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Microanatomy of the neural scaffold of the pterygopalatine fossa in humans: trigeminovascular projections and trigeminal-autonomic plexuses

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The pterygopalatine fossa (PPF) is an anatomically-hidden deep extracranial space. The neural scaffold of the PPF remains anatomically understudied in humans. Moreover, there are no anatomical data in humans pointing out the extracranial trigeminovascular distributions, in contrast to the trigeminal supratentorial ones. By anatomical microdissections, the neural scaffold of the PPF and the presence of trigeminovascular projections were evaluated. The anterior and superior approaches of the pterygopalatine fossae in nine dissected blocks of human middle skull base and the frontal cuts of two different specimens, led to several results: (1) the neurovascular contents of the PPF, embedded in the pterygopalatine adipose body, have a layered disposition; (2) the posterior neural layer is represented by a pterygopalatine cross*, centred by the pterygopalatine ganglion (PPG) that sends off ascending, descending, and medial branches and has a lateral connection with the maxillary nerve — 4 quadrants could have been defined as referring to this cross; (3) at the level of the upper lateral quadrant there are two superposed layers (i) a superficial plexus contributed by the maxillary nerve, the maxillary artery plexus and the PPG and its orbital branches (OBs) and (ii) a deep layer, consisting of the OBs proper of the PPG; (4) within the PPF and on the posterior wall of the maxillary sinus distinctive trigeminovascular projections were evidenced. The anastomoses involving autonomic and trigeminal fibres, located in the PPF passage to the orbital apex, support the complicate and polymorphous neural input to the orbit, while the evidence of a pterygopalatine trigeminovascular scaffold offers a substrate for a better understanding of various facial algias.* (Folia Morphol 2010; 69, 2: 84–91)

Key words: sphenopalatine ganglion, trigeminal nerve, maxillary artery, periarterial sympathetic plexus

INTRODUCTION

The pterygopalatine fossa (PPF) is a small area that lies deep in the cranial base and has extensive communication with contiguous cranial base areas (such as the middle cranial fossa, orbit, nasal cavity, oral cavity, and infratemporal fossa) [7]. The PPF has been called, somewhat facetiously, "the Piccadilly Circus of the face" [18].

Most of the surgical procedures that have been used for the removal of lesions involving the PPF

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were extensive transcranial or transfacial approaches. The use of an endoscopic endonasal approach has led neurosurgeons to evaluate the possibility of introducing this technique for the treatment of lesions of the pterygopalatine fossa and other areas of the skull base [14]. This makes the anteriorly-viewed anatomy and topography of the PPF highly relevant for surgery.

The PPF contents are represented by a complex array of vascular and neural structures [4]. The anterior compartment of the PPF contains the (internal) maxillary artery and its branches, while the posterior compartment of the pterygopalatine fossa contains the pterygopalatine ganglion and its branches, and the maxillary nerve [1]. Apart from the sphenopalatine vein, which runs an oblique course in or just under the anterior periosteum of the PPF, no veins of any importance are found at that level [18].

After opening the posterior wall of the maxillary sinus, the fat tissue is visualized. All of the structures of the pterygopalatine fossa are fully immersed in this fat tissue. After removing the fat tissue, all vascular, nerve, and muscle structures begin to appear [14]. This fat tissue, which I consider adequate to term the pterygopalatine adipose body, expands in individually variable degrees in the parasellar region as parasellar adipose body [17].

The PPF neural scaffold is more complex than traditionally described, and it is understudied in humans [12]. We recently produced evidence to support the fact that, at the level of the PPF, the maxillary artery plexus, well-known for being supplied by the external carotid artery plexus, is reinforced by sympathetic fibres brought by the Vidian nerve, which is supplied from the internal carotid artery plexus. Thus, the anatomic content of the PPF may be regarded as trigeminal, autonomic (equally sympathetic and parasympathetic) content, and that is how it must be regarded when the patophysiology and/or treatment of the trigeminal autonomic cephalalgias (TACs) are considered [13]. We also evaluated that the pterygopalatine ganglion (PPG) cannot be considered a constant, unique structure in humans but as a morphologically individually variable structure, at macroscopic and microscopic levels [12].

Considering that arguments can be brought to update the simplistic traditional data on the PPF autonomic content, the trigeminal influence at this level seems under-evaluated within research. This gave the general aim of the present study: to make an exhaustive evaluation by microdissections of the maxillary nerve distribution within the PPF.

