Development of the Cavernous Sinus in the Fetal Period: A Morphological Study

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Abstract

The development and morphological structure of the lateral sellar compartment (LSC), an interdural space containing the cavernous sinus (CS), cranial nerves, and internal carotid artery (ICA), was investigated by histological examination of sections of the LSC and cerebral venograms from human fetal specimens. Twenty-eight LSC coronal sections were obtained from 14 fetuses of 13–32 weeks' gestation. Venograms of 11 other fetuses of 13–32 weeks' gestation were studied to observe changes in venous drainage. The CS appeared as a collection of small venous canals with an endothelial layer. These venous canals gradually became much larger through expansion and unification. The CS and basilar venous plexus were demonstrated as a faint cluster of small vessels on venograms obtained after 13 weeks' gestation. The dura mater increased in thickness and collagen fiber networks developed around all the components in the LSC after 23 weeks' gestation. The LSC lateral wall could not be histologically differentiated as separate multiple layers. Branching and joining of the cranial nerve fascicles were completed with the envelopment of collagen fibers after 23 weeks' gestation. The ICA at 13–15 weeks' gestation ran straight within the LSC, becoming tortuous before birth. CS formation occurs through the development of venous canals without smooth muscle layers, followed by web-formation by collagen fibers in the mesenchymal interstices. LSC formation, including the dense dura mater and an internal structure like that seen in the adult, is largely completed before birth.

Key words: cavernous sinus, lateral sellar compartment, fetus, dura mater, dural sinus, development

Introduction

The term cavernous sinus is somewhat confusing, as in the narrow sense it refers to a venous pathway that is part of the intracranial venous sinus system, but in a broader sense describes a paired structure situated in the lateral sellar region that includes not only the venous pathway but also the cranial nerves, the sympathetic nerve, and the internal carotid artery (ICA) and its branches. Here, we use the term 'lateral sellar compartment' (LSC) of Parkinson¹⁹⁾ to describe the cavernous sinus in its broader sense, and the term 'cavernous sinus' (CS) for the narrow sense of the venous pathway in the LSC.

The neurosurgeon requires precise knowledge of the anatomy of the LSC for surgical or interventional intravascular treatment of LSC lesions, but

there are several unsolved problems in regard to the developmental processes and structures. There are two opposing classic concepts for the structure of the CS: a large sinusoidal venous space containing many trabeculations,^{1,3,6,12,13,24,27,28)} and a venous plexus consisting of many complex branched veins.^{4,18,19,21,23,25,26,29)} The dura mater of the lateral wall of the LSC is clearly distinguishable as a superficial layer from the deep layer of the cranial nerve complex containing the oculomotor nerve (III nerve)-trochlear nerve (IV nerve)-ophthalmic nerve (V1 nerve)-maxillary nerve (V2 nerve) complex.^{3,4,6–8,12,20,21,24,27,28)} However, the boundary between the two layers has not been clearly demonstrated in histological sections.

Previous investigations of these problems have been based on anatomical dissections and surgical findings under the microscope.^{1–4,6–9,18–21,24,27–29)} However, the delicate structures of the LSC could not be identified. Histological sections of the LSC in

the adult have found most soft tissues of the sections were damaged by the hard bones located at the cranial base.^{8,10,12,13,19,21} Compared with adult specimens, fetal tissues have the advantages of ease of preparation of histological sections because of the immature bones at the cranial base; and study of the embryological LSC development. However, only a few observations on histological sections of the human fetus have been reported.^{1,9,23}

This study investigated the human fetal LSC through a series of histological sections to examine the mechanisms of development of the CS as a part of the venous sinus system in the cranial base.

Materials and Methods

Fourteen autopsied fetuses with crown-rump (CR) lengths ranging from 70 to 270 mm were obtained (Table 1). No malformation was observed in the central nervous system or on the body surfaces of the fetuses. The gestational age, expressed in weeks starting from the first day of the last menstrual period, was determined using Shimamura's chart,²² which was based on the CR length data of embryos and fetuses of Japanese origin. Each fetus was fixed with 10% formalin for at least 3 months with its skull open. After the brain was removed, a harvested block of the cranial base, including the orbit, LSC, petrous pyramid, and clivus, was decalcified with 10% to 25% formic acid solution for several weeks. The specimens were coronally sliced in small, 5-mm-thick blocks, and fully embedded in paraffin.

