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Review Article

Embryology of the Cavernous Sinus and Relevant Veins

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The cavernous sinus (CS) is a parasellar dural envelope containing an important venous pathway. The venous channels, which have an endothelial layer and no smooth muscle layer, are located in connective tissue. In the early embryonic stages, the neural tube is surrounded by the primitive capillary plexus and undifferentiated mesenchymal tissue, the primary meninx, and initially drains into the primary head sinus (PHS) through the anterior, middle, and posterior dural plexus (ADP, MDP, and PDP). Subsequently, following enlargement of the brain and differentiation of the mesenchyme, two major primary sinuses, the pro-otic sinus and the primitive tentorial sinus, become prominent. The pro-otic sinus is the remnant of the short segment of the PHS cranial to the MDP and the stem of the MDP. The CS originates from the plexiform channels medial to the trigeminal ganglion, namely the medial tributaries of the pro-otic sinus. The stem of the pia-arachnoidal vein draining into the ADP represents the primitive tentorial sinus. It is considerably elongated due to expansion of the cerebral hemisphere, and migrates medially toward the CS. The morphological changes in the CS and primitive tentorial sinus exhibit considerable variation in cerebral venous drainage patterns. Embryological knowledge facilitates interpretation of the anatomy of the CS, and it is useful to perform safe and beneficial endovascular treatment for the CS.

Keywords ▶ cavernous sinus, embryology, pro-otic sinus, primitive tentorial sinus

Introduction

The cavernous sinus (CS) is a parasellar dural envelope extending from the superior orbital fissure to the dorsum sellae.[1] The dural envelope contains the internal carotid artery (ICA) and its branches, cranial nerves, and venous channels, which serve as a venous pathway draining the brain, orbital content, pituitary gland, dura, and bone.

The CS is a common location of dural arteriovenous fistulas and direct arteriovenous fistulas due to trauma or aneurysm rupture (carotid-cavernous fistulas), which are generally treated by endovascular embolization. It is important for transvenous embolization of these pathologies to understand the structure of venous channels in the CS and their connection with relevant veins, and embryological knowledge facilitates interpretation of the anatomy of the CS. The present review describes the classical and updated interpretations of the embryological development of the CS.

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History

Claudis Galenus (119–199 A.D.), a physician in Rome, dissected animals and first described the parasellar ICA. His original description, "parasellar carotid retia bathed in venous blood" was believed for more than 15 centuries. Andreas Vesalius (1514–1564), a renaissance anatomist, who corrected most of Galen's errors, had no interest in Galen's description of the parasellar area. In 1732, Jacques Bénigne Winslow (1669–1760) noted fibrous trabeculae in this parasellar venous structure, and introduced the term "cavernous sinus."[2,3]

From the early to middle 20th century, several studies in human embryos and fetuses made significant contributions to embryology of the cranial vascular system (**Fig. 1**).[4–8] Following Streeter's work on the development of the dural sinuses and the cerebral veins,[4,5] Padget provided comprehensive accounts of the development of the human cranial venous system, including the CS.[6,7]