Blood vessels in the brain, pia mater, and dura mater are innervated by dense networks of unmyelinated nerve fibres. For supratentorial structures, the innervation originates from the trigeminal ganglion (TG), constituting the trigeminovascular system (TVS); for subtentorial structures, the innervation originates from the dorsal roots of the upper cervical nerves [3].

The nerve cell bodies of these fibres contain several transmitters including substance P (SP) and calcitonin gene-related peptide (CGRP). Stimulation of the large cerebral vessels and the meninges produces pain following activation of the unmyelinated nociceptive fibres that innervate these structures. Similarly, stimulation of the trigeminal nerve results in release of substance P, CGRP, neurokinin A, and other transmitters from the nerve endings (following antidromic conduction) into the blood vessel walls and meninges, producing sterile inflammation, accompanied by vasodilatation and extravasation of plasma proteins. This results in pain that may be exacerbated by otherwise innocuous stimuli such as vessel pulsation [3].

A hypothesis was raised: if the TG is the provider of SP and CGRP for antidromic conduction into the cerebral blood vessels, could its vascular territory be extended beyond the skull base? If so, anatomical trigeminovascular connections should be evident in extracranial locations.

We aimed to test this hypothesis, at the level of the PPF, by microanatomical dissections and thus complete the update on the neural scaffold of the PPF and define as positive or negative the presence of a pterygopalatine trigeminovascular system (PPTVS). As our previous studies tested various approaches of the PPF *in situ*, for the present study it was decided to use only anterior approaches on middle skull base dissected specimens, which were better suited to be correlated with various microsurgical and endoscopic approaches: transnasal or transantral.

MATERIAL AND METHODS

For the present study 18 pterygopalatine fossae in 9 specimens of middle skull base were microdissected (at 4.5 × magnification) that were dissected from adult prosected specimens (sex ratio 5:4, male:female, mean age 62). Two additional middle skull base blocks were decalcified (formic acid) and were then cut serially in the frontal/coronal plane. The cadavers were made available by the Department of Anatomy of the institution of the Author and were used according to the institutional and national available ethical legislative framework (for

