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Anatomic description of the basivertebral nerve and meningeal branch of the spinal nerve in the dog

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ABSTRACT

Purpose: The existence of the basivertebral nerve and meningeal branch of the spinal nerve has not been proven in dogs to date. The objectives of this study are to 1) determine whether dogs have a meningeal branch of the spinal nerve (MBSN) and a basivertebral nerve (BVN) and to (2) describe anatomical characteristics of these two nerves. Authors also put forward a discussion on the possible clinical relevance of these findings.
Material and methods: Dissections were performed on six embalmed dogs at the Veterinary Faculty of Barcelona with the use of stereomicroscopy and microsurgery equipment.
Results: The MBSN (grossly) and BVN (grossly and histologically) were identified in the cervical, thoracic, and lumbar region in all dog specimens. In addition, other small fibers (suspected nerves) entering the vertebral body through small foramina close to the end plates were identified. Histological examination of the tissues confirmed the presence of nerve fibers (myelinated and unmyelinated) in suspected BVN samples. Results of the present study indicated that dogs have BVNs. Also, suspected nerve fibers were identified among the epidural fat, running from the intervertebral foramina, that likely represent the MBSN.
Conclusion: These findings open up the discussion on extrapolation of treatment options employed in human medicine for “low back pain”, such as BVN ablation, which is discussed in this article. Further anatomic and clinical studies of the innervation for the vertebral body, periosteum, vasculature, dorsal longitudinal ligament and anulus fibrosus are necessary to elucidate possible anatomical variants and breed differences as well as potential clinical (e.g., therapeutic) relevance.

1. Introduction

In dogs, dorsal and ventral nerve rootlets occur at each spinal cord segment bilaterally, merge and form spinal nerves (Evans and DeLahunta, 2012a). The dorsal nerve root has a ganglion that contains sensory nerve cell bodies. In general, the dorsal and ventral nerve roots merge and form spinal nerves at approximately the level of the intervertebral foramen. Four branches are known to originate from the spinal nerve: a meningeal branch (MBSN), a dorsal branch, a communicating branch, and a ventral branch. The MBSN is also known as the ‘recurrent meningeal nerve’, ‘(recurrent) nerve of Luschka’ or ‘(recurrent) sinuvertebral nerve’ (preferred in the human literature), although the accepted term included in the current Nomina Anatomica Veterinaria is ramus meningeus of the nervi spinales (World Association of Veterinary Anatomists. International Committee on Veterinary Gross Anatomical Nomenclature, 2017). In much of the human literature, this nerve is reported to consist of afferent axons and postganglionic sympathetic axons that supply the dura mater, the dorsal longitudinal ligament, the ventral internal vertebral venous plexus, the anulus fibrosus and other blood vessels located in the vertebral canal (Forsythe and Ghoshal, 1984; Pederson et al., 1956; Shayota et al., 2019). Innervation of the anulus fibrosus

