pain because of exacerbated neuronal activity [6,11].

Recent evidence suggests an important role of mast cells in triggering migraine pain. These cells are densely present in meningeal tissues, located adjacent both to nerves and to vessels, as well as in the TG itself. Injury to the sensory neurons and ATP release from different cells can promote degranulation of mast cells with the release of substances such as histamine, serotonin and proinflammatory cytokines, all of which seem to play a relevant role in the activation of TN fibers and subsequently a migraine attack [12].

The reasons for this study lie in the abundant neurological and surgical significance of trigeminal neurovascular anatomy and lack of relevant anatomic data. We applied immunohistochemistry and image analysis software to examine microvessel density (MVD) and mast cell density (MCD) in the ophthalmic, maxillary and mandibular parts of the TG and periganglionic tissue.

MATERIALS AND METHODS

Histological examination

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, No. 29/V-10. Five human trigeminal ganglions of adult individuals were used for this immunohistochemical study. They were sampled together with the dura mater during autopsy after removal of the whole brain from the cranial cavity. Each ganglion was immediately immersed in isotonic saline solution, fixed in 4% buffered formaldehyde, dehydrated, embedded in paraffin and sectioned serially in 4-μm-thick slides. After ten sections, the following four were prepared as follows: one was stained with hematoxylin and eosin (H&E), one according to the Masson trichrome method, and the next two slices were prepared for the immunohistochemical procedure. There were 10 such sets of slices from each excised ganglion. All the slices for immunohistochemical analysis were first deparaffinized and then the sections were treated for antigen retrieval prior to staining. The endogenous peroxidases were blocked by incubating the samples with 3% hydrogen peroxide solution. The slices underwent immunostaining by incubation with two mouse monoclonal primary antibodies, CD34 (DAKO A/S, M 7165, Denmark) and anti-mast cell tryptase (DAKO A/S, M 7052, Denmark). The sections with the bound antibodies that were visualized, were stained with a secondary antibody using a streptavidin-biotin-peroxidase staining technique (Universal LSAB®+Kit HPR; DAKO Cytomation K0679, Glostrup, Denmark) using as substrate-chromogen 3-amino-9-ethylcarbazole (AEC+, Code K3469, DAKO). The sections were counterstained with Mayer's hematoxylin, dehydrated and covered with a cover slip. The intensity of staining was evaluated semiquantitatively by 2 independent investigators. The intensity of all the slices was classified as strongly positive (+++). Negative controls, for assessing nonspecific staining, were performed by incubating the slices with non-immune serum, in order to determine the specificity of the immunostaining. The slices were examined under a light microscope (Leica DMLS, Germany) and photographed using a digital camera (Leica DFC295). Measurements were performed using image analysis software (Leica Interactive Measurements).

Morphometric study

Microvessel density (MVD) was defined as the mean number of microvessels visible in microscopic fields of analyzed tissue. The microvessels, mainly capillaries

and precapillaries, ranging in diameter from 5.5 μm to 8.5 μm, were identified by immunostaining of the vascular wall or variously transected independent vessels. The number of microvessels was counted in three microscopic fields of the TG parts (ophthalmic, maxillary and mandibular) in 10 slices per TG at x400 magnification (objective lens 40× and ocular lens 10×). The arithmetic mean of the 10 fields of each of 5 ganglions, measuring 341.7 μm × 250.0 μm in size each, with a corresponding area of 85425 μm^2 (0.085 mm^2) per field, was calculated for the microvessel count. We also counted the number of pseudounipolar ganglionic neurons in each field of the slices. A similar procedure was applied separately for counting immunostained mast cells and for calculating the MCD in three established microscopic fields (ophthalmic, maxillary and mandibular) of trigeminal ganglions. At 200× magnification, for the calculation of the MCD, the visible fields were 652.1 μm × 489.8 μm each, with a corresponding area of 319 400 μm^2 (0.319 mm^2) for each field.

Statistical analysis

The data were statistically analyzed with the SPSS 17.0 statistical software package (SPSS, Inc., Chicago, IL, USA). The statistical analyses comprised descriptive statistics (mean values and standard deviations) of the measured data, the Student's T-test for independent samples and one-way analysis of variance (ANOVA) followed by Bonferroni's corrective. The probability level of $P< 0.05$ was considered as a statistically significant difference.