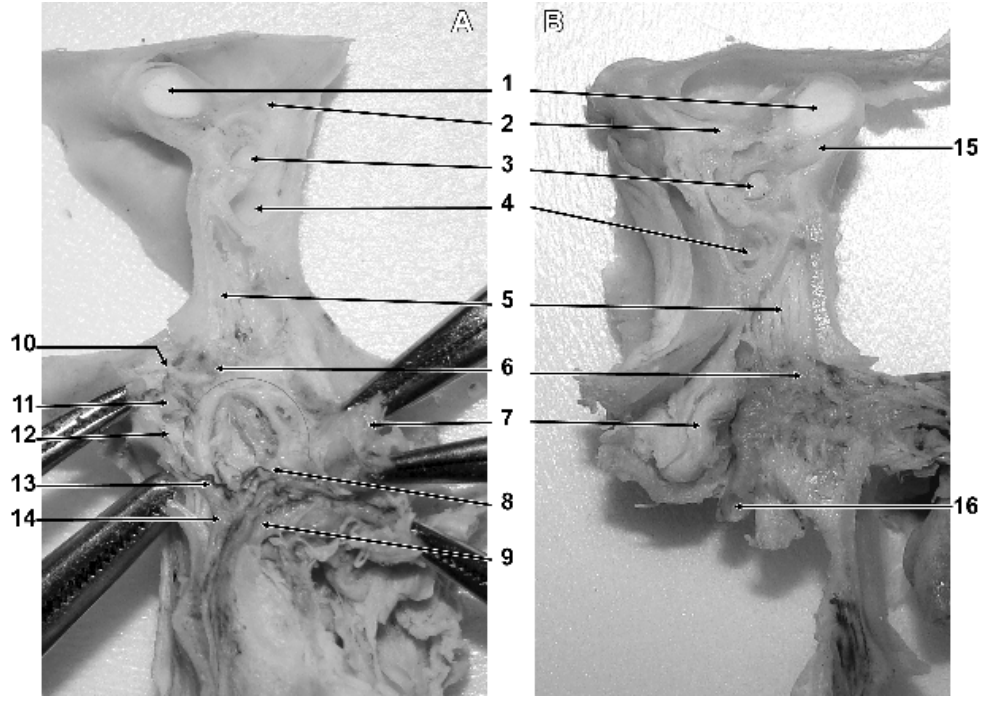

Figure 1. Frontal cut on the left side at the level of the pterygopalatine fossa (PPF): the correspondent facing slices: **A.** Anterior view; **B.** Posterior view; 1. optic nerve; 2. trochlear nerve; 3. abducens nerve; 4. inferior ophthalmic vein; 5. orbital branches of the pterygopalatine ganglion (PPG); 6. PPG; 7. maxillary nerve (MN); 8. lateral (maxillary) root of the greater palatine nerve; 9. descending palatine artery; 10. pharyngeal branch of the PPG (nerve of Bock); 11. sphenopalatine artery; 12. posterior superior nasal branches of the PPG; 13. medial (pterygopalatine) root of the greater palatine nerve; 14. greater palatine nerve; 15. ophthalmic artery; 16. maxillary artery (MA). The red circle marks a neural ring formed by the pterygopalatine nerve, superiorly, and the lateral and medial roots of the greater palatine nerve, separately emerging from the MN; within that ring, MN-to-MA fibres and PPG-to-MA neural twigs were recorded.

details see also McHanwell et al.) [8]. The anatomical blocks were first approached superiorly, and the Meckelian cavum and lateral sellar compartment (cavernous sinus) were microdissected. Then, by anterior and lateral approaches, the pterygopalatine fossae and pterygomaxillary fissures were also microdissected; the neurovascular elements at that level were accurately identified and documented in all the stages of the dissections.

RESULTS

As resulted from the anterior approaches, the PPF may be divided into an upper sphenoidal and a lower maxillary compartment. The upper compartment appeared to be located in front of the Vidian and maxillary nerve canal anterior openings, so it could have been further divided into outer and inner chambers. The inner chamber of the upper compartment lodged the main PPG, as is traditionally described, while the outer chamber was traversed in an oblique, anterior, inferior, and lateral direction, by the maxillary nerve (MN) (Fig. 1).

The contents of the PPF, evidenced after the anterior periosteum of the fossa was incised, were embedded within a consistent pterygopalatine adipose body (PPAB) (Fig. 2A) that continued superiorly into the orbital apex and extended further as parasellar adipose body (PAB), inferiorly and distinctive to the orbital adipose body.

Two distinctive, anterior, vascular, and posterior neural layers of the PPF were evidenced. Within the vascular layer, on the maxillary artery (MA) and its branches at that level, small veins of the pterygomaxillary plexus were constantly applied, extending from the pterygomaxillary fissure (PMF); the sphenopalatine vein appeared distinctively on the anterior side of the MA (Figs. 3, 4). On the anterior side of the MA was evidenced a well-configured periarterial plexus (anterior MA plexus) (Fig. 2B).

After removing or reflecting the MA, access was gained on the neural layer of the PPF. Here, the PPG and MN were constantly joined by a transverse neural link, corresponding to the pterygopalatine nerve (PPN) (Figs. 1, 2D). Distally to the pterygopalatine nerve (PPN), the MN entered the PMF and sent off the superior posterior alveolar nerves (SPANs) (Figs. 3, 5); those nerves were descending on the posterior wall of the maxillary sinus, either directly applied

