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ORIGINAL ARTICLE

Micromorphological features of mastocytes in the trigeminal and human sympathetic superior cervical ganglions

Mila Cetkovic[1], Aleksandra Milosavljevic[1], Jelena Boljanovic[2], Darko Laketic[2], Marko Simic[3], Nikola Bogosavljevic[4], Aleksandar Mircic[1], Milan Milisavljevic[2,5]

[1]Institute of Histology and Embryology, University of Belgrade, Faculty of Medicine, Belgrade, Serbia

[2]Laboratory for Vascular Morphology, Institute of Anatomy, University of Belgrade, Faculty of Medicine, Belgrade, Serbia

[3]Clinic for Orthopaedic Surgery and Traumatology, University Clinical Center of Serbia, University of Belgrade, Faculty of Medicine, Belgrade, Serbia

[4]Institute for Orthopedic Surgery "Banjica", University of Belgrade, Faculty of Medicine, Belgrade, Serbia

[5]Academy of Medical Sciences, Serbian Medical Association, Belgrade, Serbia

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Correspondence to:
Mila Cetkovic

Institute of Histology and Embryology, Faculty of Medicine, University of Belgrade, 26 Višegradska Street, 11000 Belgrade, Serbia

Email: milacetkovic06@gmail.com

Summary

Introduction: Mastocytes (Ms) are usually localized close to microvessels and terminals of the nerves innervating meninges and visceral organs. The granules of Ms contain numerous mediators that affect nerve cells and modify their reactions.

Aim: Our study was conducted with the aim of analyzing the presence and localization of Ms, and mastocytes density (MsD) in three segments of the human trigeminal ganglions (TGs): ophthalmic, maxillary and mandibular, as well as in two parts: upper and lower, of the sympathetic superior cervical ganglions (SSCGs), and establishing the correlation between the studied parameters.

Material and Methods: Five TGs and five SSCGs of adult individuals were processed for this histochemical and immunohistochemical analysis. The sections are serially sliced and stained with hematoxylin and eosin and the trichrome method of Masson, as well as for the mastocyte tryptase immunostaining.

Results: The average number of tryptase-positive (Tryp+) Ms in the marked fields on the microscope, the MsD, was 1.4 in the ophthalmic parts, 1.45 in the maxillary parts, and 1.5 in the mandibular parts of TGs. The median of numbers of Tryp+ Ms in fields on the microscope was 4.5 (from 2 to 6 Ms) in the upper segments, and 5 (from 3 to 6 Ms) in the lower segments of SSCGs. The distributions of Ms in three parts of the human TGs and two segments of the SSCGs were evenly distributed with no special morphological peculiarities. This is the first micromorphological analysis of the Tryp+Ms and MsD in human TGs and SSCGs.

Conclusion: We did not find a statistically significant difference between the means of MsD in the three segments of the TG ($p = 0.883$). We did not find a statistically significant differences between the MsD groups in two segments of the SSCGs ($p = 0.899$). We found statistically significant differences in MsD of Tryp+ Ms between TG and SSCG ($p<0.001$). MsD in two parts of the SSCG was significantly higher than MsD in three parts of TG.

Keywords: micromorphological analysis, mastocytes, mastocytes density, sympathetic superior cervical ganglion, trigeminal ganglion

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INTRODUCTION

The story of mast cells dates back to 1878, when Paul Ehrlich, in his doctoral thesis on the properties of histological stains, introduced the medical community to this previously unknown cell type (1). While doing experiments, Ehrlich noticed a new type of aniline reactive cells in connective tissue, as granular cells with spherical shape and dimensions bigger than known leukocytes (1). He named these cells "mastzellen", suggesting that they have characteristics of fixed cells of connective tissue (1).