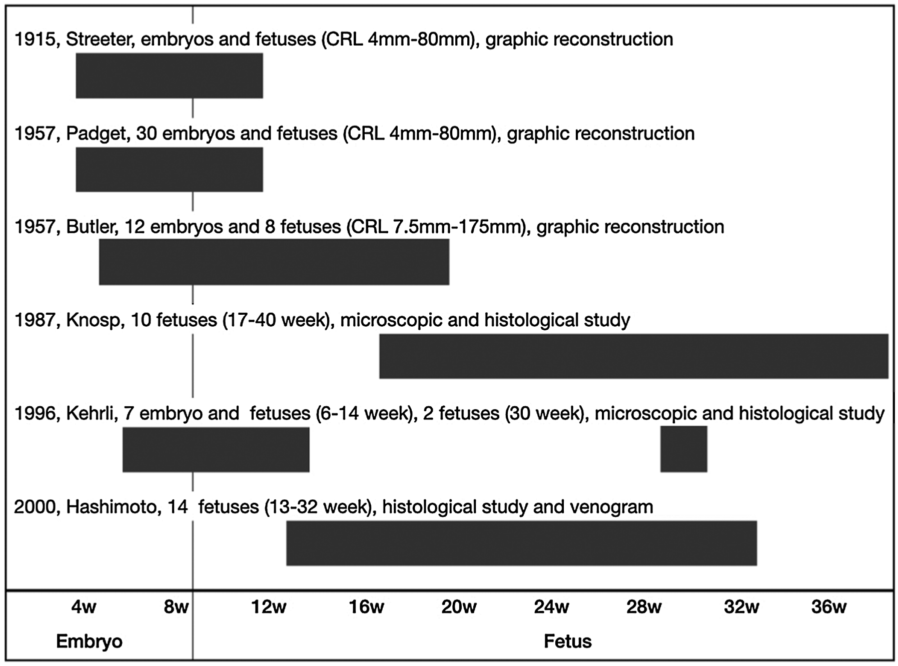

Fig. 1 Stages of embryos and fetuses in the studies of the development of the cavernous sinus.

Until the middle of the 20th century, the CS was thought to be a blood-filled channel surrounding the ICA. In 1949, Taptas described the so-called CS as an extradural space formed by the diverging aspects of a dural fold without a sinus, but having a venous plexus.[9] Subsequently, Bedford reported that the CS was essentially an unbroken venous channel without trabeculae in 80% of the sinuses examined.[10] Harris and Rhoton also described that the CS is largely an unbroken, trabeculated venous channel with three major spaces posterosuperior, anteroinferior, and medial to the intracavernous portion of the ICA.[11] Parkinson, who performed the successful direct repair of a carotid-cavernous fistula,[12] strongly advocated that the term "cavernous sinus" is inappropriate and proposed that it should be replaced with "parasellar plexus of veins" in the "lateral sellar compartment." He described that the compartment is extradural and the venous structures consist of a greatly variable plexus of markedly thin-walled veins.[13]

The commonly accepted definition of dural sinuses is that their walls consist of an inner endothelial layer and an outer layer formed by the dura mater. This definition is sufficiently precise to differentiate from a vein, which has the three distinctive layers: endothelium, media, and adventitia.[14] After the 1980s, the venous structures associated with surrounding connective tissue within the CS were investigated by several histological studies of the parasellar area in human fetuses (**Fig. 1**).[14–16]

Knosp et al. performed microscopic and histological examinations of the parasellar area in fetuses. According to their observations, the parasellar venous pathway consisted of individual vessels that were clearly separated by abundant connective tissue. The venous channels, which consisted only of an endothelial layer without a muscular layer, formed a plexiform network with several interconnections. Accordingly, they described that the so-called CS is a venous network consisting of distinct individual veins and proposed the term "cavernous venous plexus."[15]

On the other hand, Kehrli et al. described that the parasellar venous system is a sinus from an embryological and histological point of view. According to their study using serial histological sections of human embryos and fetuses, a network of endothelium-coated vessels located in the parasellar mesenchymal space was observed in embryos, and more organized and fibrous mesenchyme, partly differentiating into adipose tissue, in fetuses. The venous channels have no histological characteristics compatible with true veins, and only those of true sinuses, consisting of only an endothelial layer surrounded by fibrous trabeculae.[14]

Hashimoto et al. performed histological examination and venography of fetuses, and demonstrated the following findings. At 15 weeks of gestation, the CS was composed of sporadic small channels in the parasellar mesenchyme. The number and size of the venous lumens of the CS gradually increased with gestation. The enlarged venous lumens became close to one another after 23 weeks. Subsequently, interstitial spaces between the venous lumens were thinned and contacted each other, uniting to form large lumens. During enlargement of the venous lumens, the continuity of the endothelial layer of the lumen walls was maintained and no smooth muscle layer was observed. Along with the development of the dura mater, collagen fiber networks gradually developed in the interstitial spaces between the fragile venous lumens. These developmental processes may lead to structural variation of the CS. It may develop as a large sinusoidal venous space with trabeculation or as a venous plexus consisting of many complex branched veins in adults.[16]

Development of the Cranial Venous System in Embryos

Development of the cranial venous system was described in detail by Padget based on graphic reconstructions of serial sections of embryos and fetuses, ranging from 5 mm to 80 mm in crown-rump length, provided by the Carnegie collection, in which the blood vessels had been previously injected with dyes.[6,7]

In early embryonic stages (4–5 weeks), the neural tube is covered by a primitive capillary network. The primitive capillary plexus in the future pial layer drains into three venous plexuses in the future dural layer through many short vessels at the dorsolateral aspect of the primitive brain. The stems of these dural plexuses empty ventrally into the primary head sinus (PHS). The anterior dural plexus (ADP) drains the telencephalon, diencephalon, and mesencephalon, the middle dural plexus (MDP) drains the metencephalon, and the posterior dural plexus (PDP) drains the myelencephalon. The PHS runs medial to the 5th and 10th cranial nerve roots, and empties into the anterior cardinal vein, which is the future internal jugular vein.