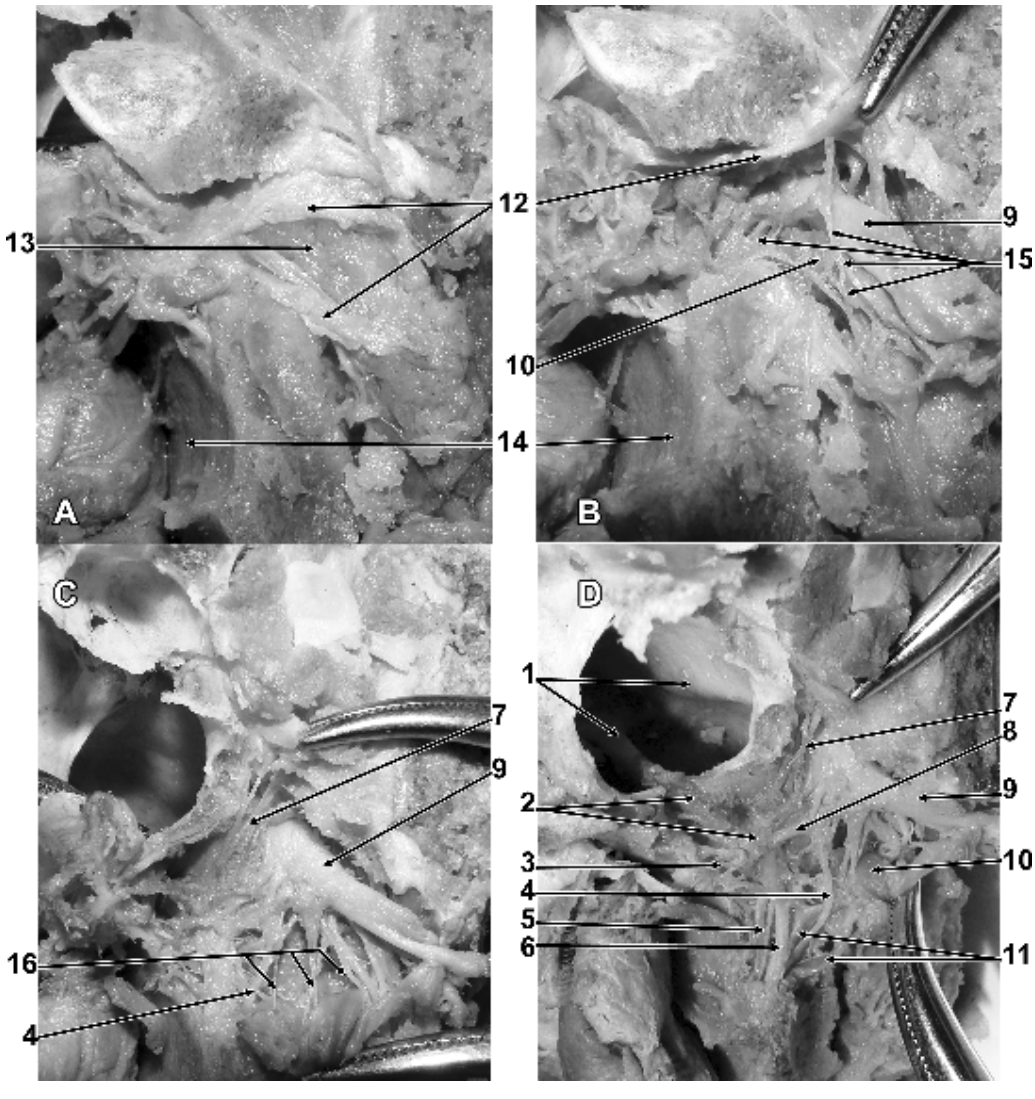

Figure 2. Anterior dissections of the left pterygopalatine fossa (PPF) demonstrate the anatomical layers: **A.** Periosteum of the anterior wall of the PPF is incised and the pterygopalatine adipose body is observed embedding the fossa contents; **B.** After removing the fat, the anterior vascular layer is evidenced and the periarterial plexus of the maxillary artery is dissected; **C.** The maxillary artery is reflected, and so the trigeminovascular fibres emerging from the maxillary nerve are evidenced; **D.** The complicate neural layer is evidenced, centred by the pterygopalatine ganglion and linked to the maxillary nerve and to the maxillary artery plexus; 1. within the sphenoidal sinus, the protrusions of the maxillary and Vidian nerve canals are evident; 2. Vidian nerve, pterygopalatine ganglion (PPG); 3. nasal branches of the PPG; 4. lateral (maxillary) root of the greater palatine nerve; 5. lesser palatine nerves; 6. greater palatine nerve; 7. orbital branches of the PPG; 8. pterygopalatine nerve, linking the maxillary nerve to the PPG; 9. maxillary nerve; 10. maxillary artery (reflected postero-laterally); 11. duplicated descending palatine artery; 12. periosteum of the anterior wall of the PPF; 13. pterygopalatine adipose body; 14. nasal surface of the perpendicular plate of the palatine bone; 15. anterior plexus of the maxillary artery; 16. trigeminovascular anatomical connections of the maxillary nerve and maxillary artery plexus.

on the periosteum or crossing over the MA and pterygomaxillary venous plexus.