Mastocytes derive from the bone marrow, from the stem cells of myeloid lineage (2). Their expansion and maturation happen in bone marrow by the influence of many cytokines, such as colony stimulating factor (CSF) and nerve growth factor (NGF) (2, 3). The specific characteristic of mastocytes is their tissue residence and not presence in the bloodstream (which is a property of most of the myeloid lineage cells) (2). Stem cells of myeloid lineage differentiate into mastocyte precursor cells, which migrate through the blood to the tissues. In tissues, mastocyte precursors differentiate into mastocytes (4). The differentiation of mastocytes is a very complex and specific process in which many other cells, neuropeptides and cytokines take part (2, 4-6). These substances work under strictly controlled conditions, which is essential for the differentiation and maturation of mastocytes (6).

Mastocytes are cells of the immune system. Their diameter varies from 10 to 20 μm and they are usually oval in shape (6). In the cytoplasm of mastocytes numerous granules are detected. These granules are basophilic, with a diameter of 0.3-2 μm and they exhibit metachromatic staining characteristics (1, 6). These granules contain many classic mediators such as: proteases (most common in mastocytes are chymase and tryptase), growth factors (transforming growth factor, nerve growth factor, vascular endothelial growth factor, etc.), proinflammatory cytokines (leukotrienes, prostaglandins) and chemokines, tumor necrosis factor (TNF), proteoglycans (most common heparin), biogenic amins (serotonin, histamine), neuropeptides (SP, CGRP, VIP, CRH and many others) (4-7).

Mastocytes are well-known participants in the inflammatory process and as of today more research has proven the orchestrating function of mastocytes in inflammatory reactions (2). Antibody-dependent mechanisms can stimulate mastocytes to release their numerous substances of inflammation (2). Mastocytes are usually localized close to microvessels and terminals of the nerves innervating meninges and visceral organs (2, 8). It is believed that the membranes of mastocytes and nerve cells are in such a close contact that they even exchange the contents of granules. Many experiments approved the influence of mastocytes on neurogenic inflammation (2, 4, 6-9). Neurogenic inflammation is a very complex process that involves interactions between the nervous and vascular systems (2). The process starts with peripheral nerve sensitization when sensitized terminals of peripheral nerves release proinflammatory mediators, like SP (substance P) and CGRP (calcitonin gene-related peptide) (2, 8). This release provokes plasma extravasation and vascular dilatation (2). At the same time, CGRP and SP have effect on mastocytes, causing their activation (2). Activated and degranulated mastocytes release mediators from their granules which affect nerve terminals to release even more proinflammatory substances (2, 8). These actions form a vicious cycle in which more and more mastocytes are activated, more nerve terminals are sensitized, which causes the amplification of neurogenic inflammation (2).

Mastocytes degranulation and activation are important factors in pathogenesis of many medical conditions (2). Their most known role is in allergies and anaphylaxis, but in the past few decades their contribution to the persistent state of pain (such as in migraine) has been reported (2, 8). It is believed that mastocyte – sensory nerve interactions take a big part in the pathophysiology of migraine (8). According to some studies, mastocytes contribute to neuropathic pain, but also pelvic pain and osteoarthritis (8). The latest studies show the function of mastocytes in sickle cell disease, atopic dermatitis, psoriasis and cancer (2, 10-13).

Our study was conducted with the aim of analyzing the presence of mastocytes and mastocyte density (MsD) in three segments of the human trigeminal ganglions (TGs): ophthalmic, maxillary and mandibular, as well as in two segments: upper and lower of the sympathetic superior cervical ganglions (SSCGs), and establishing the correlation between the studied parameters.

MATERIAL AND METHODS

Histological and immunohistochemical study

Five human trigeminal ganglions (TGs) and five sympathetic superior cervical ganglions (SSCGs) of adult individuals were processed for this histochemical and immunohistochemical study. Each ganglion was removed after specific dissection of the Meckel's trigeminal cave, for the TG, and the highest part of the posterior neck, for the SSCG. We used the isotonic saline solution for the immersion of obtained ganglions, and fixed them in 4% buffered formalin. After dehydratation, specimens were embedded in paraffin and serially sliced using the Leica RM2235 rotary microtome. The sections were serially stained with hematoxylin and eosin, the next with the trichrome method of Masson, as well as the next with the mastocyte tryptase immunostaining. We prepared sets of plates from every specimen of ganglion. We treated all specimens for the immunohistochemical staining for antigen retrieval after deparaffinization. The incubation of the slices with 3% hydrogen peroxide solution

