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REVIEW PAPER

The pia mater: a comprehensive review of literature

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Abstract
Introduction The pia mater has received less attention in the literature compared to the dura and arachnoid maters. However, its presence as a direct covering of the nervous system and direct relation to the blood vessels gives it a special importance in neurosurgery.
Method A comprehensive review of the literature was conducted to study all that we could find relating to the pia mater, including history, macro- and microanatomy, embryology, and a full description of the related structures.
Conclusion The pia mater has an important anatomic position, rich history, complicated histology and embryology, and a significant contribution to a number of other structures that may stabilize and protect the nervous system.

Keywords Pia mater · Denticulate ligament · Filum terminale · Linea splendens

Introduction

The first known description of the meninges can be traced back to the Edwin Smith Papyrus, which dates to Dynasties 16–17 of the second intermediate period of ancient Egypt. However, the description in this papyrus is limited to what is believed to be the dura mater. The Greek philosopher Aristotle, in the fourth century B.C., described two layers of the meninges, the stronger one near the bone of the skull and the finer one enclosing the brain. His descriptions were based on animal dissections. In the third century B.C., Herophilus and Erasistratus confirmed the findings of Aristotle in humans, in the first known human dissection in ancient history, done in Alexandria. Erasistratus was the first to use the term meninges (singular meninx, meaning “membrane”). In the second century A.D., Galen of Pergamon translated and added to the earlier descriptions of Herophilus and Erasistratus, and he used the terms *pacheia* and *lepte* to describe the outer thick and the inner thin layers, respectively. He found that the *lepte* covers and strengthens the brain and binds the vessels it encloses. During the Islamic Golden Age, the meninges were observed and named by an anonymous Muslim physician as *umm al-dimagh* (the mother of the brain). This was later subdivided by Haji Abbas into *umm al-ghalida* (the hard mother) and *umm al-raqiqah* (the thin mother). By the twelfth century A.D., the Italian monk Stephen of Antioch translated and described these two Arabic terms into Latin as dura (hard) mater and pia (pious) mater. Some authors believe that the use of pia is a misnomer and should have been replaced by *tenue* (thin), but Stephen chose the term pia, which has persisted. The term mater is derived from *ma-* (from *matru*, meaning mother), and the suffix -ter indicates the state of being. The arachnoid was first described by Herophilus in the third century B.C., but the first introduction and detailed description of this term is attributed to Frederick Ruysch, a Dutch anatomist, in 1699. Some authors use the term pachymeninx in regard to the dura mater and the term leptomeninx (or leptomeninges) in regard to the arachnoid and pia maters collectively [1–4]. Although the exact function of the pia mater is not clear, it does cover and potentially protects the brain. Moreover, via its specializations (denticulate ligaments, filum terminale), it affords some degree of stabilization of the spinal cord. These specialized parts of the pia and its overall

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“coating” of the central nervous system afford protection to the child's nervous system. Moreover, the pia via its perivascular space allows diffusion of solutes below 200 Å in diameter between the interstitial space and cerebrospinal fluid, thereby allowing for movement of metabolites and playing a role in the blood brain barrier [5, 6].

Anatomy

The pia mater is a delicate, highly vascular layer that directly invests the brain and spinal cord. The cranial pia mater follows the contour of the brain, covers the gyri, and descends into the fissures and sulci (Figs. 1, 2, and 3). The spinal pia mater also directly encloses the spinal cord throughout its entire length. At the level of the conus medullaris, the pia mater forms the main bulk of the thin, non-nervous, fibrous filum terminale, which extends for almost 20 cm (in adults) from the lower tip of the conus to attach mainly to the posterior surface of the coccygeal vertebrae [7–9].

In both the cranium and spine, the pia is separated from the overlying arachnoid by the subarachnoid space and cisterns. This space is traversed by networks of fine, continuous, sheet-like trabeculae that link the arachnoid and pia mater and divide the subarachnoid space into compartments. It consists of a collagen core surrounded by a leptomeningeal layer that becomes continuous with the surface of the pia mater and blood vessels in the subarachnoid space at the sites of attachments [10].