The ventral tributary of the PHS, the primitive maxillary vein, drains the optic vesicle through the lateral tributary and the olfactory region through the medial tributary. The role of drainage of the optic region is subsequently supplemented by the primitive supraorbital vein, and these veins will constitute all ophthalmic and orbital veins, which are the superior and inferior ophthalmic veins in the adult.

As the cerebral hemisphere and cerebellum expand, and the otic capsule enlarges, the PHS and the dural plexuses migrate laterally, elongating their medial tributary from the pial layer. The PHS and the internal jugular vein come to lie lateral to the cranial nerve roots, excluding the 5th nerve. Following separation of the dural and pial layers, the primary anastomoses between the dural and pial veins decrease in number. The few remaining anastomoses increase in size and constitute the pia-arachnoid vein, which is the future bridging vein.

The PHS essentially disappears except for its short segment medial to the 5th nerve, which will become the lateral wing of the CS. The new dorsal sinuses are substituted for the ventral PHS to drain the brain into the internal jugular vein. The secondary anastomotic channel between the MDP and PDP dorsal to the otic capsule, and the stem of the PDP constitute the sigmoid sinus. The ADP forms the primitive marginal sinus, which will constitute the superior sagittal sinus. The ADP and MDP, now called the tentorial plexus, will develop into the torcular and transverse sinus.

By the end of the embryonic stage, two important embryonic sinuses, the pro-otic sinus and the primitive tentorial sinus, become prominent (**Fig. 2**). These sinuses originate from the ADP and MDP. The augmented stem of the MDP and the last remaining short segment of the PHS are now called the pro-otic sinus. The ADP forms the telencephalic vein, the future superficial middle cerebral vein (SMCV), and its stem represents the primitive tentorial sinus. The stem of the ADP, the primitive venous communication between the primitive tentorial sinus and the pro-otic sinus, has already dwindled by this point.[7]

Development of the Cranial Venous System in Fetuses

Major modifications of the pro-otic and primitive tentorial sinuses occur during the fetal stages from 40 to 80 mm in crown-rump length.

The pro-otic sinus receives blood from the optic region through the primitive supraorbital and maxillary veins, runs medial to the trigeminal ganglion, and empties dorsally into the sigmoid sinus. Development of the chondrocranium and the membranous skull leads to maturation of the pro-otic sinus. The lateral tributaries, the middle meningeal sinuses, drain the primitive dura and bone. The medial tributaries constitute the CS and the inferior petrosal sinus (IPS). The CS originates from the plexiform extensions of the pro-otic sinus medial to the trigeminal ganglion. The plexiform venous channels, surrounding the ICA and the 6th nerve, and extending between the otic and basioccipital cartilages, constitute the IPS. The proximal portion of the IPS originates from the stem of the ventral myelencephalic vein, lying between the roots of 9th and 10th nerves. The stem corresponds to the remnant of the PHS joining the internal