was performed to block the endogenous peroxidases. The immunostaining occured by the treatment of slices with the following mouse monoclonal primary antibody anti-mastocyte tryptase (DAKO A/S, M 7052, Denmark, 1:100). We visualized the bound antibodies after staining with a secondary antibody, after use a Mouse/Rabbit PolyDetector DAB HRP Brown (Bio SB) detection system. We counterstained the sections with Mayer's hematoxylin, dehydrated them and covered with glass slips. Two independent researchers semi-quantitatively assessed the intensity of staining. The intensity of immune reaction has been identified as very positive (+++). The quality of immunostaining was tested using the negative control, by incubating the slices with non-immune serum without primary antibody. The colored plates were examined under a light microscope (Leica DMLS) and photographed using a digital camera (Leica DFC295). Morphometric analyses were performed using image analysis software (Leica Interactive Measurements). This research protocol and examination have been approved by the authorities of the Institute of Histology and Embryology, the Institute of Anatomy, the Institute of Pathology and the Ethics Committee of the Faculty of Medicine (No. 1322/VII-23, Date 07.07.2022).

Morphometric examination

Mastocytes density (MsD) was defined as the average number of immunostained mastocytes identified in microscopic fields of analyzed ganglionic tissue. The number of mastocytes 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×), and in two microscopic areas of the SSCG parts (upper and lower). The arithmetic mean of the 20 fields of each of the 5 ganglions, measuring 341.7 μm × 250.0 μm of each size, with a corresponding area of 85425 μm^2 (0.085 mm^2) per field, was calculated for the number of mastocyte count.

Statistical analysis

For statistical analysis we used the IBM SPSS Statistics 25.0 statistical software package (SPSS, Inc., Chicago, IL, USA). We performed statistical procedures of descriptive statistics (median, mean) of the measured data, the Mann-Whitney test for independent samples and Kruskal-Wallis test with Bonferroni's correction. The normality of distribution was tested applying the Kolmogorov-Smirnov test. The probability level of $p<0.05$ was considered as a statistically significant difference.

RESULTS

The trigeminal ganglion (TG) is the largest sensory ganglion as a part of the trigeminal nerve. It is made up of pseudounipolar nerve cells. It can be subdivided into three segments in relation to the three branches that originate from the TG. Our study of the micromorphological description of mastocytes also showed the exact morphometric characteristics of tryptase-positive mastocytes in the TGs **(Figure 1A and Figure 1B)**. The mastocytes were oval in shape **(Figure 2)**. The results presented in **Table 1** clearly show that each microscopic area of the ophthalmic segment of the TG contained from 0 to 6 (median 1, mean 1.4) mastocytes **(Figure 2A)**. The maxillary segment of the TG showed from 0 to 5 Ms (median