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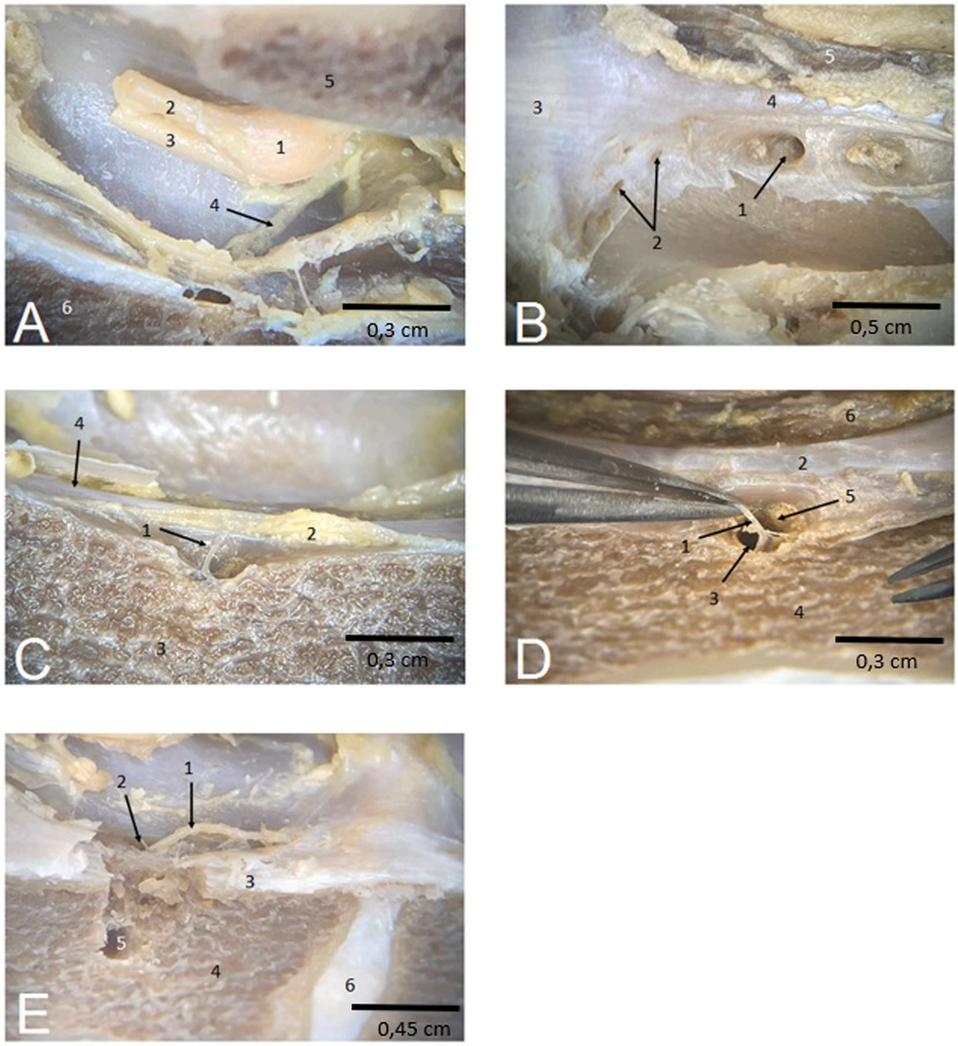

Fig. 1. Macroscopic images of the anatomical structures at different levels of the vertebral column. Cranial is to the left on all images. A: Internal right sagittal view of the vertebral canal at C7. 1) spinal ganglion, 2) dorsal root, 3) ventral root, 4) meningeal branch of spinal nerve (recurrent nerve), 5) vertebral arch, 6) vertebral body. B: Dorsal left-side view of the floor of the vertebral canal at T13. 1) basivertebral vein, 2) accessory basivertebral veins and nerves, 3) intervertebral disc and expansion of the dorsal longitudinal ligament, 4) dorsal longitudinal ligament in the midline, 5) ventral internal vertebral venous plexus (contralaterally resected). C: Median internal view (sagittal section) of the vertebral canal and vertebral body at L4. 1) nutrient artery and basivertebral nerve, 2) epidural fat, 3) vertebral body, 4) dorsal longitudinal ligament in the midline. D: Median internal view (sagittal section) of the vertebral canal and vertebral body at L4. 1) nutrient artery and basivertebral nerve, 2) dorsal longitudinal ligament, 3) basivertebral foramen and nutrient artery, 4) vertebral body, 5) basivertebral vein, 6) epidural fat and ventral internal vertebral venous plexus.E: Median internal view (sagittal section) of the vertebral canal and vertebral body at L2. 1) nutrient artery and basivertebral nerve entering the right basivertebral foramen, 2) right basivertebral foramen, 3) sectioned dorsal longitudinal ligament, 4) vertebral body, 5) opened left basivertebral foramen 6) intervertebral disc.