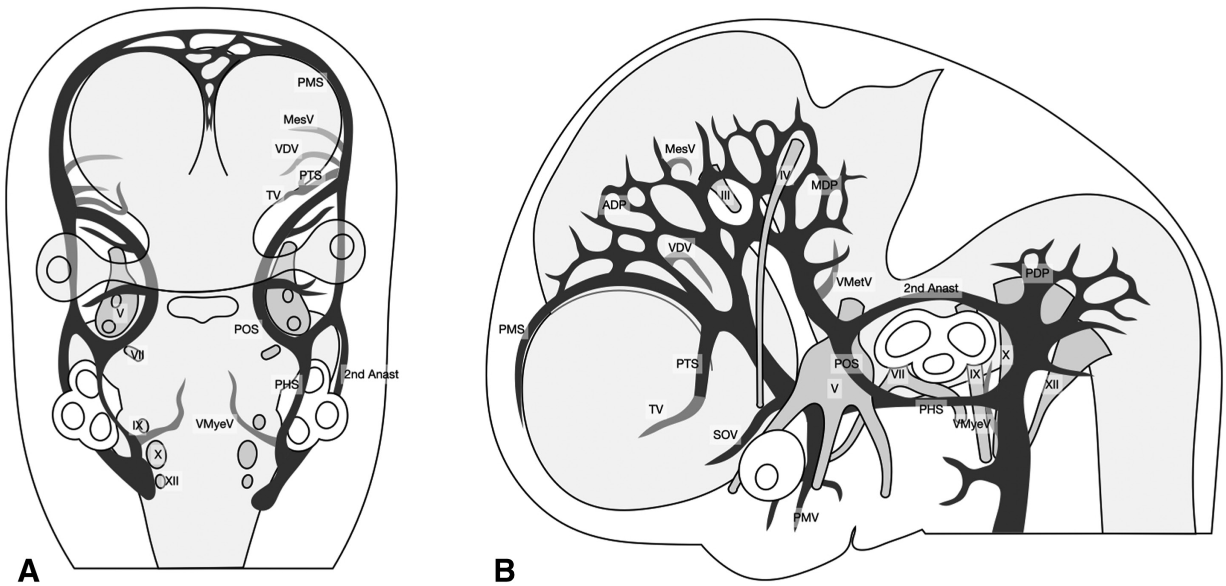

Fig. 2 Developing cranial veins in the early embryonic phase. (**A**): frontal view; (**B**): lateral view. III: oculomotor nerve; IV: trochlear nerve; V: trigeminal nerve; VII: facial nerve; IX: glossopharyngeal nerve; X: vagal nerve; XII: hypoglossal nerve; 2nd Anast: secondary anastomosis; ADP: anterior dural plexus; MDP: middle dural plexus; MesV: mesencephalic vein; PDP: posterior dural plexus; PHS: primary head sinus; PMS: primitive marginal sinus; PMV: primitive maxillary vein; POS: pro-otic sinus; PTS: primitive tentorial sinus; SOV: supraorbital vein; TV: telencephalic vein; VDV: ventral diencephalic vein; VMetV: ventral metencephalic vein; VMyeV: ventral myelencephalic vein

jugular vein. The intercavernous sinuses and the basilar sinus of the adult are the midline plexiform extensions anastomosing the bilateral CSs and IPSs, respectively.

The dorsal pharyngeal vein, a tributary of the pro-otic sinus, becomes the sphenoid emissary of the foramen ovale, communicating between the CS and the adult pterygoid plexus. The superior ophthalmic vein anastomoses with the anterior facial vein at the medial ocular angle. The anterior facial vein joins the primitive maxillary vein, and constitutes the deep facial vein, communicating with the pterygoid plexus. The liguofacial vein, which primarily empties into the internal jugular vein, becomes the common facial vein, and secondary annexation by the external jugular vein will occur.[7)]

Although the superior petrosal sinus (SPS) had been confused with the pro-otic sinus,[4,5)] Butler explained that a small plexiform tributary of the pro-otic sinus forms the SPS, which runs anteriorly around the trigeminal ganglion to the CS. However, he did not mention the pial venous drainage into the SPS.[8)] Padget described that the SPS originates from the stem of the ventral metencephalic vein. It drains the primitive cerebellum and pons, and empties into the junction of the transverse and sigmoid sinuses. Its communication with the CS is secondary and inconstant.[7)] The adult SPS receives blood from the petrosal vein, and drains into the CS via the anterior segment, or into the transverse sinus via the posterior segment.[17)]

The lateral tributary of the sigmoid sinus runs through the spurious jugular foramen, and anastomoses with the middle meningeal sinuses, which is the petrosquamosal sinus.[7)] Although the petrosquamosal sinus is usually regresses during fetal period, it can be identified in the human adult. It connects with the retromandibular vein via foramen retroauricular, or the pterygoid plexus via the foramen ovale, draining into the external jugular vein.[18)]

The superficial and deep telencephalic veins, and the ventral diencephalic vein drain into the primitive tentorial sinus. The primitive tentorial sinus runs along the ventrocaudal aspect of the cerebral hemisphere and empties into the medial segment of the primitive transverse sinus. Subsequently, the primitive tentorial sinus is considerably elongated due to significant expansion of the cerebral hemisphere, and the caudal end of the sinus becomes attenuated and plexiform, migrating toward the junction between the transverse and sigmoid sinuses. Considerable variation in the course of the primitive tentorial sinus becomes apparent thereafter. The primitive tentorial sinus can be shifted medially and incorporated into the CS.