Histology

The pia mater consists of a one- to two-cell-thick layer of leptomeningeal cells (Fig. 4). These cells have long and thin processes, which connect to each other mainly by desmosomes and gap junctions [8, 11].

Fig. 1 Base of the brain with the arachnoid mater removed and illustrating the glistening nature of the overlying pia mater

Fig. 2 Lateral cortical surface of the brain following removal of the overlying arachnoid mater to illustrate the pia mater

In their book, Key and Retzius divided the spinal pia mater into two parts, the intimal and the epipial layers [12]. The external, epipial, or intermediate leptomeningeal layer is mainly present in the spinal cord. It represents a vascular layer with almost a uniform thickness that consists of a network of collagenous fibers. The superficial fibers show an irregular arrangement, compared to the circular arrangement of the deeper fibers around the spinal cord. On each side of the spinal cord, this layer thickens and covers the collagenous core of the denticulate ligaments, as described earlier. Ventral to the anterior median fissure, it thickens and gives rise to the linea splendens, forming the sheath of longitudinal fibers around the anterior spinal artery. Along its course, this layer also dips into the anterior median fissure and is interrupted at the sites of entry and emergence of the spinal nerve rootlets, around which it forms a round margin. The subarachnoid blood vessels lie in between the strands of the epipial layer before entering the substance of the spinal cord. In the brain, the epipial layer only surrounds the medulla oblongata. Fine trabeculae were also found in the subarachnoid space of the brain, the spinal cord anchoring larger vessels in the space to the pia and arachnoid.

The underlying, avascular intimal or reticular layer closely invests the spinal cord and the brain throughout all their contours. This layer is composed of reticular and elastic fibers. In the spinal cord, it follows the anterior median fissure and

Fig. 3 Medial surface of the sagittally cut brain illustrating the interface between the arachnoid mater (*arrows*) and the deeper lying pia mater

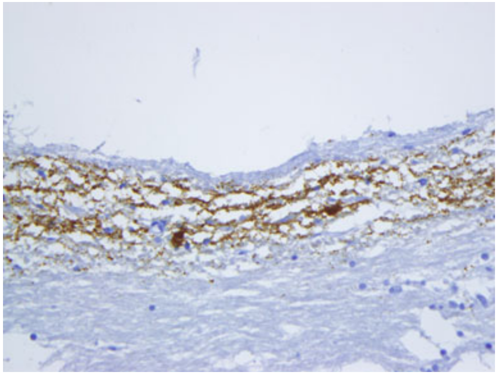

Fig. 4 Coronal section through the corpus callosum. The indusium griseum reacts with synaptophysin (synaptophysin immunostain (*brown*)) and is sandwiched between the superficial and thin pia mater and deeper corpus callosum, ×25

the posterior median septum. It also gives rise to incomplete septae, which project into the white matter at irregular intervals from the periphery of the cord. In the brain, this layer closely invests the gyri and dips into the sulci. Fine septae were also found to pass into the brain for a short distance, mainly at the site of entry or emergence of the blood vessels. Before their entry, smaller blood vessels lie directly on the intimal layer [12, 13]. The pia mater rests on the basement membrane of the glial limitans, from which it is only separated by a subpial space. This space contains collagen bundles, fibroblast-like cells, and blood vessels [8, 13].

Virchow–Robin/perivascular space

The first known description of the Virchow–Robin (VR) (Fig. 5) space was by Durand Fardel in 1842 under the name of *état criblé*. However, what he truly described was an enlarged VR space in the basal ganglia [14]. In 1851, the German pathologist Rudolf Virchow [15] described a perivascular space, which he called *disseziierende Ektasie*, between the outer lamina (tunica adventitia) and the inner and middle lamina (tunica propria) of the brain vessels. In 1859, the French anatomist Charles Philippe Robin [16] confirmed Virchow's findings and was the first to describe these spaces as normal anatomical spaces. Since then, early writings supported by Weed [17] in 1923 proposed a free communication between the VR spaces and the subarachnoid space. Later experiments involved injecting a tracer into a rat brain, which was found to collect in the perivascular space of some arteries, e.g., the middle cerebral artery, and not in the subarachnoid space. That indicated the communication between the brain interstitial and perivascular spaces [18]. More investigations revealed that the pia mater, besides following the small arteries and arterioles through its entry to the neural tissue, is also reflected over these vessels within the subarachnoid space. This forms a single-layered pial barrier between the subarachnoid space and perivascular space. It leads to a communication between the subpial and neural extracellular spaces and the perivascular space [13]. Still, however, the characteristics and composition of the limiting layer surrounding the blood vessels and separating it from the brain tissue have yet to be identified. Some authors believe it is composed of leptomeningeal cells; however, others do not believe this. The perivascular space follows the entering arteries as far as the capillaries, where the endothelial cells fuse with glial basement membrane and obliterate the space. It also follows the emerging veins for a short distance.