From the PPG emerged:

- upper branches:

— the pharyngeal branch (PhB), directed posteromedially, to the palatovaginal canal beneath the sphenoidal sinus floor (Fig. 1);

— the orbital branches (OBs), directed superolaterally, towards the orbital apex, in front of the medial part of the superior orbital fissure (Figs. 1, 2C, 2D, 4);

- medial branches:

— the posterior superior nasal branches (PSNBs) that entered the sphenopalatine foramen (Fig. 1, 2D);

- descending branches:

— the greater palatine nerve (GPN) — as it was also constantly encountered a different distinctive nerve leaving either the MN directly or the ptery-

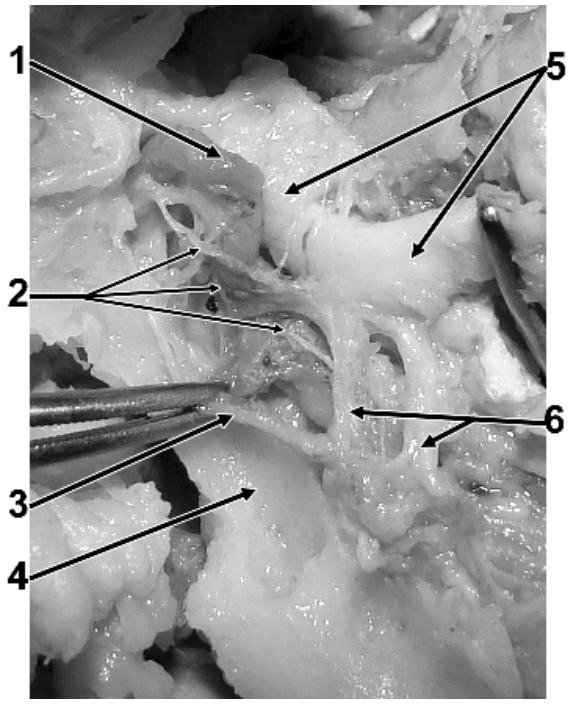

Figure 3. Trigeminovascular connections, of the maxillary nerve and the anterior plexus of the maxillary artery, within the left pterygopalatine fossa, antero-infero-lateral view; 1. maxillary artery, looping in front of the maxillary nerve; 2. trigeminovascular nerves; 3. sphenopalatine vein; 4. posterior wall of the maxillary sinus; 5. maxillary nerve; 6. superior posterior alveolar nerves.

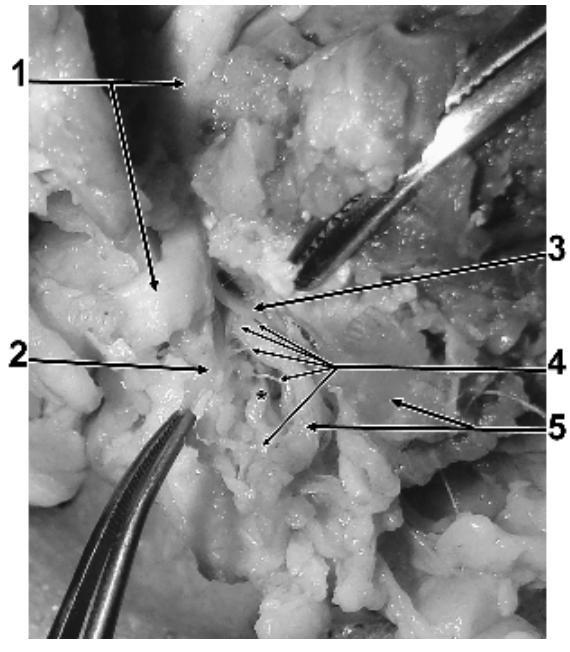

Figure 5. Trigeminovascular connections at the level of the posterior wall of the maxillary sinus (pterygomaxillary fissure), between the superior posterior alveolar nerves and the maxillary artery plexus, on the left side, viewed postero-laterally; 1. maxillary nerve; 2. superior posterior alveolar nerves, coursing directly on the posterior wall of the maxillary sinus; 3. superior posterior alveolar nerve, separated from the posterior sinusal wall by the vascular layer at this level; 4. trigeminovascular connections of the superior posterior alveolar and maxillary nerves and the maxillary artery plexus; 5. lateral pterygoid muscle, maxillary artery. Venous elements of the pterygomaxillary plexus are also visible (*).