in either healthy or degenerated disc material is a controversial subject and inconsistent in dogs (Forsythe and Ghoshal, 1984; Worth et al., 2019; Willenegger et al., 2005; Bergknut et al., 2013; Innes and Melrose, 2015; Brisson, 2010). The MBSN was not identified in the thoracolumbar vertebral canal of dogs in one study (Forsythe and Ghoshal, 1984). The authors noted difficulty in distinguishing 'tiny veins' and 'connective tissue strands' from nerve fibers. No nerves were found within the vertebral canal. There is considerable intra- and interspecies variability in the anatomy of the spinal nerves and its branches (Forsythe and Ghoshal, 1984). Basivertebral veins are paired tributaries that arise within the vertebral bodies and ascend through osseous canals in the vertebral bodies and join the paired longitudinal vertebral venous plexuses (Bezuidenhout, 2012). However, basivertebral nerves (BVN) are not reported in the veterinary canine anatomy textbooks and the question arises whether there are nerve fibers running parallel with the basivertebral veins exiting from to the vertebral body through the same osseous channels. Nonetheless, although further studies focusing on either the MBSN or BVN are lacking, most veterinary anatomy textbooks depict the anatomy as described above, reflecting what is known from human, primate and other vertebrate anatomy studies (Evans and DeLahunta, 2012). The primary purpose of this study was to (1) determine whether dogs have a meningeal branch of the spinal nerve (MBSN) and a basivertebral nerve (BVN) and to (2) describe their anatomical characteristics.

2. Material and methods

Six (6) dog cadavers were dissected to study the anatomy of the MBSN and BVN at the cervical, thoracic, and lumbar vertebral canal. The six (6) dog cadavers used came from the dissection room of the Anatomy Unit of the Veterinary Faculty of the Universitat Autónoma de Barcelona. They were euthanized for medical reasons unrelated to the vertebral column or nervous system and donated by owners following the approved donation program of the University and used for anatomical dissections. All the specimens were dissected by one author (VAG). Dog breeds included beagle (2 males, 1 female), poodle (female), Irish setter (female), and German shepherd dog

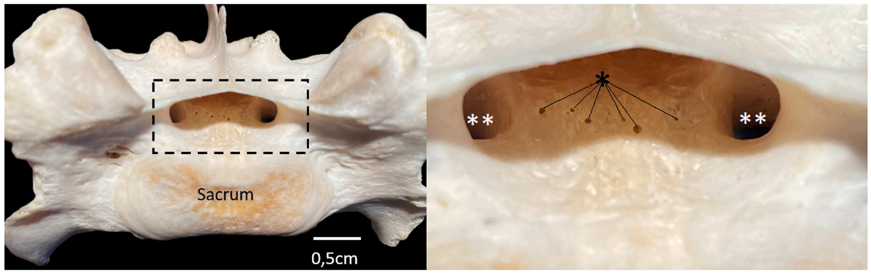

Fig. 2. Cranial view of the sacrum of a dog (anatomical specimen from archives). The inset is magnified on the right, where small foramina (*) on the bottom of the vertebral canal are noticeable. ** = foramina for the S1 ventral spinal nerve branches.

(male). Cadavers were fixed with a 10% formaldehyde buffered solution injected via the common carotid artery. The cadavers were then preserved for a few weeks (variable) at 4–6ºC. Vertebral columns, including epaxial musculature, were isolated by atlantooccipital decapitation and gross sharp dissection. To evaluate the MBSN and BVN, two approaches were followed: a) continuous laminectomy and removal of the spinal cord, and b) a sagittal section of frozen vertebral columns and removal of the spinal cord. The first method (a) allowed a complete view of the ventral aspect of the vertebral canal (a dorsal laminectomy was performed in on vertebral columns of 2 specimens), and the second (b) enabled a better approach to the intervertebral foramen from the medial aspect (a sagittal section of frozen vertebral columns was performed in 4 specimens). Dissection was performed from that point onward with the use of stereomicroscopy and microsurgery equipment.

The presence of the MBSN and BVN was studied grossly at the cervical, thoracic and lumbar vertebrae. Of samples acquired from one representative specimen, the presence of the nerve fibers was studied histologically at multiple levels where good quality sampling was subjectively possible (C7, T13 and L4). The structures preliminary identified as the BVN and MBSN were isolated, resected and submitted in 10% formalin buffer. Hematoxylin-eosin (HE) staining was performed.

3. Results

In included canine specimens, the dissection identified small nerve fibers at all levels between C2 and L7 among the epidural fat reaching the vertebral venous plexus from the intervertebral foramina that likely represent the MBSN (Fig. 1A and E). Also in all canine specimens, nerve fibers passing through the basivertebral foramen into the basivertebral canal were identified as the BVN (Fig. 1C, D and E). In addition, other small fibers (suspected nerves) entering the vertebral body through small foramina close to the end plates were identified (Fig. 1B). The latter are located close to the lateral expansion of the dorsal longitudinal ligament dorsal to the intervertebral disc (Fig. 1B). A connection between the MBSN and BVN could not be confirmed or excluded in the specimens studied.