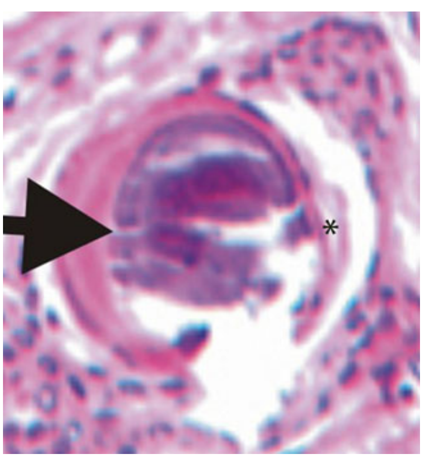

Fig. 5 Cross section thorough an intracerebral artery with intraluminal thrombus (*arrow*). Note the small Virchow–Robin space (*asterisk*) outside of the artery lumen

Although the VR space is separated from the subarachnoid space, some substances may still easily pass between the two of them. This explains the extension of certain pathological conditions, e.g., infections, from the subarachnoid space. This fluid-filled space also manifested certain types of macrophages, unrelated to pathological conditions, which have more activity than neural microglial cells. Other functions of the perivascular space include its role as a conduit for the CSF to reach the draining lymphatics [19].

Embryology

Early investigations regarding the development of the meninges proposed a common origin from the neural tube ectoderm. However, this had been opposed by later authors starting with Schwann [20] in 1839. His [21], in 1865, described an origin from a mesenchymal tissue surrounding the neural tube, a theory that was accepted by later authors. This mesenchymal tissue was later named *meninx primitiva* (or primitive meninx) by Salvi [22] in 1898. This layer was further divided by two cellular condensations proposed by His [21] into endomeninx (or secondary meninx) and ectomeninx. The former contributes to the leptomeninx, while the latter contributes to the pachymeninx (or dura mater). However, the mesenchymal characteristics of the *meninx primitiva* have been questioned by some investigators and were later found to consist of different cells of various sources, including mesodermal and ectodermal cells. Other authors believed that the dura mater develops from the mesenchymal layer and the leptomeninges develop from the neural tube ectodermal cells, mainly neural crest cells [4].

In 1986, O'Rahilly and Müller [3] found that the perimedullary tissue (*meninx primitiva*) surrounds the neural tube almost entirely, except at the area of direct contact between the future spinal cord with the notochord and at the roof of the future brain. This tissue consisted of two layers: the inner layer, which gives rise to the future leptomeninges, and an outer layer, which gives rise to the pachymeninx. Two condensations were found to arise at the outer and inner parts of the outer layer. The outer condensation contributes to the skeletogenous layer of the future scalp, and the inner condensation contributes to the dural limiting layer. From the inner layer of the mesenchyme, signs of the pia mater are seen early in human development. It was found to closely invest the neural tube and adhere to the supplying blood vessels. In the same layer as well, leptomeningeal meshwork and spaces can also be seen, which gradually give rise to the future subarachnoid space. Within this space, numerous trabeculae were found to link the developing pia mater and dura mater [3, 23]. According to Haymaker and Adams, the denticulate ligaments are the first of the spinal meninges to differentiate from the primary meninx [24].