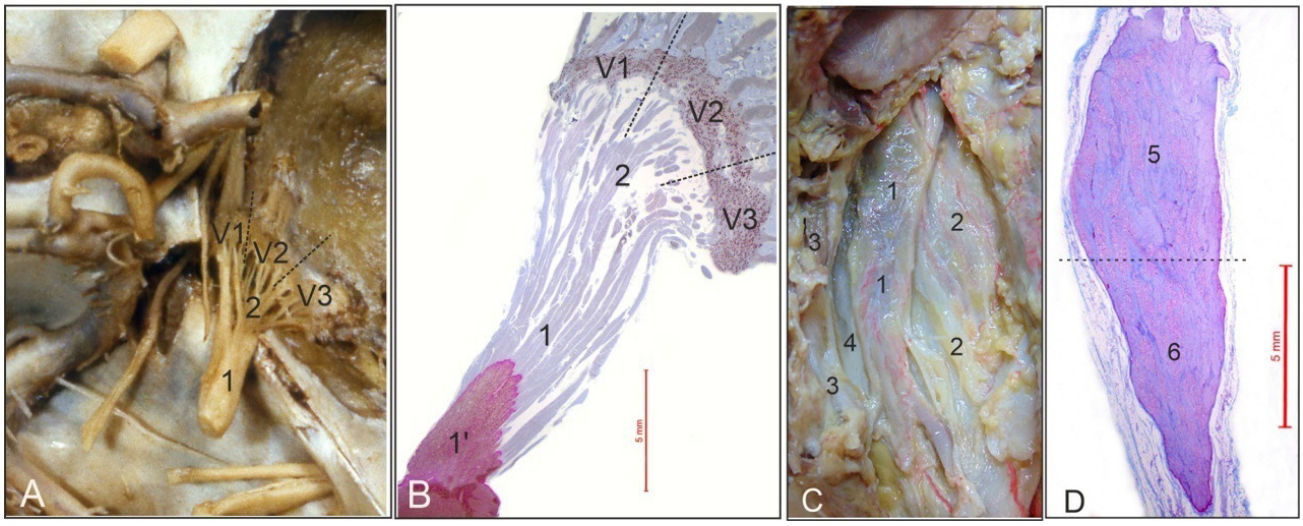

Figure 1. Microanatomical description of the trigeminal nerve (TN) and human trigeminal ganglion (TG) unite: **A** – anatomical dissection (view from above to the base of skull); **B** – histological TN-TG specimen stained with the Masson trichrome method. The intracranial part of TN (1), close to the pons composed of myelin originated from oligodendrocytes (1'). Intracaval plexiform part of TN (2) forms the TG, with ganglionic nerve cells in the ophthalmic (V1), maxillary (V2) and mandibular (V3) segments. Microanatomical description of the sympathetic superior cervical ganglion (SSCG): **C** – anatomical dissection (view from behind after removal of the vertebral column); **D** – SSCG section stained with the trichrome staining method of Masson. SSCG (1), posterior to the internal carotid artery (2), internal jugular vein (3) and vagus nerve (4). Upper (5) and lower (6) parts of the SSCG.

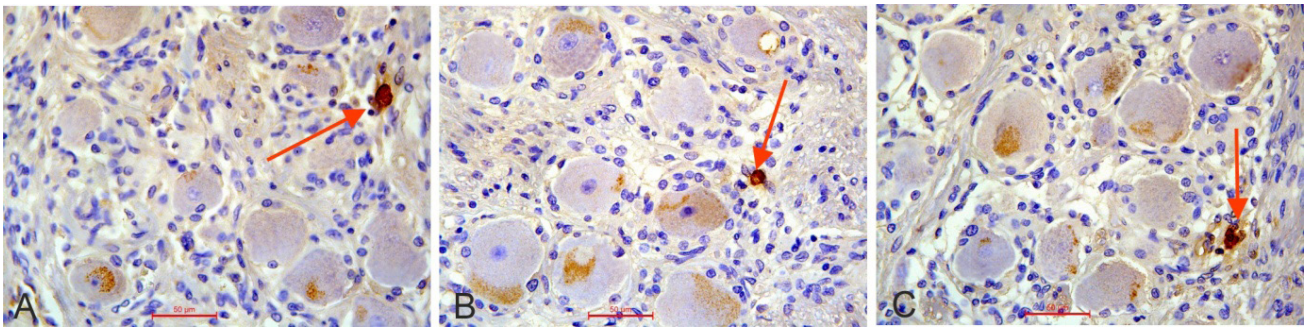

Figure 2. Nerve cells of T Ginophthalmic, V1 (**A**), maxillary, V2 (**B**) and mandibular, V3 (**C**) segments of the TG with satellite glial cells. Rare tryptase-positive mastocytes close to the nerve cells are labeled with arrows (mastocytes tryptase immunostaining, MsTryp).

1, mean 1.45) **(Table 1) (Figure 2B)**. The MsD presented in the mandibular segment had from 0 to 5 mastocytes per microscopic field of the TG (median 1, mean 1.5) **(Table 1) (Figure 2C)**. Using the Kruskal-Wallis test, we did not find a statistically significant difference in MsD between the three segments of the TG (p = 0.883) **(Figure 4)**.