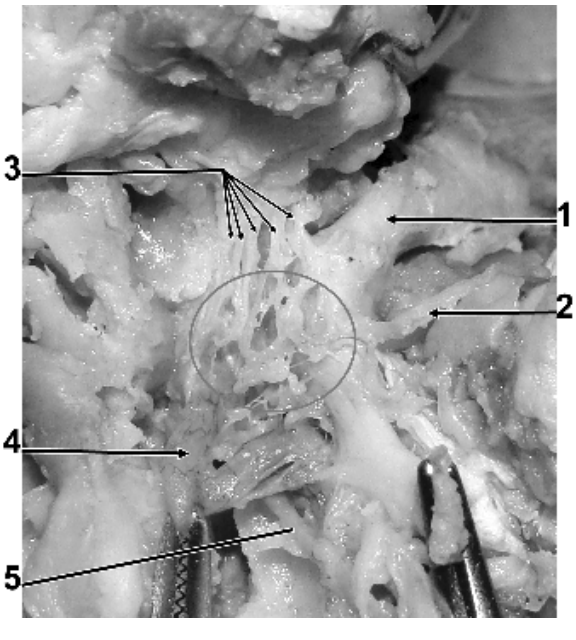

Figure 4. Trigeminal-autonomic pterygopalatine plexus (red circle) on the posterior surface of the maxillary artery, within the left pterygopalatine fossa (PPF), antero-infero-lateral view; 1. maxillary nerve; 2. zygomatic nerve, reflected; 3. orbital branches; 4. maxillary artery, reflected; 5. sphenopalatine vein — the anterior vein of the PPF, tributary of the pterygomaxillary plexus.

gopalatine nerve and running in the greater palatine canal; the one emerged from the PPG was defined as the medial (pterygopalatine) root of the GPN, while the one that emerged from the MN/pterygopalatine nerve was defined as the lateral (maxillary) root of the GPN — these two roots could unite at the entrance of the greater palatine canal (Fig. 1A) or could enter separated within the canal (Fig. 2D);

- the lesser palatine nerves, on the antero-medial side of the GPN (Fig. 1, 2D);

Based on the course of the PPG branches, a neural pterygopalatine "cross" (PPC) could have been considered in the frontal/coronal plane: the cross was centred by the PPG — the upper arm corresponded to the vidian nerve (nerve of the pterygoid canal), the lower arm was made by the GPN medial root, the inner arm was made by the PSNBs, and the outer arm was represented by the PPN (Fig. 6). Thus, four quadrants were defined, referring to that PPC:

— a superolateral quadrant, traversed by the OBs of the PPG;

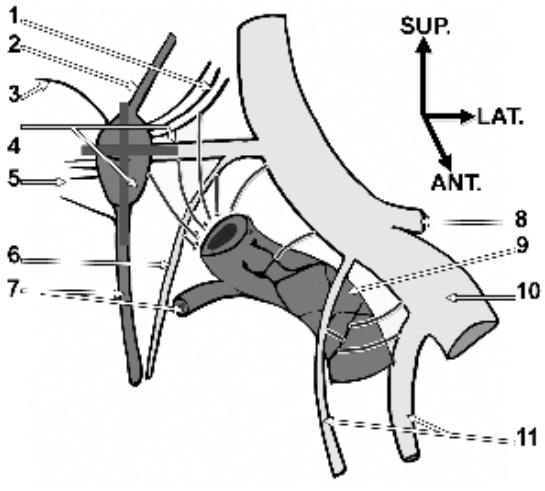

Figure 6. Schematic drawing depicting the anastomoses of the maxillary nerve and branches, on the one hand, and the pterygopalatine ganglion (PPG) and efferents, on the other hand, with the maxillary artery plexus, on the left side, anterior view; 1. orbital branches of the PPG; 2. Vidian nerve; 3. pharyngeal branch of the PPG; 4. PPG, pterygopalatine nerve; 5. nasal branches of the PPG and greater palatine nerve; 6. lateral (maxillary) root of the greater palatine nerve; 7. greater palatine nerve, descending palatine artery; 8. zygomatic nerve; 9. maxillary artery; 10. maxillary nerve; 11. superior posterior alveolar nerves. The blue cross marks the pterygopalatine neural cross.