Structure originating from pia mater

Denticulate ligaments

In 1739, Johann Jacob Huber, a Swiss anatomist, made the first detailed and accurate description of the denticulate (or dentate) ligaments (Fig. 6) [25]. In the midline of either side of the spinal cord, a barely perceptible thickening of the pia mater gives rise to 20 or 21 pairs of thin, longitudinal, triangular septae that insert into the internal surface of the dura mater at regular intervals. These pass between the ventral and dorsal roots of the spinal nerves, separating the spinal canal into anterior and posterior compartments. They end at the level of the conus medullaris, where the last pair of ligaments are broader and fibrous and turn downward and join with the filum terminale in a fork-like manner. At the apex of these triangular sheaths, a prong-like continuation merges with the dura mater. These prongs are longer in the cervical region [24, 26, 27]. Occasionally, the denticulate ligaments may have a free lateral margin [27]. The first (or intracranial) denticulate ligament is considered to be important in neurological surgeries, as it is likely to be encountered with approaches to the craniocervical region [28]. In a study of the first denticulate ligaments of 15 cadavers (30 sides), Tubbs et al. [28] found that it is present in all but one left side of a cadaver. In all cases, these ligaments arise medially from the spinomedullary junction of the spinal cord, extend between the vertebral artery and spinal accessory nerve, and attach laterally to the outer layer of the dura mater of the marginal sinus at the foramen magnum inferior to the hypoglossal nerve rootlets. In all cases, the ventral rootlets of the first spinal nerve were present and concealed by the first denticulate ligaments. The dorsal rootlets were, however, present on only 14 sides (46.7 %). The posterior spinal artery and its branches traveled posterior to this ligament on 28 sides (93 %) and anterior to it on the remaining sides [28].

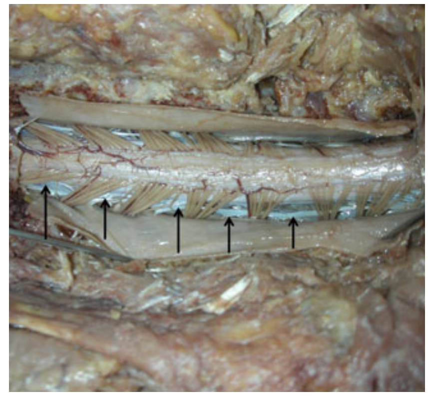

Fig. 6 Exposed intradural contents of the spinal canal in an adult cadaver. Note the denticulate ligaments (*arrows*)

The function of the denticulate ligaments is still not very clear. In earlier literature, the function of these ligaments was thought to be for stabilizing the spinal cord. Thus, it was assumed that they may tether the cord in various pathological conditions. However, later studies on the denticulate ligaments revealed that a wide range of movement is allowed before these ligaments become taut. Movements were tested in cranial–caudal, anterior–posterior, and lateral directions, and there was a wider range of movements as the spinal cord descended, which is expected as the denticulate ligaments become thinner. However, even with the wide range of movements allowed, the denticulate ligaments still provided means of limitation, as a cut or avulsion of the ligaments will further increase the cord's mobility, mainly in the cranial–caudal axis [26, 29].

Histological studies of the denticulate ligament have shown that it consists of a dense collagenous core that is thicker laterally. On its medial end, this core adheres to the subpial collagen, and at its lateral end, it fuses with the dural collagen. This fibrous core is surrounded by a leptomeningeal layer that is continuous with the cellular layer of the pia mater and arachnoid [24, 27, 28].

Lumbar intrathecal ligaments

In an experimental study on 56 cadavers, Kershner et al. [30] described the presence of lumber intrathecal ligaments. These ligaments (average of 18 per specimen) were found in the cauda equina, below the first lumber vertebra, but not below the second sacral intervertebral foramen. In most cases, these ligaments attached the dorsal spinal roots to the surrounding dura mater and sometimes bound the ventral roots to the dorsal roots in a longitudinal or vertical manner. Histological examination showed a fibrous core consisting mainly of collagen bundles and, to a lesser degree, elastin. Fibroblasts were scattered along the length of the ligament and were more densely found near sites of attachment. This core is surrounded by leptomeningeal cells that become continuous with the pia mater of the spinal roots. The broad-based attachments at both sides, along with their histological characteristics, contribute to the fact that the intrathecal ligaments need a greater force to disrupt the arachnoid. The similarities between these ligaments and the denticulate ligaments suggest that the intrathecal ligaments represent remnants from fetal development of the denticulate ligaments [30].