Our sections showed the rare presence of the tryptase positive mastocytes (Ms) between the TN axons themselves, always near the longitudinal microvessels that accompany the nerve fibres. The numerous populations of Ms were identified in the subdural connective tissue surrounding the TG.

The sympathetic superior cervical ganglion (SSCG) is located deep in the lateropharyngeal space, posterior to internal jugular vein and the internal carotid artery. It contains multipolar sympathetic neurons. Topographically, it can be subdivided into an upper part, which sends axons to the internal carotid nerves, and a lower part, from which axons for external carotid nerves originate. Our analysis also included the exact morphometric characteristics of Ms in the SSCGs and surrounding area **(Figure 1C and Figure 1D)**. The tryptase-positive brownish mastocytes (Ms), oval in shape, had a different mean radius **(Figure 3)**. As shown in **Table 1** each microscopic area of the proximal segments of the SSCGs contained from 2 to 6 (median 4.5, mean 4.35) mastocytes **(Figure 3A and Figure 3B)**. The mastocytes density (MsD) of the distal segments of the SSCGs had from 3 to 6 (median 5, mean 4.45) Ms **(Table 1) (Figure 3C and Figure 3D)**. We did not find a statistically significant differences between the MsD groups in two segments of the SSCGs ($p = 0.899$) **(Figure 4)**.

Tryptase-positive mastocytes (Tryp+ Ms) were very often located among the nerve fibers of sympathetic nerves, usually close to microvessels, and in the perigan-glionic fibrous tissue.

Kruskal-Wallis test showed overall statistically significant differences in MsD between the three segments of trigeminal ganglions: ophthalmic, maxillary and mandibular, and two microscopic segments of the SSCG: proximal and distal ($p<0.001$) **(Table 1) (Figure 4)**.

DISCUSSION

The most common localization of mastocytes is in parts of the body that communicate with outer environment, such as mucosa of the digestive system, mucosa and submucosa of the respiratory system, brain, skin, hair follicles and dura mater (6). Some studies explain that mastocytes are connected to endothelial cells of blood vessels owing to the connections between their membranes and that they take part in forming the so-called perivascular environment (6). Our research demonstrated the homogenous and modest presence of Tryp+ Ms in all three parts of the TG. According to our research the mean number of