Serial coronal sections of 3- μ m thickness were prepared from each block. These serial sections from 28 LSC blocks of 14 specimens were stained with elastica van Gieson and Masson trichrome (elastica Masson) to distinguish the soft tissue elements of the LSC from other tissues.

The serial sections were observed in detail under a light microscope. Photographs were taken of the coronal sections traversing both the horizontal portion of the ICA and the pituitary gland in all specimens except No. 2. The areas of the LSC, CS, and ICA were measured on the photographs using a Graphtec Digitizer (Model KD-4310A; Okura Co., Ltd., Fukuoka), and the area ratio (%) of the CS or ICA to the LSC was calculated for each specimen. The area of the LSC was defined as the parasellar structure enveloped by the meningeal and periosteal layers of the dura on each side of the coronal section. When the periosteum was not continuous on the photographs because of the immature sphenoid bone, a continuous, smooth line of the periosteal layer was assumed.

We selected 11 specimens with CR lengths ranging from 65 to 259 mm to observe the developmental changes in the CS and CS-related venous systems from the venous injection materials of human fetuses obtained in our previous studies.^{14,15,30}

Results

I. Development of the LSC

During the stage of 70–95 mm CR length, which

Table 1 Development of the cavernous sinus and internal carotid artery in the fetal period

Specimen	CR length (mm)	GA (wk)	CS/LSC (%)*		ICA/LSC (%)*		Basal venous plexus			Anast
			Left	Right	Left	Right	ICA	V2	V3	
1	70	13	1.9	1.2	0.97	1.16	+	–	–	–
2	90	14	NE	NE	NE	NE	+	–	–	–
3	95	15	8.0	4.8	0.93	0.53	+	–	–	–
4	128	18	3.5	5.8	1.26	0.81	+	–	–	–
5	140	19	6.7	20.2	0.69	0.91	+	–	+	–
6	165	21	6.0	10.1	1.38	0.83	+	+	+	–
7	180	23	7.9	5.4	1.22	0.75	+	–	+	–
8	180	23	17.2	12.1	4.02	3.92	+	–	+	–
9	183	23	21.6	24.2	1.31	1.69	+	–	+	–
10	195	25	11.4	13.0	1.69	1.74	+	–	+	+
11	230	28	24.4	26.5	2.17	1.89	++	–	++	+
12	240	29	37.3	45.9	8.22	8.56	++	–	+	–
13	253	31	37.0	21.2	4.15	2.56	++	–	++	–
14	270	32	30.9	39.9	3.30	5.15	++	++	++	+

*Area ratio (%) of the cavernous sinus (CS/LSC) or internal carotid artery (ICA/LSC) to the lateral sellar compartment observed on coronal sections. Anast: anastomosis between sphenoparietal and cavernous sinuses, CR: crown-rump, GA: gestational age, NE: not examined. V2: maxillary nerve, V3: mandibular nerve.

Fig. 1 Photomicrograph of the coronal section of the lateral sellar compartment (LSC) at the stage of 95 mm crown-rump length (15 weeks' gestation) traversing the pituitary gland (pg) and the horizontal portion of the internal carotid artery (ICA). Cartilaginous foundations are seen in the sphenoid body (sb) and petrous part. The meningeal layer (ml) of the primitive dura forms a loose membrane in the lateral and superolateral portions of the LSC where part of the arachnoid membrane (am) is not clearly distinguished. The meningeal layer of the dura folds to form a thin diaphragma sellae (ds) over the pituitary gland, wrapping around its side and bottom, and continues to the same structure on the opposite side. The periosteal layer (pl) of the dura is formed on the surface of the sphenoid cartilage. The cavernous sinus is observed as a collection of many irregularly shaped venous lumens (*) dotting the immature mesenchyme of the LSC, inferior to which the internal carotid venous plexus (vp) communicates. The oculomotor nerve (3) enters the LSC medial to the anterior petroclinoid fold (ap). The trochlear (4) and abducens nerves (6) are both separated into several nerve fascicles. The sympathetic nerve (sn) plexus passes into the LSC along the ICA. The tentorial sinus (ts) runs in the meningeal layer of the dura lateral to the anterior petroclinoid fold. The trigeminal ganglion (tg) and posterior clinoid process (cp) are shown. pc: petrous cartilage. Elastica van Gieson and Masson trichrome stain, $\times 50$.