According to Padget's work, the pro-otic sinus belongs to the outer dural layer, whereas the primitive tentorial sinus, which is directly continuous with the stem of the SMCV, belongs to the inner dural layer.[7)] The transition

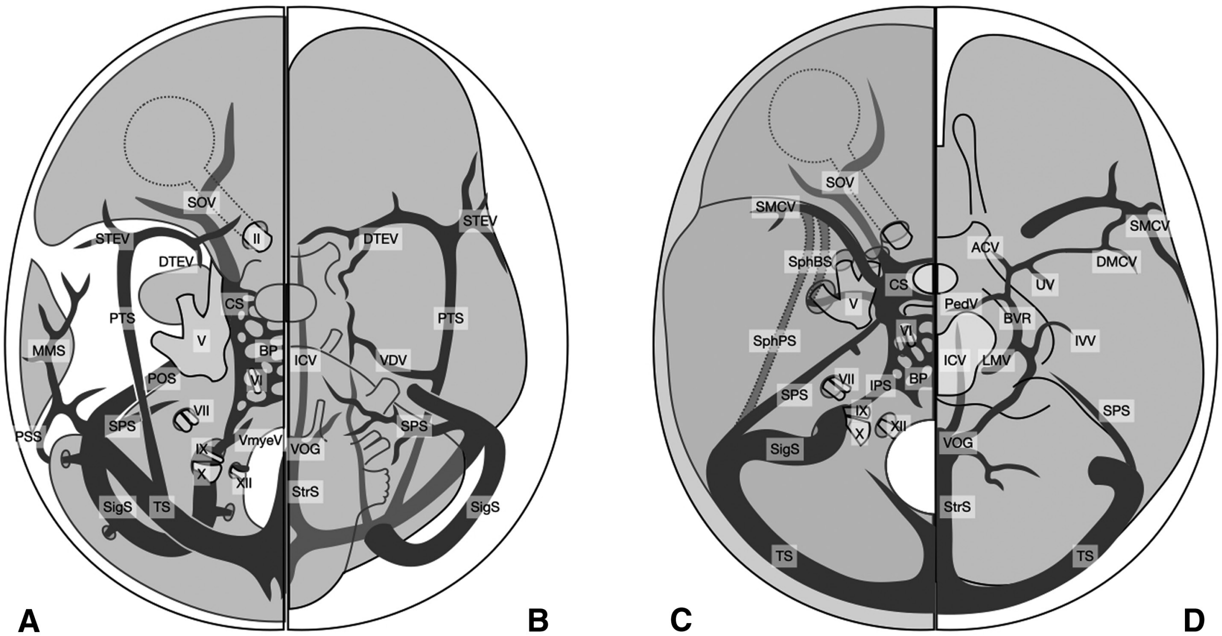

Fig. 3 Developing cranial veins in a fetus (**A**, **B**) and infant (**C**, **D**). **A**, **C**: superior view; **B**, **D**: inferior view. The superior view (**A**, **C**) represents the development of the cavernous and IPS, and the superficial middle cerebral vein. The inferior view (**B**, **D**) represents the development of the basal vein of Rosenthal. II: optic nerve; V: trigeminal nerve; VI: abducens nerve; VII: facial nerve; IX: glossopharyngeal nerve; X: vagal nerve; XII: hypoglossal nerve; ACV: anterior cerebral vein; BP: basilar plexus; BVR: basal vein of Rosenthal; CS: cavernous sinus; DMCV: deep middle cerebral vein; DTEV: deep telencephalic vein; ICV: internal cerebral vein; IPS: inferior petrosal sinuses; IVV: inferior ventricular vein; LMV: lateral mesencephalic vein; MMS: middle meningeal sinus; PedV: peduncular vein; POS: pro-otic sinus; PSS: petrosquamosal sinus; PTS: primitive tentorial sinus; SigS: sigmoid sinus; SMCV: superficial middle cerebral vein; SOV: superior ophthalmic vein; SphBS: sphenobasal sinus; SphPS: sphenopetrosal sinus; SPS: superior petrosal sinus; STEV: superficial telencephalic vein; StrS: straight sinus; TS: transverse sinus; UV: uncal vein; VDV: ventral diencephalic vein; VMyeV: ventral myelencephalic vein; VOG: vein of Galen