The findings at the level of the axis mirrored those of the entire cervical column. The findings at the level of the sacrum were also comparable to those of the lumbar vertebrae; the fused sacral vertebrae S1–3 had small foramina along the floor of the vertebral canal allowing for the passage of small veins, nutrient arteries and small nerve fibers (Fig. 2). Within the vertebral foramen of the atlas, a small foramen was identified laterally. This foramen connects with the external surface of the vertebra close to the transverse foramen (Fig. 3). This foramen allows for the passage of the vein that connects the ventral internal vertebral venous plexus with the vertebral vein. No nerve fibers passing through this foramen were identified.

Histological examination of the structures identified as the MBSN and other small fibers mentioned above were unsuccessful due to the small size of the samples. Examination of the samples of the structures identified as the BVN confirmed presence of nerve branches surrounded by strands of collagen fibers, running in the proximity of blood vessels and penetrating inside the vertebral body (Fig. 4A). They contained several eosinophilic fascicles of nerve fibers with dark basophilic axons, lined by elongated and basophilic nuclei of Schwann cells, and covered by a thin epineurium (Fig. 4B). Several nodes of Ranvier were observed along small nerve fibers confirming the presence of myelin sheaths (Fig. 4C and D). Fig. 5 provides a schematic overview of the anatomy of the vertebra and associated nerves and vessels. The MBSN and BVN are depicted.

4. Discussion

This study showed definitively that dogs have a BVN, with gross anatomical and histological confirmation. It should be noted that the BVNs were identified at the level of the basivertebral foramen and passing into the basivertebral canal, but that the Nomina Anatomica Veterinaria does not include any of these terms in the latest version thereof (World Association of Veterinary Anatomists. International Committee on Veterinary Gross Anatomical Nomenclature, 2017). These terms derived from human anatomy may be included in the next edition of the Nomina Anatomica Veterinaria. Small nerve fibers were identified within the epidural fat reaching the vertebral venous plexus from the intervertebral foramina that likely represent the MBSN, but the presence of nerve fibers was not confirmed histologically. Although the dog, as a vertebrate species, would be expected to have a MBSN and BVN, the presence of the MBSN and BVN had not been confirmed to date. Confirmation of their existence opens the discussion of extrapolation of treatment modalities aimed at the BVN from the human phenomenon of 'low back pain'. Of note, the term 'low back pain' is frequently used in human literature, but this term is not correctly extrapolated to dogs with similar clinical presentations or issues resulting in caudal lumbar or lumbosacral hyperesthesia.

The use of modern techniques probably made it possible to identify these small anatomical structures in this study in contrast to researchers in the past (Forsythe and Ghoshal, 1984). Indeed, the differentiation between 'tiny veins' and 'connective tissue strands' from nerve fibers was difficult and was facilitated by high-resolution magnification and the use of microsurgery equipment. The use of modern equipment facilitates the dissection of small structures such as nerves and is for instance employed in anatomical studies on human foetuses or animal models of nerve grafting (Karykowska et al., 2021; Sinis et al., 2011). In regard to the small fibers (suspected to be nerves) entering the vertebral body close to the end plates through small foramina, we propose to employ the following terms for these anatomical structures: 'accessory basivertebral nerves' and 'accessory basivertebral foramina'. Although there was little doubt that these fibers were indeed nerve fibers, future studies employing immunohistochemical techniques that identify axonal or Schwann cell markers should enable further confirmation.