Fig. 2 Photomicrograph of the coronal section of the lateral sellar compartment (LSC) at the stage of 128 mm crown-rump length (18 weeks' gestation) traversing the pituitary gland (pg) and the horizontal portion of the internal carotid artery (ICA). Ossification of the sphenoid cartilage (sc) has gradually progressed with formation of a thick periosteal layer (pl) of the dura. Irregularly shaped venous lumens (*) of the cavernous sinus in the immature mesenchyme have gradually increased in number. The oculomotor nerve (3) enters the LSC medial to the anterior petroclinoid fold (ap). The trochlear (4) and abducens nerves (6) are separated into several nerve fascicles. Sympathetic nerve fascicles surrounding the ICA, trigeminal ganglion (tg), and posterior clinoid process (cp) are shown. am: arachnoid membrane, ml: meningeal layer. Elastica van Gieson and Masson trichrome stain, $\times 40$.

corresponds to 13–15 weeks' gestation, the cartilaginous foundations which become the sphenoid bone were surrounded by immature mesenchyme of

the LSC in the coronal sections. In the cartilaginous sphenoid, small ossification centers were already observed at various locations, including the body of the sphenoid, the lesser wing, and the greater wing (Fig. 1). During the same period, ossification of the otic capsule was also observed in the petrous cartilaginous foundation. During the stage of 128–183 mm CR length (18–23 weeks' gestation), when ossification progresses rapidly, the body of the sphenoid abruptly elevated from the middle cranial fossa and expanded in the anteroposterior direction, with the lesser wing expanding more in the antero-superolateral direction (Figs. 2–4).

The primordium of both dura mater and arachnoid membrane was observed on the surface of the LSC during the stage of 70–95 mm CR length

Fig. 3 Photomicrograph of the coronal section of the lateral sellar compartment at the stage of 180 mm crown-rump length (23 weeks' gestation) traversing the pituitary gland (pg) and the horizontal portion of the internal carotid artery (ICA). Ossification extends to the whole sphenoid body (sb) with formation of a thick periosteal layer (pl) of the dura. The meningeal layer (ml) of the dura has become gradually denser. Some of the cavernous sinus venous lumens (*) have enlarged, becoming close to one another. The ophthalmic (on) and maxillary nerves (mn) each consist of many nerve fascicles. Sympathetic nerve (sn) fascicles are observed around the ICA. Collagen fiber networks (arrows) are newly formed around the nerve fascicles and the ICA. The oculomotor (3), trochlear (4), and abducens nerves (6) are shown. Elastica van Gieson and Masson trichrome stain, $\times 30$.

Fig. 4 Photomicrograph of the coronal section of the lateral sellar compartment (LSC) at the stage of 240 mm crown-rump length (29 weeks' gestation) traversing the pituitary gland (pg) and the horizontal portion of the internal carotid artery (ICA). A completely ossified sphenoid body rises from the middle cranial fossa, and the dense meningeal (ml) and periosteal layers (pl) of the dura are formed. Dilated cavernous sinus lumens (*) are situated side by side and unite to form larger lumens with regressed abluminal spaces (arrowheads). The cavernous sinus has significantly developed in the area medial to the complex of the oculomotor (3), trochlear (4), ophthalmic (on), and maxillary nerves (mn). Collagen fiber networks (arrows) have clearly and uniformly developed around all the components of the LSC. One of the sympathetic nerve (sn) fascicles around the ICA joins the abducens nerve (6) and both are covered together with a common collagen fiber sheath. sb: sphenoid bone. Elastica van Gieson and Masson trichrome stain, $\times 30$.

(13–15 weeks' gestation). The primitive dura mater was histologically distinguished from the arachnoid membrane after the stage of 180 mm CR length (23 weeks' gestation) and formed a definite meningeal layer of the dura consisting of dense collagen fibers at the stage of 230 mm CR length (28 weeks' gestation) (Figs. 3 and 4). During the same period, a thick periosteum, which corresponded to the medial wall of the LSC, was formed on the surface of the developing sphenoid bone (Figs. 3 and 4). The meningeal and periosteal layers of the dura met and fused at the lateral edge of the LSC and extended laterally to cover the inner surface of the middle cranial fossa. The meningeal layer of the dura folded to form a thin diaphragma sellae over the pituitary gland, wrapping around its side and bottom, and continued

to the same structure on the opposite side. Consequently, the pituitary gland was contained in a pocket formed by the caving of the meningeal layer of the dura (Figs. 1–4).