RESULTS

Intraganglionic microvessel density

Micromorphological characteristics of the human TN and TG were studied in longitudinal sections of the whole specimen (Fig. 1). Immunopositive blood vessels of the TN and TG showed a strong immune reaction against the CD34 protein of endothelial cells (Figs. 2A-F). Each microscopic field of the TG ophthalmic part included from 86 to 139 microvessels (mean 101.42±12.5). The MVD of the TG maxillary part was 102.98±10.66 (89-132). The mean number of

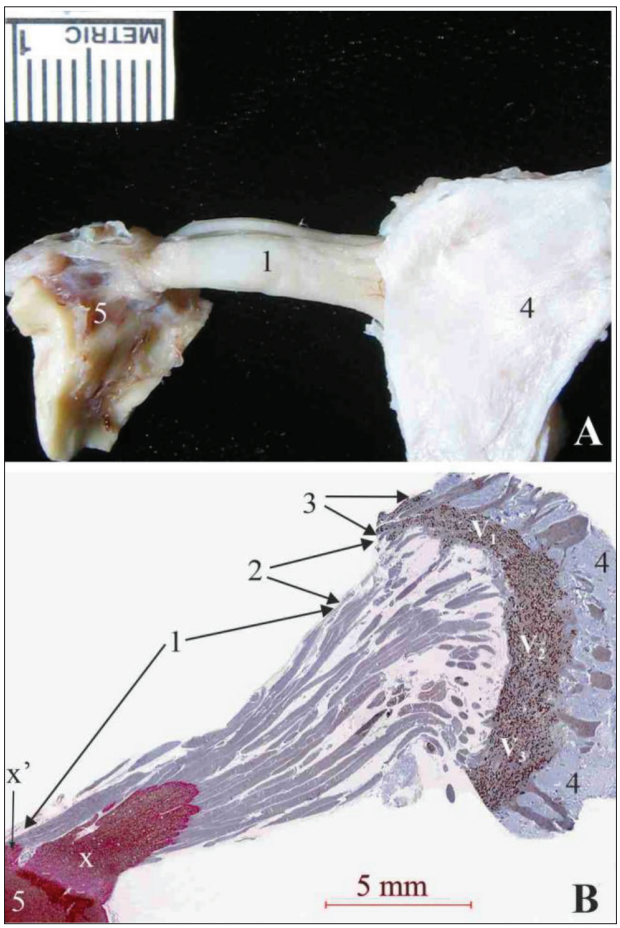

Fig. 1. Micromorphological characteristics of the human trigeminal nerve (TN) and trigeminal ganglion (TG) complex: **A** – native specimen; **B** – immunostained specimen against glial fibrillary acidic protein (GFAP) and neuron specific enolase (NSE). Cisternal segment of TN (1), showing the longer extent of central myelin (the root entry zone) in its sensory root (x) than in the motor root (x'), and the central myelin-peripheral myelin transition zone. Plexal segment of TN (2) enters the zone of the TG (3), which contains neurons in the ophthalmic (V1), maxillary (V2) and mandibular (V3) parts; (4) dura mater and fascicles of trigeminal branches; (5) pons.

microvessels presented in microscopic fields of the TG mandibular part was 104.18±13.36 (78-134). One-way ANOVA found no statistically significant differences in MVD between the three parts of trigeminal ganglions: ophthalmic, maxillary and mandibular ($P=0.529$) (Table 1) (Fig. 3). The distribution of microvessels in all three parts of the TG was uniform with no specific micromorphological differences (Figs. 2D-F).

The number of the ganglionic neurons in the same fields of the mentioned slices ranged from 14-22 (mean 17.86±2.54) for the ophthalmic part of the TG,

Table 1. Microvessel density (MVD) and number of neurons in three parts of the trigeminal ganglion (TG): ophthalmic, maxillary and mandibular.