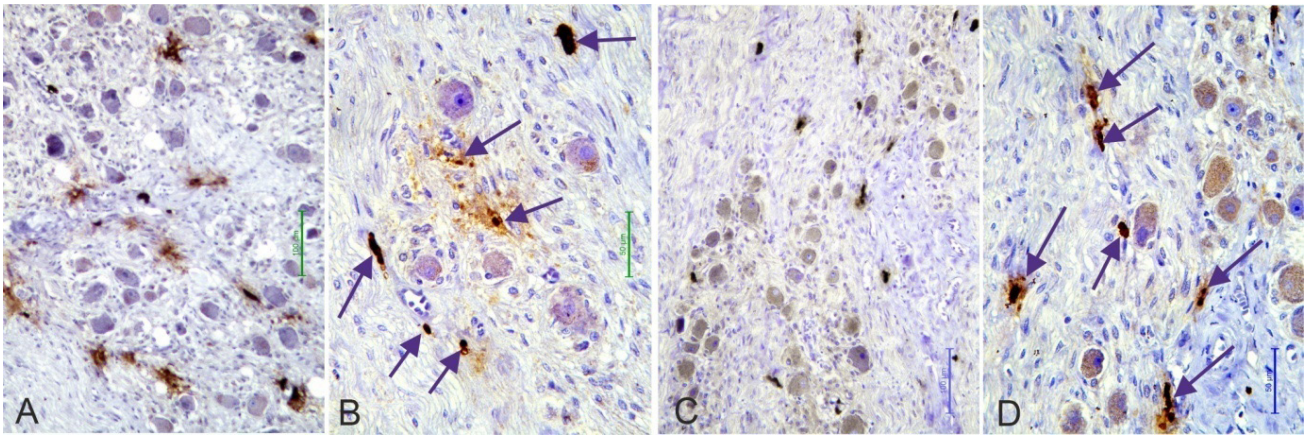

Figure 3. (**A**) Proximal segment of SSCG section and (**B**) a detail of closer view with tryptase-positive mastocytes (arrows) close to the ganglionic nerve cells (Ms tryptase immunostaining, MsTryp). (**C**) Distal segment of SSCG section and (**D**) a detail of closer view with tryptase-positive mastocytes (arrows) close to the ganglionic nerve cells (mastocytes tryptase immunostaining, MsTryp).

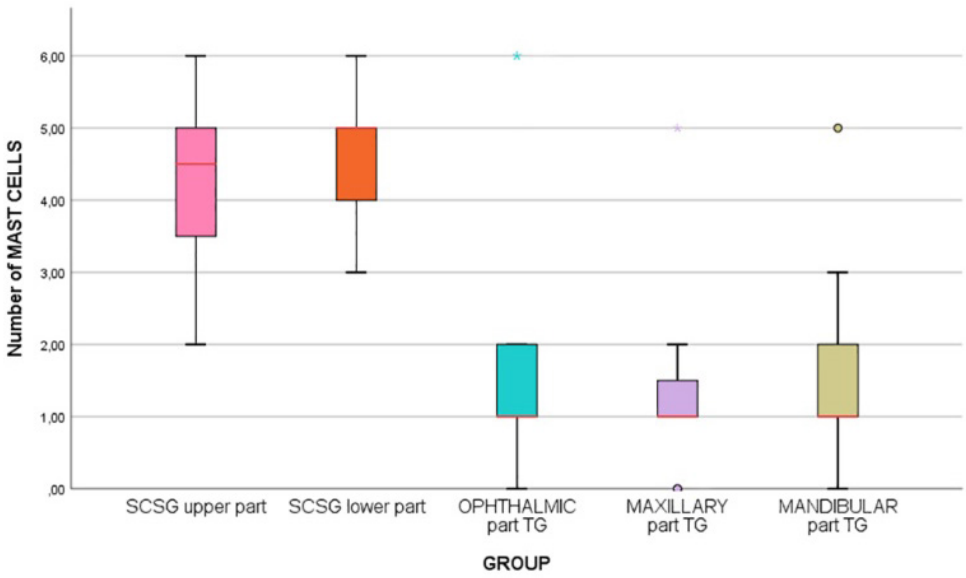

Figure 4. Comparison of mastocytes density (MsD) defined by MsTryp in microscopic areas of the SSCG parts: proximal and distal; no statistically significant differences were found between two groups ($p = 0.899$). Comparison of mastocytes density (MsD) in three segments of TGs: ophthalmic, maxillary and mandibular; no statistically significant differences were found among three segments ($p = 0.883$). Quantitative analysis revealed that MsD in two parts of the SSCG was significantly higher than MsD in three parts of TG ($p<0.001$), Kruskal-Wallis test and Bonferroni multiple comparison test.

Table 1. Mastocytes density (MsD) in three segments of the trigeminal ganglions (TGs): ophthalmic, maxillary and mandibular, and in two parts of the sympathetic superior cervical ganglions (SSCGs): proximal and distal.

Number of mastocytes/area		median (range) mean	p-value	p-value overall
Trigeminal ganglions	Ophthalmic segment	1 (0-6) 1.4	0.883	<0.001
	Maxillary segment	1 (0-5) 1.45		
	Mandibular segment	1 (0-5) 1.5		
Sympathetic superior cervical ganglions	Proximal part	4.5 (2-6) 4.35	0.899	
	Distal part	5 (3-6) 4.45		