In parallel with the ossification of the sphenoid cartilage and formation of the dural envelope of the LSC, loose collagen fibers appeared around the nerve fascicles and vessels in the immature mesenchyme of the LSC after the stage of 180 mm CR length (23 weeks' gestation) (Fig. 3). The collagen fibers gradually increased in number with gestational age, and at the stage of 230 mm CR length (28

Fig. 5 Enlarged part of the photomicrograph in Fig. 4 taken at the stage of 240 mm crown-rump length (29 weeks' gestation), showing dilated cavernous sinus venous lumens (*). The walls of the lumens are lined with a layer of endothelial cells with no smooth muscle layer. Small nerve fascicles and small vessels are sometimes enclosed in the thin abluminal spaces (arrowheads). A sympathetic nerve (sn) fascicle joins one of four abducens nerve (6) fascicles and both are covered with a common collagen fiber sheath. Collagen fiber networks (arrows) are uniformly shown around the venous lumens and nerve fascicles (nf). Elastica van Gieson and Masson trichrome stain, $\times 200$.

weeks' gestation) they formed distinct networks that surrounded all the components in the LSC, including venous lumens, nerve fascicles, and arteries, and continued to the meningeal and periosteal layers of the dura (Figs. 4 and 5).

II. Development of the CS

During the stage of 70–95 mm CR length (13–15 weeks' gestation), the CS was observed as a collection of many small irregularly shaped lumens dotting the immature mesenchyme of the LSC (Fig. 1). The number and size of the venous lumens gradually increased with gestation, and some lumens enlarged to become close to each other after the stage of 180 mm CR length (23 weeks' gestation) (Figs. 2 and 3). After the stage of 230 mm CR length (28 weeks' gestation), formation of large venous lumens was observed. Abluminal spaces between the venous lumens were reduced and thinned to become membranous, resulting in the venous lumens being situated side by side or uniting to form large lumens (Fig. 4). Small arteries and small nerve fascicles were sometimes enclosed in the thin abluminal spaces (Figs. 4 and 5). During enlargement of the venous

Fig. 6 Development of the cavernous sinus (CS) in the fetus is indicated by the percentage-area of the CS compared to the lateral sellar compartment (CS/LSC), in the coronal section traversing the pituitary gland and the horizontal portion of the internal carotid artery. The CS/LSC ratio gradually increases after the stage of 150–200 mm crown-rump (CR) length (20–25 weeks' gestation) and exceeds 50% at birth, when the CR length is usually over 300 mm.²²⁾ $Y = 5.699 - 0.095X + 0.001X^2$ ($R^2 = 0.734$).

lumens, the continuity of the endothelial layer of the lumen walls was maintained, and no smooth muscle layer, commonly seen within venous walls, was observed (Fig. 5). With the development of the dura mater, collagen fiber networks gradually developed in the abluminal spaces between the fragile venous lumens (Figs. 3–5). The CS showed significant development in the area medial to the III, IV, V1, and V2 nerves or the trigeminal ganglion, as seen in the adult (Figs. 3 and 4).

Figure 6 shows the area ratios of the CS to the LSC in the coronal sections plotted against CR length (Table 1). The area ratio gradually increased after the stage of 150–200 mm CR length (20–25 weeks' gestation) and was estimated to be more than 50% at birth, when the CR length would exceed 300 mm.²²⁾

At the stage of 70 mm CR length (13 weeks' gestation), the CS communicated anteriorly with the common ophthalmic vein located lateral and inferior to the annular tendon in the superior orbital fissure, and posteriorly with the basilar venous plexus. The CS on either side connected through the

Fig. 7 Venogram of the fetus at the stage of 110 mm crown-rump length (17 weeks' gestation) showing the cavernous sinus (1) connecting to the ophthalmic vein (2) anteriorly and the inferior petrosal sinus (3) and pterygoid venous plexus (4) inferiorly. The pro-otic sinus, which is the origin of the cavernous sinus, seems to have already regressed and is not observed. The middle cerebral veins (5) drain through the tentorial sinus (6), which empties into the transverse sinus (7). A newly formed superior petrosal sinus (8) is revealed posterior to the cavernous sinus. The basal vein (9) and internal cerebral vein (10) join together to form the great vein of Galen (11), emptying into the straight sinus (12). The superior sagittal (13), occipital (14), and sigmoid (15) sinuses, vertebral venous plexus (16), and internal jugular vein (17) are shown.