Trigeminal ganglion	Ophthalmic part	Maxillary part	Mandibular part
Number of microvessels/field: min-max (M±SD)	86-139 (101.42±12.5)	89-132 (102.98±10.66)	78-134 (104.18±13.36)
Nº of neurons/field: min-max (M±SD)	14-22 (17.86±2.54)	13-23 (17.68±2.42)	12-21 (17.34±2.32)

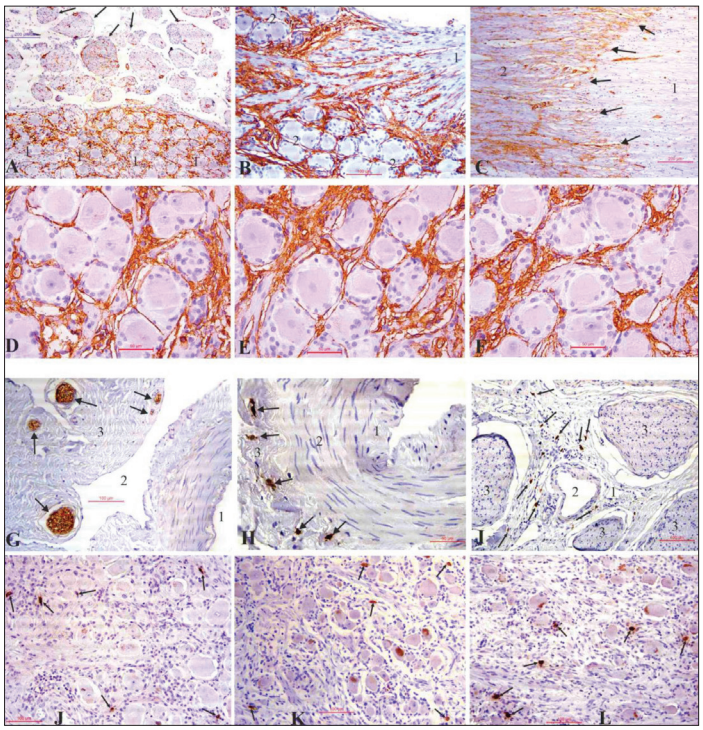

Fig. 2. Immunohistochemical characteristics of the human trigeminal nerve (TN) and the trigeminal ganglion (TG) blood supply (CD34 immunostaining). **A** – Fine network of TG intraganglionar microvessels (1), and the vascular supply of the plexal segment of TN fascicles (arrows) in the transverse section. **B** – Parallel microvessels of the plexal segment of TN fascicles (1), and the intraganglionar (2) vascular supply of the TG in the longitudinal section. **C** – Dense network of microvessels over the glial dome of a transition zone (arrows) of the TN root entry zone, between the parapontine part of the TN with less vascularized central myelin (1), and more distal part with well vascularized peripheral myelin (2). **D**, **E**, **F** – Ganglionic neurons of ophthalmic (V1), maxillary (V2) and mandibular (V3) parts of the TG surrounded by microvessels. **G** – Immunoreactivity against neurofilament protein (NFP) in sensory axons (arrows) of dura matter (3), close to the middle meningeal vein (2) and artery (1). **H**-**L** – Immunohistochemical characteristics of mast cells related to the human trigeminal nerve (TN) and the trigeminal ganglion (TG) (mast cell tryptase immunostaining). **H** – Transverse section of the middle meningeal artery with internal elastic lamina (1), tunica media (2), and adventitial coat (3) rich in mast cells (arrows). **I** – Transverse section through the distal part of the TG exposing connective tissue with vein (1), artery (2) and a large group of mast cells (arrows) between fascicles (3) leaving the TG. **J, K, L** – Mast cells of ophthalmic (V1), maxillary (V2) and mandibular (V3) parts of the TG.

from 13-23 (mean 17.68±2.42) for the maxillary part, and from 12-21 (mean 17.34±2.32) for the mandibular part of the TG (Table 1) (Figs. 2D-F). One-way ANOVA showed that the distribution of the neurons has no significant statistical difference in three parts of the TG (P=0.555).