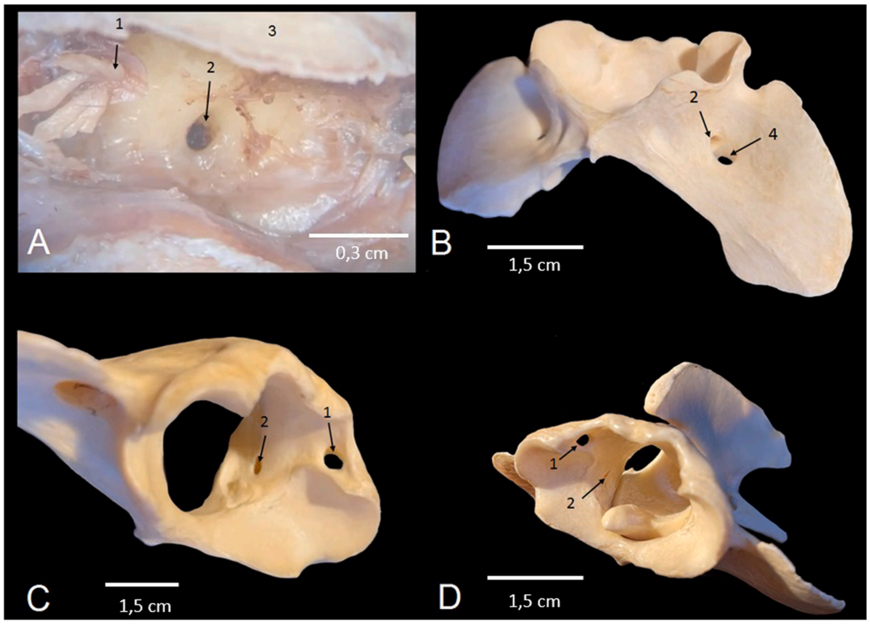

Fig. 3. Macroscopic images of the atlas (and axis) of a dog. 1) lateral vertebral foramen, 2) foramen for the vein that drains the internal venous plexus, 3) sectioned dorsal arch, 4) transverse foramen. A: Median to lateral view of the atlas from the inside. The spinal nerve C1 exiting the lateral vertebral foramen is seen (1). Cranial is to the left of the image. B: Ventral oblique view of the atlas of a dog (anatomical specimen from archives). Cranial is at the top of the image. C: Right cranial oblique view of the atlas of a dog (anatomical specimen from archives). Ventral is at the bottom of the image.D: Left oblique view of the atlas and axis of a dog (anatomical specimens from archives). Ventral is at the bottom of the image.

In this study, it was observed that the MBSN and BVN were entirely located outside of the ventral internal vertebral venous plexus. Indeed, the BVN was most clearly visualized only after partial removal of the internal vertebral venous plexus and basivertebral vein, both closely associated with the nutrient artery and vertebral periosteum (i.e., most outer layer of the dura mater). This is consistent with the anatomy of other nerves closely associated to vascular structures, such as several cranial nerves and sympathetic nerve fibers at the level of the cavernous sinus (Evans and DeLahunta, 2012b).

At the level of the atlas, a BVN was not identified, although a vein passing from the vertebral canal lumen connecting to the vertebral vein via a small foramen was identified. Observations in this study concur with the statement that the sacrum lacks typical basivertebral veins (Bezuidenhout, 2012), although there are foramina that allow for the passage of numerous small vessels that likely have a comparable function and may be viewed as smaller counterparts of those seen at other vertebral levels.

There are several limitations to this study, including the small sample size and lack of histological confirmation of nerve tissue in the structures identified as the MBSN. However, despite the small sample size, the macroscopical (for the MBSN and BVN) and histological (for the BVN) confirmation of the presence of these nerves can be viewed as confirmation of the existence thereof in dogs. Possible variations and further confirmation of these findings could be obtained by larger studies in the future.

Further anatomic and clinical studies of the innervation of the vertebral body, periosteum, vasculature, dorsal longitudinal ligament and anulus fibrosus of dogs are necessary to elucidate possible anatomical variants and breed differences as well as potential clinical relevance. The authors elaborate on the clinical therapeutic relevance of the MBSN and BVN in human medicine in the remainder of this discussion, as it offers insights and inspiration for future studies.

4.1. Potential clinical relevance of vertebral innervation

General note: the difference between 'nociception' and 'pain' is often underrecognized in literature and leads to considerable confusion. Readers are referred to 'de Lahunta's Veterinary Neuroanatomy and Clinical Neurology', 5th Edition, Elsevier, for a discussion on this subject.