between the arachnoidal vein and dural sinus is gradual and varies considerably. The final position of the primitive tentorial sinus in the middle cranial fossa can vary from a medial to a lateral position (**Fig. 3A** and **3C**). The adult remnant of the primitive tentorial sinus can connect with the CS, the pterygoid plexus, the SPS, or the transverse sinus.

Cerebral expansion leads to not only alteration of the primitive tentorial sinus but also to development of a shorter route, the basal vein of Rosenthal. The basal vein develops by a longitudinal pial anastomosis between pia-arachnoidal veins draining the telencephalon, diencephalon, and mesencephalon, and empties into the great cerebral vein of Galen (**Fig. 3B** and **3D**).[7)] The uncal vein originates from the deep telencephalic vein, and can therefore communicate with the basal vein, the SMCV, and the CS. Accordingly, there are several variations in uncal venous drainage pattern.[19)]

Development of the Mesenchymal Tissue Surrounding the CS

Development of the meninges is complicated. O'Rahilly and Muller described that the human cranial meninges start with the formation of the mesenchyme surrounding the neural tube, which is referred to as the primary meninx.[20,21)] This mesenchyme originates from several sources, including the primitive streak and neural crest. The dense mesenchyme, the skeltogenous layer, develops between subcutaneous tissue and the primary meninx. The blood vessels that lie on its internal aspect will become veins and dural sinuses.

The leptomeninges first develop between the cerebral wall and the internal part of the dural limiting layer, followed by the dura mater in the external part of the dural limiting layer. The development of the dura starts at the level of the mesencephalic flexure. Mesenchymal cells from the notochord and the prechordal plate extend rostrally into the mesencephalic flexure.

The mesencephalic flexure surrounds mesenchymal tissue called "plica ventralis encephali meninges." Cho et al. examined the developmental processes of the plica ventralis in human embryos and fetuses. According to their observations, the plica ventralis evolves into the bilateral lateral mesenchymal condensations and the primitive diaphragma sellae between them. The tentorium cerebelli corresponds to the tongue-like folds of the lateral mesenchymal condensation, whereas the parasellar area including the CS originates from the loose mesenchyme continuous with the contents of the lateral condensation.[22)]

Recent Insight Regarding Development of the CS

Mitsuhashi et al.[23)] proposed a concept of three intracavernous longitudinal venous axes. They described that the CS is a complex of venous channels from embryologically different origins, which developed in the parasellar mesenchymal space. Each venous channel has a distinct function of venous drainage even after morphological alterations through embryological development. These longitudinal venous axes are divided by the ICA and cranial nerves. The venous channels medial to the ICA drain the chondrocranium and pituitary gland. The venous channels lateral to the cranial nerves are exclusively for cerebral venous drainage. The intermediate axis between the ICA and the cranial nerves drains directly from the orbit and membranous skull, with contributions from the other two axes. This concept is useful to improve our understanding of the complex venous anatomy of the CS.

Summary

The CS is a parasellar dural envelope containing an important venous pathway. The venous channels in the CS consist of only an endothelial layer, surrounded by connective tissue. In the early embryonic stages, the neural tube is covered by the primitive capillary plexus and undifferentiated mesenchymal tissue, the primary meninx. Subsequently, enlargement of the brain and differentiation of the mesenchyme lead to considerable changes in the cranial venous system by anastomosis, alteration, and regression of the venous channels. The CS develops by coalescence of complex venous channels of different origins accompanied by the development of the brain, optic and otic apparatuses, meninges (pia, arachnoid, and dura), and bone (chondrocranium and membranous skull). The morphological changes in the CS and relevant veins continue during the fetal period, and demonstrate considerable variation in the cerebral venous drainage pattern, especially in the connection between the SMCV and the CS.

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Disclosure Statement

The author has no conflicts of interest with regard to the manuscript.

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