Density of mast cells

Analysis of the population of mast cells revealed the precise morphometric characteristics of tryptase-positive mast cells in the trigeminal ganglions (Table 2). The mast cells were oval in shape with a mean diameter ranging from 11.06-14.28 μm (mean, 12.8±0.83 μm), and a mean area ranging from 92.4-153.7 μm (mean, 124.89±16.46 μm^2). As can be seen from Table 3, each microscopic field of the ophthalmic part of the TG was comprised of an average of 1.34±1.04 mast cells (from 0 to 6). The MCD of the maxillary part of the TG was 1.26±0.85 mast cells (from 0 to 5). The MCD presented in the microscopic fields of the mandibular part of the TG was 1.46±1.07 mast cells (from 0 to 6) (Table 3) (Figs. 2J-L, 4B). One-way ANOVA found no statistically significant differences between the groups of MCD in the three parts of trigeminal ganglions (P=0.600).

The tryptase positive mast cells (MC) were very rarely found between the fibers of the TN and were always in close vicinity of blood vessels (Fig. 4A). The TREZ, the proximal central myelin root portion of TN, was the least populated part of the nerve with mast cells. The presence of mast cells was noted in the adventitial coat of the middle meningeal artery, close to their branches, and between the layers of highly innervated dura mater (Figs. 2G, H and Fig. 4C). The mean number of mast cells presented in the microscopic fields of dural tissue peripheral to the TG was 6.8±1.03 (from 5 to 8 MC). The largest population of mast cells was found in the periganglionic fibrous tissue of the TG, medially close to the cavernous sinus, laterally next to the foramen spinosum

Table 2. Metric characteristics of tryptase-positive mast cells in the trigeminal ganglion.

	M (μm)	SD (±μm)	SE (±μm)	SE (±μm)	Min (μm)	Max (μm)
R2	10.63	1.135	0.166	0.166	8.279	13.214
R1	14.978	1.378	0.201	0.201	9.348	17.15
RM	12.804	0.83	0.121	0.121	11.06	14.281
C	39.406	2.521	0.385	0.385	35.344	45.761
	M (μm²)	**SD (±μm²)**	**SE (±μm²)**	**SE (±μm²)**	**Min (μm²)**	**Max (μm²)**
Area	124.889	16.464	2.401	2.401	92.402	153.711

R2 – shorter diameter; R1 – longer diameter; RM – mean diameter; C – circumference; M – mean, SD – standard deviation; SE – standard error.

Table 3. Mast cell density (MCD) in three parts of the trigeminal ganglion: ophthalmic, maxillary and mandibular, and in periganglionic tissues.

Number of mast cells/field: min-max (M±SD)	Ophthalmic part	Maxillary part	Mandibular part
Trigeminal ganglion	0-6 (1.34±1.04)	0-5 (1.26±0.85)	0-6 (1.46±1.07)
	Periganglionic tissues		
Dural tissue peripheral to TG	5-8 (6.76±1.03)		
Periganglionic fibrous tissue of TG	7-14 (11.36±1.71)		

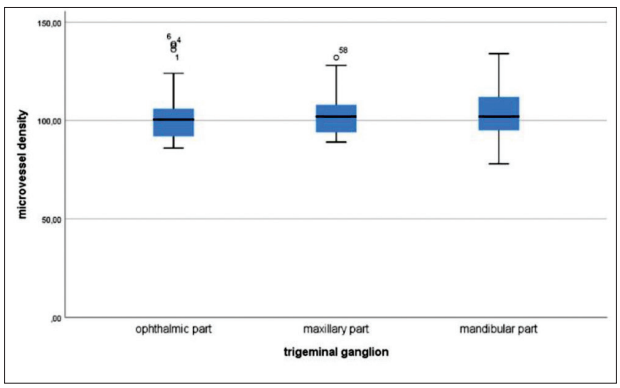

Fig. 3. Comparison of microvessel density (MVD) defined by CD34 in three parts of trigeminal ganglions: ophthalmic, maxillary and mandibular.

and middle meningeal artery (MMA), and surrounding the arborization of the TG into the ophthalmic, maxillary and mandibular nerves. We identified 7 to 14 (mean 11.4±1.71) mast cells per microscopic field (Table 3) (Fig. 2I).