intercavernous sinus between the dural layers below the pituitary gland and above the sphenoid bone (Figs. 1–3). The inferior draining pathways from the CS communicating with the pterygoid venous plexus included the internal carotid venous plexus passing through the foramen lacerum observed at the stage of 70 mm CR length (13 weeks' gestation), and the sphenoid emissary veins surrounding the mandibular nerve (V3 nerve) after the stage of 140 mm CR length (19 weeks' gestation). The number of these venous pathways abruptly increased after the stage of 230 mm CR length (28 weeks' gestation) (Table 1, Fig. 7). Other emissary veins draining to

the pterygoid venous plexus along the V2 nerve were seen in two specimens (Table 1). The sphenoparietal sinus was observed anastomosing to the CS on one side in three specimens after the stage of 195 mm CR length (25 weeks' gestation) (Table 1).

Venography of the fetus revealed developmental changes in the CS and CS-related venous systems. After the stage of 70 mm CR length (13 weeks' gestation), the CS and basilar venous plexus were demonstrated as a faint cluster of small vessels connecting with the ophthalmic vein anteriorly, the inferior petrosal sinus posteriorly, and the pterygoid venous plexus inferiorly (Fig. 7). The inferior venous pathways connecting with the pterygoid venous plexus abruptly increased in size after the stage of 225 mm CR length (27 weeks' gestation) (Table 1).

III. Development of the nerves in the LSC

At the stage of 70 mm CR length (13 weeks' gestation), the positions and running directions of the cranial nerves in the immature LSC mesenchyme were comparable to those in the adult. The V3 nerve branched out from the trigeminal ganglion, and the V1 and V2 nerves ran anteriorly in the lateral part of the LSC, reaching the superior orbital fissure and the foramen rotundum, respectively. The III and IV nerves entered the LSC near the posterior clinoid process and ran anteriorly to the superior orbital fissure. The abducens nerve (VI nerve) ran through the basilar venous plexus and coursed in the inferolateral region to the horizontal portion of the ICA to reach the superior orbital fissure (Fig. 1).

The V1, V2, and V3 nerves and the sympathetic nerve plexus coming through the foramen lacerum consisted of many nerve fascicles in the LSC. The III, IV, and VI nerves were separated into two to five fascicles in the LSC. The separation and intermingling of the nerve fascicles sometimes made the nerves difficult to distinguish from one another (Figs. 1–5). With the CS significantly developing in the region medial to the III, IV, V1, and V2 nerves after the stage of 180 mm CR length (23 weeks' gestation), these cranial nerves were placed close to the meningeal layer of the dura with the V2 nerve bordering the inferolateral margin of the LSC.

With the development of the dura mater, the collagen fiber networks gradually increased in size around the trigeminal ganglion and all nerve fascicles, continuing to the meningeal and periosteal layers of the dura (Figs. 3–5). In some specimens, a sympathetic nerve fascicle was joined with the VI nerve, both covered with a common collagen fiber sheath (Figs. 4 and 5).

Fig. 8 Development of the internal carotid artery (ICA) in the fetus is indicated by the percentage-area of the ICA compared to the lateral sellar compartment (ICA/LSC), in the coronal section traversing the pituitary gland and the horizontal portion of the ICA. The ICA/LSC ratio is approximately 1% before the stage of 140 mm crown-rump length (19 weeks' gestation), and gradually increases to more than 6% at birth, when the CR length is usually over 300 mm.²²⁾ $Y = 1.693 - 0.022X + 1.306e^{-4}X^2$ ($R^2 = 0.444$).

IV. Development of the ICA in the LSC

During the stage of 70–95 mm CR length (13–15 weeks' gestation), the ICA entered the LSC at the region inferolateral to the cartilaginous sphenoid and coursed in the LSC mesenchyme almost straight in the antero-supero-medial direction to the region medial to the anterior clinoid process (Fig. 1). When the sella turcica developed in the superoinferior and anteroposterior directions as the ossification of the sphenoid progressed, the ICA transformed into an S-shape with anterior, medial, and lateral loops.