A significant part of the global human population is affected by what is known and described as 'low(er) back pain' and its economic impact range in the tens to hundreds of billions of dollars annually (Hoy et al., 2012; Pai and Sundaram, 2004). Among the many different aspects involved, the role of innervation of the vertebral osseous structures and intervertebral discs has both (patho)physiological and therapeutic implications. For instance, after establishing that vertebral bone is indeed innervated, the sympathetic and parasympathetic innervation of bone has been shown to influence bone remodeling and a link between the central nervous system and skeleton was established (Elefteriou et al., 2014; Tomlinson et al., 2020; Antonacci et al., 1998; Bajayo et al., 2012; Buonocore et al., 2010). As nociception requires innervation, the presence of nerve fibers in the vertebral body and intervertebral disc has received extensive attention. The nature of nerve fibers and neurotransmitters (including major nociceptive neurotransmitters such as substance P, protein S-100, PGP 9.5 and CGRP) and receptors involved have been studied (Tomlinson et al., 2020; Bailey et al., 2011; Fras et al., 2003; Kim et al., 2020; Ohtori et al., 2002; Steverink et al., 2021). These studies have made it clear that vertebral body innervation is not solely afferent (e.g. nociceptive) but efferent (i.e. general visceral efferent) as well. A review on bone innervation in humans noted that innervation is most dense in the periosteum, followed by marrow and cortex and that the thoracic vertebrae showed the greatest innervation (e.g., nerve fibers) in the human skeleton (a finding that the present study on dogs was unable to confirm or refute) (Kim et al., 2020). The regional (micro)anatomy of vertebral innervation has been studied and reported on extensively in human as well as other species such as the rat (Antonacci et al., 1998; Baiavo et al., 2012; Buonocore et al., 2010; Bailey et al., 2011;