DISCUSSION

Within the sensory ganglions of adult vertebrates, each nerve cell body is tightly enveloped in a single sheath of satellite glial cells (SGC), homeostatic cells which are surrounded by connective tissue, thus forming a discrete morphological and functional unit [10,13]. Trigeminal ganglionic cells, surrounded by a layer of SGC, are in close contact with a dense capillary network [9]. With to the characteristic arrangement of satellite glial cells and their relationships with the surrounding structures, we can conclude that all molecules from the blood vessels of the interstitial connective tissue must penetrate the sheath built by SGC in order to reach neurons. A gap of 20 nm between the SGC and ganglionic soma allows for rapid and controlled bidirectional communication, which is believed to regulate neuronal activity [14]. In the central nervous system, the astrocytes form a close contact with blood vessels via endplates, but there is no such interconnection between SGC and blood vessels. Consequently, the only control of the transfer of molecules to neurons is the SGC sheath [15]. It has been reported in the literature that SGC

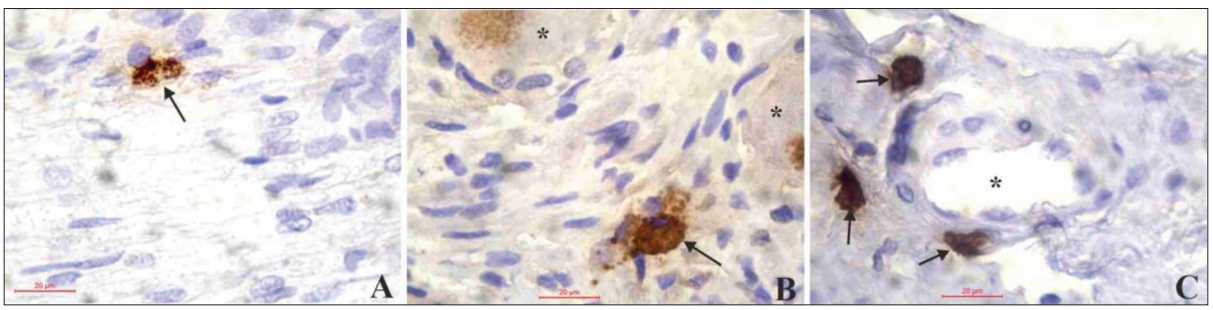

Fig. 4. High-magnification view showing: **A** – trigeminal nerve mast cell (arrow); **B** – trigeminal ganglion mast cell (arrow), and ganglionic neurons (asterisks); **C** – perivascular dural mast cells (arrows) related to small blood vessel.

represent "the blood-nervous tissue barrier of the peripheral nervous system" (a homologue of the central nervous system blood-brain barrier), although there is partial movement of substances from the connective tissue and vessels to the neuron [10,14].

The TG receives its arterial supply from two sources, medially from the internal carotid artery (ICA), and laterally from the middle meningeal artery (MMA) [16,17]. A group of authors reported that the trigeminal branches arising from the MMA were significantly smaller, feeding the medial third of the TG, when compared to larger trigeminal arteries originating from the ICA for the supply of lateral two thirds of the TG [8]. They also presented and described an intraganglionic network of capillaries, injected with black India ink and gelatin, i.e., tortuous microvessel coils in the form of nests for spherical SGC-ganglionic cell units. According to the study, a very dense and curved intraganglionic capillary network was visually apparent, possessing a uniform density of microvessels throughout the TG [8]. The intraganglionar microcirculation, the so-called microcirculatory bed, is composed of capillaries that form spatial loops surrounding the trigeminal ganglion somata [9]. In one study [18], the components of the microcirculatory bed exhibited the highest incidence in the mandibular division of the fetal TG, and the lowest in the maxillary division of the TG. During gestation, the highest increase in average MVD was noted in the mandibular part of the TG, as compared to the V1 (lower increase) and V2 (lowest increase) parts of the TG. Because of the high metabolic demands of ganglionic cells, the above-described difference in MVD could explain the most frequent effect of the maxillary part of the TG in pathogenesis of trigeminal neuralgia [18]. However, in most cases, trigeminal neuralgia is caused by compression of the sensory portion of the trigeminal nerve root (TNR) by blood vessels in the area of entrance into the pons [2,19].