Tryp+ Ms found in the three segments of TG was 1.4 in the ophthalmic, 1.45 in the maxillary and 1.5 in the mandibular segment. Our earlier preliminary study of microvascularization, also referred to MsD in TGs, identified, among other findings, very similar results to the current values: the mean number of Tryp+ Ms in TGs was 1.34 in the ophthalmic, 1.26 in the maxillary and 1.46 in the mandibular part (14). Reviewing the available literature, we did not find any similar studies reporting results on the number of Ms in the TGs. The findings of the present research indicated the homogenous presence of Tryp+ Ms in the proximal and distal segments of the SSCGs, and the MsD had a value of 4.35 and 4.45 respectively. Comparing our findings with the previous results, 4.5 and 4.7 of Tryp+ Ms per field, from an extended examination of micromorphological characteristics of sympathetic neurons in the SSCGs, we absolutely confirmed the values of MD found in the two examined parts of SSCGs (15). This original contribution to the scientific literature, with no similar results is the first description of the MsD in the SSCGs.

Our final comparison of higher average value of MsD in two parts of the SSCGs with the lower number of mastocytes identified in three parts of the TGs showed a statistically significant difference in MsD of Tryp+ Ms between TG and SSCG. There are rare attempts to explain the role of Ms in the two studied ganglions, as well as their influence on neurons function. The assumption is that the above results on the presence of Ms indicate that the release of stress hormones occurs in response to physiological stress, activating Ms, which leads to the excitation of ganglionic nerve cells in the SSCG (16). Sympathetic vasoconstriction of the brain arteries and arterioles is a consequence of stimulation of SSCG ganglionic neurons. Restriction of cerebral circulation and reduction of pressure in microvessels is a mechanism by which the brain is protected from increased intra-arterial pressure (17). Cerebral vasospasm as a consequence of

subarachnoid hemorrhage following aneurysm wall rupture is causally related to neuroinflammation, which may also have activation of Ms from the TG and SSCG as a potential factor in its occurrence (18, 19). The question is whether the number of Ms can have a specific effect on the stimulation and function of ganglion nerve cells in the SSCG. Larger number of Ms in the vicinity to the nerve fibers and nerve bodies, possibly change the function of neurons, and augment nerve damage, inflammation and nociception to induce hyperalgesia (6). Mastocytes have role both in peripheral and central sensitization (2). Neurogenic inflammation starts with peripheral nerve sensitization. Central sensitization is a state of continuous excitation of nociceptive neurons of the central nervous system (2). Mastocytes present in the dura mater, brain and ganglions may have direct interactions with these nociceptive neurons (2, 10). These interactions depend not only on the proximity of mast cells to nociceptive neurons and their pathways, but also on their complex interplay with surrounding glial cells—including satellite glial cells within ganglia (2). All of these factors trigger the release of substances from mastocytes and glial cells, thereby amplifying neuroinflammation (2). Some studies suggest that quite a small number of mastocytes in the brain is sufficient to cause neuroinflammation and for this reason mastocytes are thought of as pivotal participants of central sensitization process (2, 10).

Degranulation of mastocytes happens within minutes after they are stimulated (2, 4). Secretory granules loaded with proteases, cytokines, biogenic amines and many other mediators degranulate through the activation of FceR1 (2, 4). Activation of this high-affinity IgE receptor causes actin and microtubule cytoskeletal rearrangements. Microtubule polymerization facilitates the translocation of secretory granules to the plasma membrane (4). Activated FceR1 leads to the activation of Lyn and Syk, which help fusion of granules and membranes and lead to the degranulation of mastocytes (4). Degranulation of mastocytes is the first very important step in inflammation process. When mastocytes release their contents into the blood stream, clinical manifestations of these actions are visible. This investigation suggests that Ms are of great interest for further understanding of the patophysiology of headaches and pain conditions, together with microvessels, sensory nerve fibers and sympathetic neurons. Inhibition of Ms degranulation should be possible therapeutic treatment for these conditions (13, 20). Future research should aim to validate our findings on MD and compare them with the data on microvessel and ganglionic neuron density in the TGs and SSCGs in order to establish correlations between the obtained data.