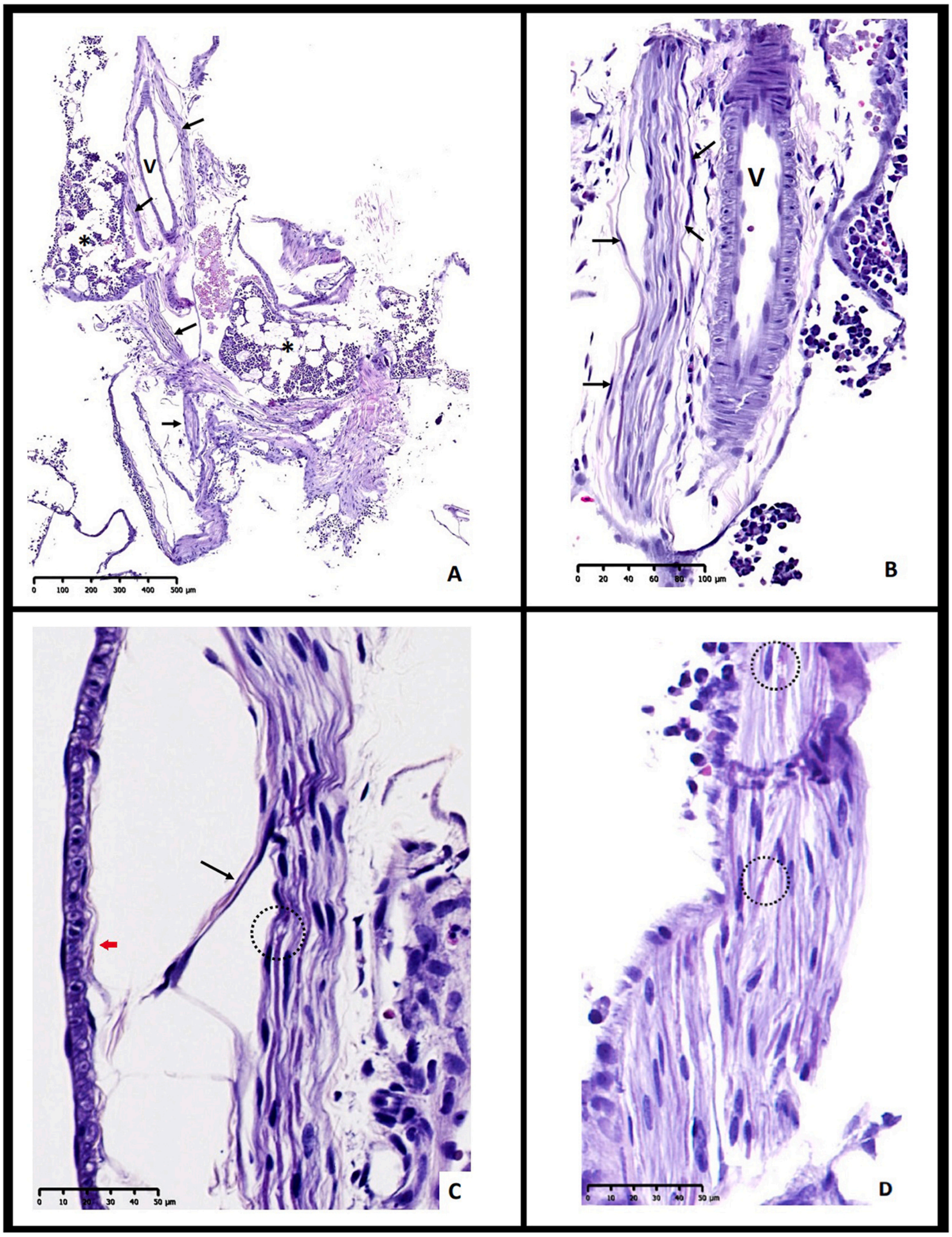

Fig. 4. Microscopy photographs of the histology of the basivertebral nerve (specimen acquired at the level of L4 vertebra). Hematoxylin-eosin stain. Scale bar in figures.A: Nerve branches (black arrows) surrounded by thin strands of collagen fibers running along a blood vessel (V) and entering the vertebral body across vertebral bone marrow (asterisks). B: Perineurial cells (black arrows) bordering a nerve fascicle near a blood vessel (V).C: A nerve fiber containing a basophilic axon (black arrow) leaving the nerve and reaching the tunica media of the adjacent arteriole (short red arrow). A node of Ranvier (dotted circle) is present in the remaining nerve fibers.D: Thin basophilic axons myelinated by Schwann cells. Two nodes of Ranvier (dotted circles) are present.

Fras et al., 2003; Kim et al., 2020; Steverink et al., 2021; Edgar, 2007; Kojima et al., 1990; Nakamura et al., 1996; Shayota et al., 2019; Quinones et al., 2021). The sinuvertebral nerve (MBSN in the dog according to the Nomina Anatomica Veterinaria) and the BVN have received particular attention and the reader is referred to the reference list for review of this subject in addition to illustrations providing helpful insights. Such detailed reports are sporadic in veterinary species such as the dog (Evans and DeLahunta, 2012a), although the value of the canine model for what is described as 'low (er) back pain' (mostly focusing on the intervertebral disc) is well-recognized (Tellegen et al., 2018a; Willems et al., 2017; Mern et al., 2021).

The value of the dog as an animal model for intervertebral disc degeneration in humans has been reviewed in detail (Bergknut et al., 2012). Many pathophysiological (e.g., type of degeneration and its background), gross post-mortem (e.g., collapse of disc space), histopathological (e.g., loss of congruity in the anulus fibrosus), biochemical (e.g. glycosaminoglycan content) and clinical aspects (e.g. signs of 'low back pain') are comparable between dogs and humans (Bergknut et al., 2012; Willems et al., 2015, 2017, 2018b). Despite some differences between humans and dogs, relating for instance to the shorter life span and difference in biomechanics involved, the dog provides as good model for research focusing on treatment modalities for intervertebral disc degeneration.

Acknowledging the existence of innervation of vertebral structures and its potential role in "low back pain" in humans, therapeutic modalities focused on impeding signal transmission (i.e., nociception) at the level of the vertebra were developed. One example is radiofrequency ablation of the BVN. BVN ablation is the (thermal) destruction of the BVN and its intraosseous branches. BVN ablation