Dorsal and dorsolateral septae that arise from the partially fenestrated intermediate (or epipial) leptomeningeal layer have been found traversing the subarachnoid space in almost all the areas of the spinal canal [27]. The epipial layer is considered as the outer layer of the pia mater [12, 19] and is discussed in further details below.

The filum terminale

The filum terminale (nervus impar) is a fibrous band that extends from the tip of the conus medullaris to blend with the periosteum of the posterior surface of the coccyx (Fig. 7). It was divided by Luschka into two components: intradural compartment (filum terminale internum) and extradural compartment (filum terminale externum or coccygeal ligament) [31, 32]. The limitation between these two parts is marked by the site of fusion between the intradural part and the dura mater of the dural sac. This fusion may occur at any level from L5 to S3, mainly at the level of S2 [33] (upper one third) [31]. Although this fusion mostly occurs in the midline, it may occur off of the midline dorsally, which makes it difficult to find during surgery [33]. In an experimental study on 41 adult cadavers (age 30 to 84 years) by Pinto et al. [31], the initial point of the filum teminale (the point at which the angled lateral aspect of the conus medullaris met the straight lateral aspect of the filum) was used to define the precise origin of the filum. In most of the cases, it started at the level of the middle one third of the L1 vertebra and ranged from the lower one third of the T11 to the L2–L3 intervertebral space. In their study, they described the length and thickness of the intradural parts of the filum terminale, which differ in regard to age, weight, height, and any previous abnormalities or operations. The mean length of the intradural compartment was 156.4 mm. The filum was thicker at the initial point, with mean thickness of 1.38 mm, and thinner as it descended, with a mean thickness of 0.76 mm at its midpoint [31]. According to Tarlov [34], the length of the intradural compartment was 4.2 cm in newborns and 15 cm in adults. Rauber [35], on the other hand, reported that the length of the internal filum is about 16 cm.

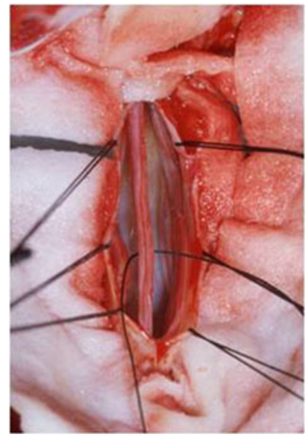

Fig. 7 Surgically exposed filum terminale (under silk suture) in a patient with fat infiltration

In their description of the filum terminale externum in 15 adult cadavers (age 57 to 90 years), Tubbs et al. found that the length of the filum terminale externum in all the specimens ranged from 7 to 10.5 cm (mean, 8 cm) and with a mean width of 1 mm. In none of the specimens did tension applied on the extradural compartment result in any movement of the intradural compartment [32]. The mean length of the extradural part was similar to that measured by Rauber [35]. In Tarlov's experiment study, however, the length of this part in newborns and adults was 2.2 and 7.5 cm, respectively [34].

Early studies described the filum terminale simply as a fibrovascular band, and little attention was given to study this important structure, until the beginning of the twelfth century. The filum terminale consists of fibrous connective tissue and vascular layers (Fig. 8). However, other types of tissue are scattered within this cord and play significant roles in many of its pathologies. The bulk of the filum terminale is made of connective tissue layers consisting mainly of collagen fibers and, to a less extent, elastin and elaunin fibers. These fibers are organized as longitudinal bundles, lined by transverse, delicate fibers. The distribution of this connective tissue component is almost homogenous in any part of the filum terminale [36]. Tarlov [34] mentioned that this connective tissue represents a thickened pial