CONCLUSION

This is one of the first analyses of micromorphological characteristics of human tryptase-positive mastocytes and mastocytes density (MsD) in three segments of the human trigeminal ganglions (TGs): ophthalmic, maxillary and mandibular, as well as in two parts: proximal and distal of the sympathetic superior cervical ganglions (SSCGs), showing very high statistically significant differences in MsD compared to the TG and SSCG. This micromorphological description of the human tryptase-positive mastocytes in the trigeminal ganglions and in the sympathetic superior cervical ganglions showed that these cells need particular attention in the therapeutic treatment.

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Author Contributions: Conception and study design: MĆ, AMil, JB, DL. Histological analysis, data collection and data analysis: MĆ, AMil, JB, AMir. Manuscript preparation and interpretation of the data: MS, NB, MM. Writing the manuscript: MĆ, JB, AMil, DL. Critical revision of the manuscript: MS, NB, AMir. Final approval of the manuscript before submission: MĆ, AMil, JB, MS, DL, NB, AMir, MM.

Ethical approval: This research protocol and examination have been approved by the authorities of the Institute of Histology and Embryology, the Institute of Anatomy, the Institute of Pathology and the Ethics Committee of the Faculty of Medicine (No. 1322/VII-23, Date 07.07.2022).

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MIKROMORFOLOŠKE KARAKTERISIKE MASTOCITA U TRIGEMINALNIM I HUMANIM SIMPATIČKIM GORNJIM VRATNIM GANGLIONIMA

Mila Ćetković[1], Aleksandra Milosavljević[1], Jelena Boljanović[2], Darko Laketić[2], Marko Simić[3], Nikola Bogosavljević[4], Aleksandar Mirčić[1], Milan Milisavljević[2,5]

Sažetak

Uvod: Mastociti (Mt) se obično nalaze u blizini mikrosudova i završetaka nerava koji inervišu moždanice i unutrašnje organe. Granule Mt sadrže brojne medijatore koji utiču na nervne ćelije i modifikuju njihove reakcije.

Cilj rada: Naše proučavanje imalo je za cilj da se analizira prisustvo i distribucija mastocita (Mt), kao i gustina mastocita (GMt) u tri dela humanih trigeminalnih gangliona (TG): oftalmički, maksilarni i mandibularni, kao i u dva dela: proksimalni i distalni, humanih simpatičkih gornjih vratnih gangliona (SGVG), kao i da se postavi korelacija između proučavanih parametara.

Materijal i metode: Pet TG i pet SGVG odraslih osoba obrađeno je za ovu histohemijsku i imunohistohemijsku studiju. Preparati su serijski sečeni i obojeni hematoksilinom i eozinom i Masson trihrom metodom, a sledeći isečci su pripremljeni za imunohisthemijsko bojenje triptaze mastocita.

Rezultati: Prosečan broj triptaza-pozitivnih (Trip+) Mt u mikroskopskim poljima, GMt, bio je 1,4 u oftalmičkim delovima, 1,45 u maksilarnim delovima i 1.5 u mandibularnim delovima TG. Broj Trip+ Mt u mikroskopskim poljima bio je od 2 do 6 (Med = 4,5) u proksimalnim delovima i od 3 do 6 (Med = 5) u distalnim delovima SGVG. Distribucije Mt u tri dela humanih TG i dva dela SGVG bile su uniformne, bez specifičnih mikromorfoloških varijacija. Ovo je prva mikromorfološka analiza Trip+ Mt i GMt u humanimTG i SGVG.

Zaključak: Nismo pokazali statistički značajnu razliku između aritmetičkih sredina GMt u tri segmenta TG (p = 0.883). Takođe, nismo pokazali statistički značajnu razliku između grupa GMt u dva segmenta SGVG (p = 0.899). Postojala je statistički značajna razlika u GMt Trip+ Mt između TG i SGVG (p<0.001). GMt u dva dela SGVG bila je značajno veća nego GMt u tri dela TG.

Ključne reči: mikromorfološka analiza, mastociti, gustina mastocita, simpatički gornji vratni ganglion, trigeminalni ganglion.

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