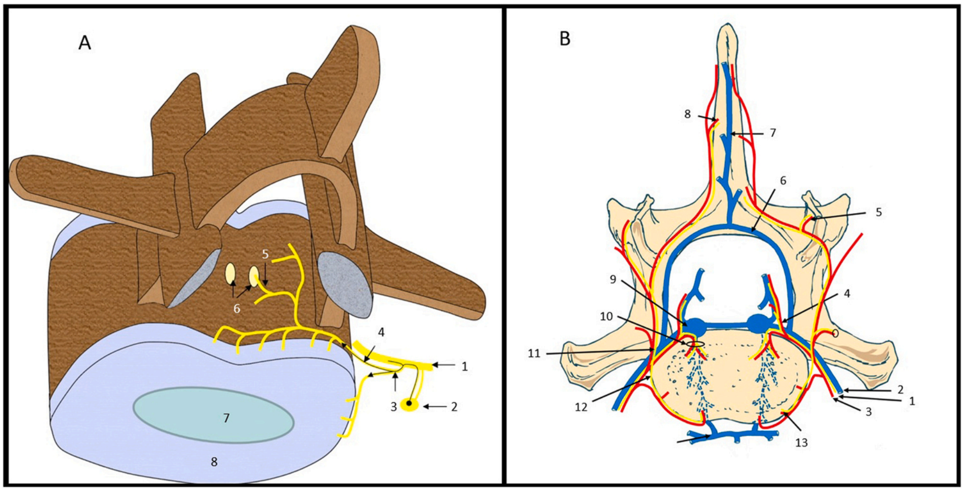

Fig. 5. Schematic figures of the basivertebral nerve and the anatomical relationships with the vertebrae, discs, and vessels. A: 3-dimensional dorsal-oblique view of a vertebra with intervertebral disc, vessels and nerves. 1. spinal nerve, 2. ganglion of the sympathetic trunk, 3. recurrent course, 4. meningeal branch of spinal nerve (sinuvertebral nerve), 5. basivertebral nerve, 6. basivertebral foramina, 7. nucleus pulposus, 8. anulus fibrosus. B: 2-dimensional rostrocaudal view of a vertebra with vessels and nerves. 1. spinal nerve, 2. intervertebral vein, 3. spinal artery, 4. radicular artery and nerve fibers for the meninges, 5. nutrient artery and nerve fibers, 6. interarcuate branch, 7. interspinous vein, 8. nutrient artery and nerve fibers, 9. ventral internal vertebral plexus, 10. nutrient artery, basivertebral vein and basivertebral nerve, 11. dorsal branch (spinal nerve), 12. ventral branch (spinal nerve), 13. ventral external vertebral plexus.

in humans with “low back pain” is reportedly indicated when patients have 1/ chronic back pain for at least 6 months, 2/ failed to adequately improve despite attempts at nonsurgical management, and 3/ Type 1 or Type 2 Modic changes on MRI (Becker et al., 2017; Urits et al., 2021). There is growing evidence that damage to the highly innervated vertebral endplates can result in ‘vertebrogenic pain’ transmitted through branches of the basivertebral nerve (Becker et al., 2017; Urits et al., 2021; Michalik et al., 2021; Truumees et al., 2019; Smuck et al., 2012; Fischgrund et al., 2020; Lorio et al., 2020). This technique, although not only ablating the nerves but also hematopoietic and fat tissues in vertebral bone marrow, has shown promise in multiple studies (Becker et al., 2017; Urits et al., 2021; Michalik et al., 2021; Truumees et al., 2019; Smuck et al., 2012; Fischgrund et al., 2020; Lorio et al., 2020). To the authors’ knowledge, no studies have been performed exploring the potential benefits of this technique in canine “low back pain”. There is a single report of the application of BVN ablation in an ovine model (Bergeron et al., 2005). A recent review on canine degenerative disc disease (significant degenerative lumbosacral stenosis where “low back pain” is a key clinical feature) acknowledged the possible role of the BVN (Worth et al., 2019).

5. Conclusions

This study provides definite evidence of the existence of a BVN in dogs and allows for discussion on its role in canine disc- and vertebral pathology-related discomfort and extrapolation of therapeutic measures such as employed in human medicine. Future studies focusing on the nature of the nerve fibers encountered in this study (e.g., autonomic (sympathetic), somatic efferent, somatic afferent or (most likely) a combination thereof), their exact anatomical courses and intraspecies variations will provide more information of importance to facilitate this discussion.

Ethical statement

Cadavers were acquired by the Anatomy Unit of the Veterinary Faculty of the Universitat Autónoma de Barcelona adhering to ethical guidelines as currently applicable at this site.

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CRediT authorship contribution statement

Santifort K: Project development, data analysis, manuscript writing; **Glass E**: Project development, manuscript editing; **Meij B**: Project development, manuscript editing; **Bergknut N**: Project development, manuscript editing; **Pumarola M**: Data analysis, data acquisition, manuscript review, manuscript editing; **Aige Gil V**: Project development, data analysis, data acquisition, manuscript writing and review, manuscript editing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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