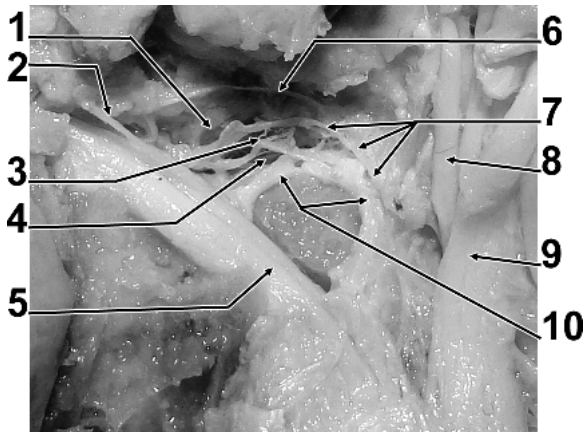

Figure 7. The left pterygopalatine fossa (PPF) — superior view demonstrating the distribution of the trigeminal-autonomic plexus within the supero-lateral quadrant of the pterygopalatine cross; 1. maxillary artery and its plexus; 2. periorbital branch of the maxillary nerve, emerging proximally to the zygomatic nerve origin and distinctive to it; 3. trigeminal-autonomic plexus; 4. orbital branches proper of the pterygopalatine ganglion; 5. maxillary nerve, within its canal; 6. recurrent lateral periorbital branch of the plexus within the orbital apex; 7. branch of the trigeminal--autonomic plexus of the PPF entering the wall of the lateral sellar compartment; 8. abducens nerve; 9. ophthalmic nerve; 10. posterior periosteum of the PPF, at the level of the anterior root of the major sphenoidal wing.

— a superomedial quadrant, corresponding to the PhB of the PPG;
— a narrow inferomedial quadrant, extended as the greater palatine canal;
— a larger inferolateral quadrant, inferior to the PPN and containing the lateral (maxillary) root of the GPN, extending to the lower compartment of the PPF and the PMF.

Distinctive anatomical connections were constantly encountered, joining the MN and MA plexus; these trigeminovascular fibres were direct connections in the PPF (Figs. 2D, 3) or were indirect, joining the SPANs and the MA plexus on the posterior wall of the maxillary sinus (Fig. 5).

At the level of the lateral quadrants determined by the pterygopalatine "cross" there were two layers of trigeminovascular connections:
— trigeminovascular connections of the MN and the anterior plexus of the MA;
— a distinctive plexus was evidenced on the posterior side of the MA, superposed over the PPN (Fig. 4); as this constantly encountered plexus was supplied by the MN, the PPG, and the OBs but was also linked to the MA plexus, it was considered as a trigeminal-autonomic plexus of the PPF. Orbital branches emerging from that plexus were evidenced, distinctive to the OBs proper of the PPG and located superficially to the latter (Figs. 4, 7), entering the retro-orbital plexus and seeming to distribute in the periorbit of the orbital apex and to the lateral sellar compartment (in addition, direct periorbital branches of the MA anterior plexus, the MN, and the retro-orbital plexus were recorded).

Thus, it seemed opportune to define two layers of orbital branches leaving the PPF:
— a superficial layer, mainly trigeminal-autonomic, supplied by fibres of the maxillary nerve and MA plexus and anastomosed with the OBs of the PPG;
— a deep layer, mainly represented by the OBs proper of the PPG.

DISCUSSION

It appears from the present study that, distally to the foramen rotundum, the maxillary nerve contributes with fibres (a) directly to the arterial plexus of the maxillary artery and its branches (arterial trigeminal branches) and (b) to the trigeminal-autonomic plexus located in the upper lateral quadrant of the pterygopalatine cross, beneath the roof of the fossa (anastomotic trigeminal branches).

On the extracranial trigeminovascular distribution

The present study gave evidence that sustains the existence of an anatomically defined PPTVS and thus confirms the working hypothesis. This PPTVS is

represented by the projections, either of the MN or the superior posterior alveolar nerves, on the periarterial plexuses of the maxillary artery and its branches within the PPF and on the posterior wall of the maxillary sinus. However, it still remains for this anatomical PPTVS to be proven functional, by evaluating in experimental studies the discharge of the trigeminal nociceptive peptides, SP and CGRP, via the maxillary nerve, on the maxillary artery. The possibility of the PPTVS being functional has been suggested by very few identified studies. Stjärne et al. [15] detected in the pig CGRP and SP immunoreactive fibres in the maxillary portion of the trigeminal nerve and around the sphenopalatine artery and vein, as well as around the nasal dorsal vein. Okamura et al. [9] demonstrated neurogenic inflammation of canine labial arteries, involving the mediation of the sensory nerve-derived CGRP. Thus, the extracranial trigeminovascular projections seem not to be inexistent, but understudied.