Figure 8 shows the area ratios of the ICA to the LSC in the coronal sections plotted against CR length (Table 1). The area ratio was approximately 1% before the stage of 140 mm CR length (19 weeks' gestation), and was estimated to increase to more than 6% at birth, when the CR length would exceed 300 mm.²²⁾

Discussion

The calvarial dura mater consists of the meningeal

Fig. 9 Diagram showing the coronal section of the lateral sellar compartment (LSC) traversing the pituitary gland (pg) and the horizontal portion of the internal carotid artery (ICA). The meningeal layer (ml) of the dura is widely peeled from the LSC lateral wall. The meningeal layer of the dura folds to form a thin diaphragma sellae (ds) over the pituitary gland, wrapping around its side and bottom, and continues to the same structure on the opposite side. The periosteal layer (pl) of the dura on the surface of the sphenoid bone (sb) meets and fuses with the meningeal layer at the lateral edge of the LSC. The location of the nerves and ICA of the LSC is quite similar to those in adults, i.e., the ICA and the abducens nerve (6) are situated medial to the cranial nerve complex containing the oculomotor nerve (3)-trochlear nerve (4)-optic nerve (on)-maxillary nerve (mx) complex. The oculomotor and trochlear nerves enter the LSC near the posterior clinoid process. The abducens nerve runs through the basilar plexus and courses in the inferolateral region to the ICA. The nerves are separated into several fascicles in the LSC. The ICA courses in the LSC almost straight in the antero-supero-medial direction to the region medial to the anterior clinoid process. mn: mandibular nerve, tg: trigeminal ganglion.

(inner) and periosteal (outer) layers, between which most of the dural sinuses are situated in an endothelial layer.^{25,26)} The LSC is very different from these common dural sinuses because it contains not only the CS but also nerves and the ICA inside the dural envelope. The LSC is defined as the superior orbital fissure anteriorly, the posterior petroclinoid fold and clival dura mater posteriorly, and the inner surface of the middle cranial fossa inferolaterally where the meningeal and periosteal layers of the dura meet and fuse.^{4,7,8,19,21,24–28)}

I. Lateral wall of the LSC

Various theories relating to the structural nature of the LSC lateral wall have been proposed. Recently, the meningeal layer of the dura, called the superficial layer, was observed to be separated from the III-IV-V1-V2 nerve complex, called the deep layer.^{3,4,8,20,21,24,27,28} We examined the structural nature of the LSC lateral wall based on histoarchitectural changes during the fetal period, and found that the locations of the LSC components at the stage of 70 mm CR length (13 weeks' gestation) were quite similar to those of adults, that is, the ICA, the VI nerve, and the CS are situated medial to the III-IV-V1-V2 nerve complex (Fig. 9). According to our study, the meningeal layer of the dura becomes distinct from the arachnoid membrane after the stage of 180 mm CR length (23 weeks' gestation) and is subsequently accompanied by dense collagen fibers after the stage of 230 mm CR length (28 weeks' gestation). The collagen fiber networks seem to be distributed uniformly in the fetal LSC and extend continuously to the meningeal layer of the dura. Consequently, the LSC lateral wall is difficult to identify histologically as distinct multiple layers, at least during the fetal period.

During surgical operations involving the adult LSC, some membranous or fibrous connective tissues are increased in volume in the LSC,^{3,4,7,27,28} and the amount of interfascicular connective tissue varies between the different cranial nerves.²⁰ These findings indicate that development of the collagen fiber networks after birth is not always uniform. It is possible that the development of collagen fibers in the meningeal layer of the dura after birth causes differences in tissue density, which makes distinction between the meningeal layer and the III-IV-V1-V2 nerve complex possible in the adult LSC.^{3,4,6-8,20,21,24,27,28}

II. Morphological development of the CS

Our study made the following observations about the developmental processes and histoarchitecture of the CS. The CS at the stage of 70–128 mm CR length (13–18 weeks' gestation) is a complex consisting of many fine tubular venous spaces which develop in the immature LSC mesenchyme. These venous spaces meander, join, and intertwine among themselves (Fig. 10). We defined the venous spaces as the venous canals of Krivosic.¹⁰ The walls of the venous canals are formed of only an endothelial layer, with no smooth muscle layers, unlike common venous walls.