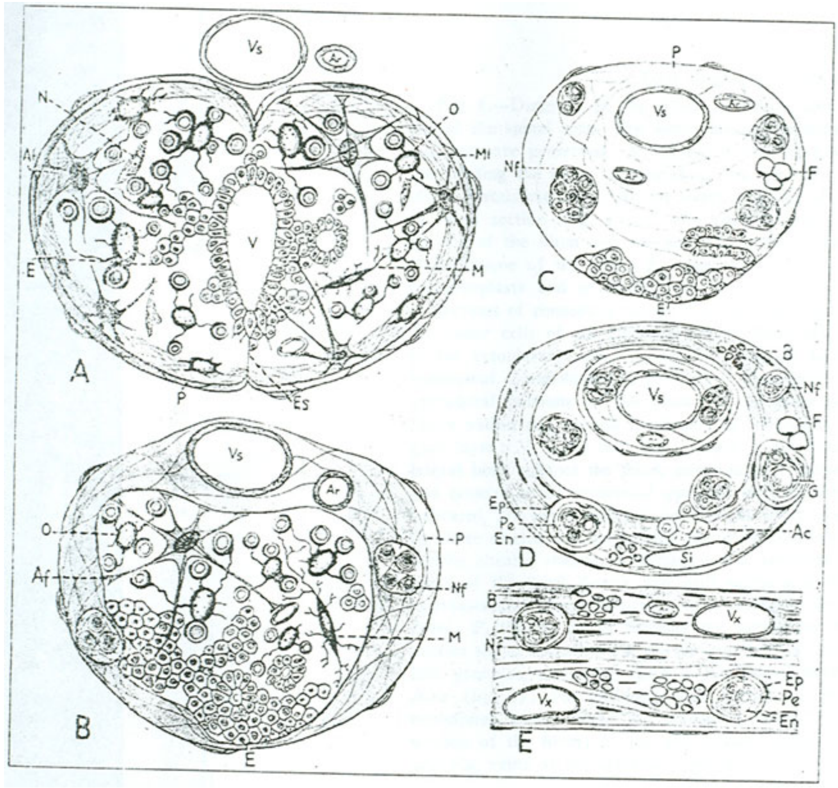

Fig. 8 Diagrams made of various cross sections through the filum terminale. *A* is a cut through the middle segment of the terminal ventricle; *B* is at the site of fusion of the central canal; *C* is at the site of near disappearance of ependyma; *D* is a cut made at the transition of intra- to extradural filum terminale. *Ac* arachnoid cells, *Ap* protoplasmic astrocyte, *Af* fibrous astrocyte, *Ar* artery, *Cx* fusion of the extradural filum with coccygeal periosteum, *De* dural elastic tissue, *En* endoneurial sheath with endothelial cells, *Eo* bibroblasts of the endoneurium, *Ep* epineurium, *Es* ependymal spongioblast, *G* ganglion cells, *M* microglia, *M1* marginal neuroglial layer, *N* nerve cells, *Nr* nerve roots of the third to fifth sacral and first coccygeal segments, *O* oligodendrocytes, *Os* satellite oligodendrocytes, *P* pia mater, *Pe* perineurium, *S* Schwann cells, *Si* sinusoid, *Sw* Schwann cell, *T* transition from intradural to extradural filum, *T* terminale ventricle, *Vs* anterior spinal vein, *Vx* veins of extradural filum. After Tarlov [34]

sheath, whose size increases caudally and is thinnest dorsally. He also added that the lumen of this connective tissue sheath forms a V shape, with the apex directed caudally. The limbs of the V represent the passage of the nerve fibers, and between the limbs of the V, which become increasingly thickened toward the apex, the nerve and interstitial structure of the filum is contained.

In 1892, Tourneux [37] mentioned that at the transition between the conus medullaris and the filum, the central canal flattens and continues within the filum as far as the vicinity of the dural cul-de-sac. He also mentioned the presence of medullary nerve cells, which also decrease in number until they totally disappear 1 mm below the dural sac. These findings were confirmed by Rauber [35] in 1909, who added that the medullary nerve cells were observed clinging to the sides of the filum. In 1933, Harmeier [38] described the microscopic characteristic of the intradural filum terminale. Large collections of the ependymal cells were found in certain places without definite arrangement and in other places surrounding irregular cavities. Excessive numbers of corpora amylacea were also found beneath the pia mater and also scattered throughout the filum. Ganglion cells were also found at the periphery, and neuroblasts were scattered within the tissue. Axons were also described extending all the way down, and myelin was abundant in the proximal half of the filum. As the filum terminale internum progresses downward, the amount of nerve tissue decreases gradually until it becomes confined as a peripheral thin layer [38].