Our immunohistochemical examination of the TG specimens presented rich microvasculature coils around the ganglionic cells. The mean number of CD34-positive microvessels varied per microscopic field as follows: 101.42 for the ophthalmic, 102.98 for the maxillary, and 104.18 for the mandibular part of the TN. The density of CD34-positive microvessels was not significantly different in any of the three parts of the TG. The uniform distribution of microvessel density throughout the TG confirmed the existence of a functionally homogenous vascular pattern for all three parts of the ganglion, ophthalmic, maxillary and mandibular. The uniform intraganglionic microvessel density in different segments of the TG indicates that within the ganglion there are no zones of lesser vascularization that could be the site of potential ischemia and possible reaction of the nerve cells. The mean number of ganglionic neurons contained in the same microscopic fields was 17.86, 17.68 and 17.34 for ophthalmic, maxillary and mandibular, respectively, with no significant statistical difference in number in the three parts of the TG. It was reported that the elevated energy and oxygen demand of sensory neurons is fully served by the extensive network of capillaries within the ganglion [20].

Mast cells produce and release after degranulation nerve growth factor (NGF), amongst several mediators that can induce inflammation. NGF is an important neuropeptide during nervous system development. It is involved in hyperalgesia and tissue neurogenic inflammation and is also a potent factor of maturation and degranulation for mast cells [21].

Spatial and functional interactions between mast cells and peripheral nerves have been observed in different tissues. Their close relationship suggested that the mast cells could be important for nerve growth and repair, as well as during inflammatory processes. Increased MCD, followed by prominent expression of NGF, has been demonstrated in the appendiceal wall in cases of acute appendicitis [22].

The products of degranulation of activated meningeal mast cells could be a major source of migraine pain. Released serotonin is the most powerful pronociceptive neurotransmitter to stimulate the meningeal sensory nerve fibers. It contributes to meningeal neuroinflammation in the local neuroimmune unit composed of trigeminal afferent fibers and dural mast cells, causing the long-lasting pain in migraine [12,23].

Our investigation demonstrated the homogenous and modest presence of tryptase-positive mast cells in all three parts of the TG. The mean number of tryptase-positive mast cells identified in the three parts of TG was 1.34 in the ophthalmic, 1.26 in the maxillary and 1.46 in the mandibular part.

Meningeal afferents surrounded by multiple mast cells from the local neuroimmune unit have been suggested as a major source of migraine pain [12]. Outside of the TG, in the adventitial sheath of the middle meningeal vessels and between the layers of dural fibrous covering, the density of tryptase-positive mast cells was significantly higher, with an average of 6.8 mast cells per observed microscopic field. The highest mean number of mast cells of 11.4 per microscopic field was found in the periganglionic subdural tissue related to the vessels that irrigate the TG and are derived from their lateral and medial origins, and in the tissue surrounding the ramification of the TG in three large nerves, the ophthalmic, maxillary and mandibular. The intense presence of mast cells is associated with a high supply in blood vessels, and innervated areas surrounding the TG confirmed the existence of the interaction between mast cells and sensory nerves [12,23-25]. Data obtained in this study could be useful in explaining the mechanism of migraine pain. The intraganglionar uniform distribution of a small number of mast cells and an intense and balanced arterial supply in all three parts of the TG confirm the theory that the highest density of mast cells, sensory nerves and vessels in periganglionic dural and subdural tissues are the major contributing factors in the development of pain in migraine. Inhibition of mast cell degranulation is currently the main therapeutic goal for this neurological condition.

CONCLUSIONS

The density of CD34-positive microvessels, the mean number of ganglionic neurons and the density of tryptase-positive mast cells showed no significant statistical differences in three parts of the TG, the ophthalmic, maxillary and mandibular. The distribution of microvessels, neurons and mast cells in all three parts of the TG was uniform with no specific micromorphological differences. The highest density of mast cells was observed in periganglionic dural and subdural tissues.

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Author contributions: ALJM, ABM, AD, and MĆ designed the study and contributed to the literature review. ABM, JB, JĐ and DĆ contributed to data acquisition. ALJM, AGM, DĆ and MĆ performed the histological analysis. JĐ and AD designed the statistical study. BŠ, AGM, JB and JĐ wrote the article. BŠ finalized article writing and revision. All authors approved the final version of the manuscript.

Conflict of interest disclosure: The authors declare that they have no conflict of interest.

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