As fetal development progresses, especially after the stage of 180 mm CR length (23 weeks' gestation), the size of the inner spaces of the venous canals

Fig. 10 Diagrams showing the development of the cavernous sinus venous canals. upper: Meandering, small-caliber venous canals with an endothelial wall join each other in the lateral sellar compartment mesenchyme in the beginning of the fetal stage. lower: Venous canals gradually enlarge and unite with each other with the regression of interstitial tissue.

becomes increasingly variable. The canals dilate more and more, and unite with the progression of the thinning and regression of the immature mesenchyme, which forms the interstices between the canals (Fig. 10). During these processes, the continuity of the endothelial lining is maintained, and small nerve fibers and vessels are sometimes enclosed in the thinned interstices. In parallel with the development of the dura, collagen fiber networks in the mesenchymal interstices also develop to serve as a flexible internal framework that sustains the fragile venous canals after the stage of 230 mm CR length (28 weeks' gestation).

Depending on variations in development,^{9,13} the CS may occur as a large sinusoidal venous space with trabeculation^{1,3,6,12,13,24,27,28} or as a venous plexus consisting of many complex branched veins in adults.^{4,18-20,25,26,29} Trabeculation in the CS is surely a relic of the venous walls and interstitial tissues, as described by Krivosic.¹⁰ However, the process of CS formation is not a simple regression of mature veins,¹⁵ but rather the development of venous canals

with no smooth muscle layers; that is, an enlargement and uniting of the venous canals followed by web-formation by collagen fibers in the interstices.

III. Developmental changes in the venous drainage related to the CS

Our morphological studies suggested that the blood volume of the CS increases rapidly after the stage of 150–200 mm CR length (20–25 weeks' gestation). The mechanism of this increase is uncertain, but at least three factors may be involved. Firstly, some reduction of the neighboring venous pathways in the fetal period, such as the pro-otic sinus,^{5,16,17)} may cause an increase in the blood volume of the CS. Secondly, transitional venous hypertension may occur, as an increase in the intracerebral blood volume, following expansion of the cerebral hemispheres during fetal months 4.5 and 7, causes venous hypertension at the poorly developed jugular sinuses.¹⁴⁾ The transitional increase in venous pressure at the regular sinuses may be conveyed to the CS through the inferior petrosal sinus or basilar venous plexus and stimulate development and enlargement of the CS. Thirdly, a secondary anastomosis may occur between the CS and the sphenoparietal sinus, which is suspected to be a remnant of the tentorial sinus collecting the superficial and deep middle cerebral veins.^{16,17)} The secondary anastomosis is probably formed during the fetal period, as observed in our three specimens after the stage of 195 mm CR length (25 weeks' gestation), and as described by Masaki¹¹⁾ and Knosp et al.,⁹⁾ although Padgett^{16,17)} suspected that the secondary anastomosis was a change that occurred after birth.

Fetal venography in this study showed the CS and basilar venous plexus as a faint cluster of small vessels. We confirmed that these vessels were connected with the ophthalmic vein anteriorly, the inferior petrosal sinus posteriorly, and the pterygoid venous plexus inferiorly, after the stage of 70 mm CR length (13 weeks' gestation). Both the venograms and histological sections indicated that the inferior venous drainage of the brain, which drains into the pterygoid venous plexus via the CS, seems to increase abruptly after 27–28 weeks of gestation. The CS drains into the pharyngeal and pterygoid plexuses as well as towards the superior and inferior petrosal sinuses in human fetuses aged 4 months old.²³⁾

Small scatterings of venous channels without trabeculation were seen in 9% of 23 adult specimens,¹³⁾ and a complete unilateral defect of the CS was found in one of 10 fetal specimens.⁹⁾ These variations in the formation and size of the CS prob-

ably relate to the different developmental processes of the neighboring venous pathways which continue from the fetal stage to after birth.

IV. Development of the nerves and ICA in the LSC

The cranial nerves in the LSC sometimes branch out and join with other branches.^{3,6,7,10,12,13,19,27)} In our observations of several specimens, the fascicles between the VI and sympathetic nerves were joined together and sheathed by common collagen fibers. The direct connections between the intermingling nerve fascicles in the LSC seem to be completed during the fetal period, so each and every branching and joining of the nerve fascicles is probably enveloped by the collagen fiber sheath after the stage of 180 mm CR length (23 weeks' gestation). In the specimens with poorly developed interfascicular collagen fibers, the cranial nerves may be divided in the LSC, as is occasionally found in some adults.^{6,7,12,13,20)}