In must also be taken into account that the maxillary nerve may be a tyrosine hydroxylase (TH) provider, as was demonstrated by the marked TH-staining of the zygomatic nerve as it enters the orbit, in humans [16]. As some of the neurons of the human trigeminal ganglion are TH-positive (TH sensory neurons, personal unpublished data), the possible catecholaminergic quality of the PPTVS must also be kept in mind. This is not at all speculative, as it has already been proven that primary sensory neurons express catecholaminergic transmitter traits in the normal adult rat [5, 6].

The PPTVS may be one anatomical substrate involved in the neurovascular orofacial pain (NVOP), as the NVOP diagnostic criteria include (1) facial pain attacks, (2) severe, unilateral oral and/or perioral pain that may refer to orbital and/or temporal regions, (3) at least one of the following characteristics: toothache with no local pathology, throbbing, or wakes, (4) ipsilateral lacrimation and/or conjunctival injection, (5) ipsilateral rhinorrhea and/or nasal congestion, and (6) ipsilateral cheek swelling [2]. Additionally, PPTVS involvement in the trigeminal autonomic cephalalgias (TACs) is not negligible.

On the orbital trigeminal-autonomic input via the PPF and the MA plexus

The OBs of the PPG are described in the Anatomy of Gray as „[...] two or three delicate filaments, which enter the orbit by the inferior orbital fissure, and supply the periosteum. According to Luschka, some filaments pass [...] to the mucous membrane of the posterior ethmoidal and sphenoidal sinuses". Since then, various studies, most of them performed by Ruskell, have improved knowledge on these nerves.

It was demonstrated in the present study that the input of the PPF to the orbit uses two distinctive anatomical paths: one represented by a plexus located beneath the periorbital roof of the fossa and contributed by all the major neural components of the PPF — the PPG and its OBs, the MN, and the MA plexus; and the other, deeper than the previous and directly applied on the bony scaffold, represented by the OBs proper of the PPG. This trigeminal-autonomic plexus (of the PPF roof) appeared mainly as a supplier of the inferior periorbit at the orbital apex and an anastomotic path to the lateral sellar plexus. A comparable distribution was also evidenced in primates [11]. Ruskell, referring to his previous work of that time (Ruskell 1965, 1968), stated the parasympathetic content of the OBs; in the paper cited here, he described in primates 9–13 such branches that enter the orbital apex in one or two groups, some of these being periosteal or entering the orbit through the periosteum, and most of these passing towards the abducens and ophthalmic nerves in a retro-orbital position. Ruskell also evidenced that the OBs often divided at least once and occasionally anastomosed within the pterygopalatine fossa (no other details of these anastomoses are given), thus offering a correlate of the comparative anatomy for the findings reported in this paper. On the direct periorbital distribution of the MN and the MA plexus that was evidenced by the present study, no available references were found.

In humans it was demonstrated that one group of OBs of the PPG pass dorsally, join the retro-orbital plexus at the orbital apex, and a number of *rami lacrimales* advance from the plexus to enter the lacrimal gland; thus the traditional assumption that secretomotor nerves pass to the gland via the zygomatic and lacrimal nerves was considered unlikely and clinical measures to reduce lacrimation based on that assumption and involving severance of ophthalmic branches was considered as not indicated [10]. Such recurrent branches of the retro-orbital plexus to the lateral orbital wall were also evidenced during the present study.

Due to the anatomically demonstrated connections of the MA plexus with the OBs it appears reasonable to speculate a possible contribution of the superior cervical ganglion via the external carotid plexus to the orbit and to the lateral sellar plexus. Tracing studies can further evaluate this hypothesis, passing the limits of the microdissection method.

If the identity of the OBs fibres or their function remains a debatable topic, as thought by Ruskell in 1970 [11], the existence of extracranial trigeminovascular projections at the level of the PPF is not deniable and must be taken into account when considering the clinical pictures of various pain syndromes such as the NVOP or the TACs. Moreover, the neuropeptidergic content of these fibres should be evaluated.

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