Tarlov's [34] description of the microscopic anatomy of the filum terminale was more detailed. He found that at the transition between the conus medullaris and the filum, the difference between anterior and posterior horns, becomes gradually less pronounced with lack of demarcation of the gray and white maters. Nerve cells still can be seen, mainly within the first 3 cm of the intradural portion of the filum terminale. These nerve cells were occasionally large, multipolar cells. Some of these cells exhibit degenerative changes. Tracts of nerves fibers could also be seen continuing within the filum and gradually becoming less pronounced to attain a peripheral position in the filum. In the periphery, they become surrounded by Schwann cells and endoneurium and occasionally contain nerve cells. Many of these fibers were myelinated. The central canal may disappear and reappear again within the filum, and it may also reach the dorsal border of the filum. In certain cases, the central canal bifurcates to form various numbers of outpouchings, which appear as multiple cavities in cross section. Large numbers of glial cells are present within the intradural portion of the filum, and most of the time, these constitute the main bulk of the filum. These glial cells are similar to those found in the central nervous system and consist of ependymal cells, astrocytes, oligodendrocytes, and microglial cells. These cells are assumed to play their expected function and are present mainly within the cranial part of the filum terminale and disappear caudally. The ependymal cells were the most abundant and the last to disappear of all the interstitial cells, as they extend as far as the first 2 cm of the extradural part of the filum. Ependymal cells assume many shapes, surround the cavities, and are scattered in many parts of the filum. Corpora amylacea were also described, and they represent the most common form of the degeneration products within the filum [34]. These structures are covered by the connective tissue sheath described above.

At the site of transition between the intradural and extradural portions, the filum becomes surrounded by arachnoid and dural layers. The arachnoid surrounds bundles of nerve fibers and the central portion of the filum. The cuboidal cells of the arachnoid at this level project into the fibrous stroma of the dural layer. Caudally, these become applied as a sheath with flattened lining cells that gradually disappear. The nerve fiber bundles become surrounded by the dural layer, which forms the epineurium. However, within the few first centimeters, all nerve fibers acquire a perineurium and an epineurium. Myelinated and non-myelinated nerve fiber bundles become less conspicuous gradually as they migrate laterally to their foramina of exit until they finally disappear. Small bundles of nerve fibers, however, were described along the entire course of the filum terminale. The filum finally blends with the periosteum on the dorsum of the coccyx. Psammoma bodies were found at the junction between the two parts of the dura, mainly in older subjects [34]. According to Tubbs et al0 no glial or ependymal cells rests were found in this part of the filum, and a variable number of smooth muscle bundles were embedded within the fibrous stroma [32].

Reissner's fiber, named after the German anatomist Ernst Reissner (1824–1878), is a pretentious thread present in the central canal of most vertebrates, mainly the lesser vertebrates. It extends from the caudal end of the subcommissural organ of the epithalamus, through the lumen of the cerebral aqueduct, fourth ventricle, and central canal of the spinal cord into the rostral part of the filum terminale where it expands into an irregular, terminal, hyaline mass. Beyond the point where the fiber terminates, the filum contains an empty lumen extending caudally for a short distance [39]. The function of this fiber was proposed to be related to control of the flexure and pose of the body [40].

Blood supply of the filum terminale is mainly provided by a single artery, the artery of the filum terminale. It arises from the bifurcation of the anterior arterial spinal axis at the level of the conus medullaris. It then descends on the ventral surface of the filum and becomes progressively smaller. It gives rise to smaller arterioles, and no arterial vascularization is usually observed on the dorsal surface. Venous drainage occurs by the vein of the filum terminale, which also travels along the ventral surface of the filum terminale behind the artery. It has an almost constant caliber, which is larger than the arterial caliber. At the level of the conus medullaris, it continues with the anterior spinal vein. No veins were observed on the dorsal surface of the filum. Microscopically, small veins, venules, small arteries, arterioles, and capillaries spread in apparently uniform fashion within the filum, both in the central region and in the periphery [41].

Conclusion

The pia mater has an important anatomic position, rich history, complicated histology and embryology, and a significant contribution to a number of other structures that may stabilize and protect the nervous system of the child.

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