The ICA during the stage of 70–95 mm CR length (13–15 weeks' gestation) enters the LSC at the inferolateral region of the cartilaginous sphenoid body, and runs almost straight supero-antero-medially in the LSC mesenchyme (Fig. 9). The entrance of the ICA among fetuses aged 16–26 weeks is located at the junction of the anterior and middle thirds along the anteroposterior axis of the LSC, which is more anterior than that of the adult, and the ICA is much narrower at one and a half times the width of the VI nerve.¹⁾ In our study, the area ratio of the ICA to LSC increased gradually after the stage of 140 mm CR length (19 weeks' gestation). The ICA is fixed by the dura mater where the ICA pierces the LSC, and seems to wind gradually with ossification of the sphenoid and petrous cartilages to form an S-shape with anterior, medial, and lateral loops, as demonstrated by cerebral angiography of the fetus,¹⁵⁾ and suspected in infant autopsy cases.²⁹⁾

Conclusions

The formation of the LSC, an interdural space including the CS, cranial nerves, and ICA, and sustained by internal collagen fiber networks, is largely completed before birth. The CS emerges as a collection of many small venous canals with only an endothelial layer in the LSC mesenchyme. The venous canals gradually expand and unite to form much larger structures. The CS and basilar venous plexus appear as a faint cluster of small vessels after 13 weeks of gestation. The inferior venous pathways connecting with the pterygoid venous plexus abruptly increase in size after 27 weeks of gestation.

The dura mater of the LSC develops in parallel with ossification of the sphenoid. After 23 weeks of gestation, the meningeal layer of the dura is clearly distinguishable from the arachnoid membrane, and the collagen fiber networks develop around all the components in the LSC. The LSC lateral wall cannot be histologically differentiated as separate multiple layers. The branching and joining of the intermingling nerve fascicles in the LSC are completed during the fetal stage by envelopment of the collagen fibers after 23 weeks of gestation. The ICA runs straight in the LSC mesenchyme at 13–15 weeks gestation, and becomes tortuous and forms an S-shape before birth.

Acknowledgment

We thank Akio Ohnishi, M.D. (Department of Neurology, University of Occupational and Environmental Health) for lending us the Graphtec Digitizer, and Ms. Rieko Maeda for preparing all histological sections.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan, 1994–1995.

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Commentary

The authors report a unique anatomical study of the fetal cavernous sinuses in 14 specimens of different gestational age. The studies were done in serial coronal histological sections and examined under the light microscope. The description and evolution of this complex area is well elucidated by this study. Also the reason for the double layered lateral wall is clearly evident from this report. The outer layer of the lateral wall is the dura mater, while the inner layer, with the cranial nerves, arises from the connective tissue of the lateral sellar compartment (LSC) which undergoes canalization with time. This connective tissue in the LSC is solid in the early fetus but enlarges and is filled with venous channels during the maturation process. It also explains why the inner layer is often incomplete with venous channels running through it.

I congratulate the authors on this excellent work which is quite painstaking as such, but also the logistical problems of obtaining cadaver fetal material

must have been a huge undertaking.

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Many anatomical studies of the cavernous sinus area of the human adults have been performed by anatomical dissection and surgical findings. The authors have provided a clear description of the developmental process and structures of the cavernous sinus in the human fetus. The following important anatomical statements will contribute to a better understanding of this inaccessible area.

- 1) The meningeal layer of the dura becomes distinct from the arachnoid membrane at 23 weeks' gestation.
- 2) The lateral wall of the adult cavernous sinus consists of two layers, that is, a superficial dural layer and a deep connective tissue layer. These structures are formed at 23 weeks' gestation.
- 3) The cavernous sinus venous canals are winding and small caliber at 13-18 weeks' gestation, and then gradually enlarge and unite with each other at 23 weeks' gestation, and finally form large venous lumens at 28 weeks' gestation.
- 4) The cavernous sinus and basilar plexus are connected with the ophthalmic vein anteriorly, the inferior petrosal sinus posteriorly, and the pterygoid venous plexus inferiorly after 13 weeks' gestation.
- 5) The ICA is in contact with the ossification of the sphenoid at 19 weeks' gestation, and this must be taken into consideration during the transsphenoidal approach.
- 6) Branching and joining of the cranial nerve fascicles are completed with the envelopment of collagen fibers after 23 weeks' gestation.

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