Normal and Abnormal Embryology and Development of the Intracranial Vascular System

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KEYWORDS

• Embryological development • Brain morphology
• Vascular system • Angiogenesis

The development of the blood-vessels of the head demonstrate[s] the embryologic principle of what may be termed integrative development. [The vascular apparatus] reacts continuously in a most sensitive way to the factors of its environment, the pattern in the adult being the result of the sum of the environmental influences that have played upon it throughout the embryonic period. […] This apparatus is continuously adequate and complete for the structures as they exist at any particular stage; as the environmental structures progressively change, the vascular apparatus also changes and thereby is always adapted to the newer condition. […] For each stage it is an efficient and complete going-mechanism, apparently uninfluenced by the nature of its subsequent morphology.

George L. Streeter, 1918

Oxygen cannot diffuse beyond 150 to 200 μm in a living tissue at 37°C. As a consequence, the vascular system develops in such a way that it continuously adapts the supply of oxygen and other nutrients to the needs and the morphology of the evolving brain. Schematically, 4 overlapping consecutive steps can be described.

1. Initially (weeks 2–4) the exposed neural plate and groove and the open neural tube are simply fed by diffusion from the amniotic fluid (**Fig. 1**).[1]
2. After closure (week 4) the neural tube is surrounded by a dense connective tissue, the meninx primitiva (weeks 5–8) (for review, see Ref.[2]). This meninx primitiva contains primitive vascular loops (meningeal meshwork)[3] developed by vasculogenesis from the primitive dorsal aorta and cardinal veins, and through them connected with the primordial vascular organ initially developed over the yolk sac (**Fig. 2**).[4,5]
3. As the cephalic portion of the neural tube grows and expands to form the 3 primary brain vesicles (rhombencephalic, mesencephalic, and prosencephalic vesicles), the meninx primitiva further evolves and to better supply the neural tissue invaginates into the roofs of the prosencephalic and rhombencephalic vesicles, forming the primordia of the choroid plexuses (weeks 5–7).[1] At this stage, diffusion of nutrients to the neural tissue is both peripheral from the meninx primitiva and ventricular from the developing choroid plexuses.[1] From the point of view of the morphogenesis of the cerebral vasculature, this plexular differentiation is crucial: it leads to the early differentiation of specific choroid feeders within the meningeal vascular meshwork from which all brain arteries eventually evolve (for review, see Ref.[6]): from that stage, the final arterial pattern is already recognizable.[7] By contrast, the venous outflow that is specifically adapted to the choroid stage is only transitory and the veins will continue to adapt passively to local circulatory factors until after birth, even though

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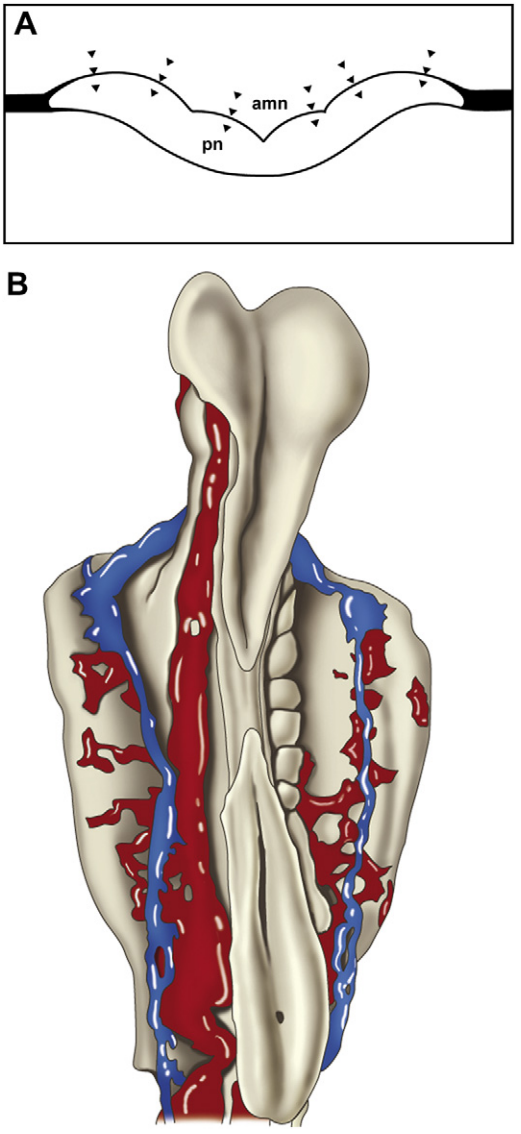

Fig. 1. Week 4. The neural tube is not closed yet, and the neural plate (pn) receives oxygen and nutrients from the surrounding amniotic fluid (amn) (*A*). Endothelial vasculogenesis is building up the cardiovascular organ system that already extends toward the cephalic extremity of the embryo (*B*).

the gross venous pattern can be recognized at the end of the first trimester.[6,8]

4. When the neural tube becomes too thick to be nourished by extrinsic diffusion alone, intrinsic capillaries develop by sprouting (angiogenesis) from the vessels of the meninx primitiva covering the brain surface. According to the same principles, they will supply the most demanding areas: first the ventricular-subventricular proliferative germinal zone already at the second month, then much later in the last trimester the developing cortex when it becomes widely connected and functional.[1,9] Together with the development of the early intrinsic vasculature, the meninx primitiva undergoes progressive changes resulting in the fluid-filled leptomeninges and the dense dural coverings and reflections,[10] as well as the opening of the fourth ventricular outlets.

THE PRIMITIVE PERINEURAL VASCULAR MESHWORK

Shortly after its closure (week 4), the neural tube becomes embedded in a solid mesenchyme that forms the meninx primitiva (see **Fig. 2**). This meninx primitiva of the forebrain (anterior neural plate) derives from the neural crest of the more caudal posterior diencephalic and mesencephalic segments.[2,11] The meninx primitiva of the developing spinal cord, hindbrain, midbrain, and posterior diencephalon derives from the somitic mesoderm.[2]

Vasculogenesis produces the vascular organ system and the first blood cells; it extends to the meninx primitiva and forms the first arteriovenous loops.

The vascular system as an organ system derives from a differentiation of lateral and posterior mesodermal cells that migrate toward the yolk sac and form blood islands or hemangioblastic aggregates.[4,5] These aggregates differentiate into peripheral endothelial cells and central hematopoietic cells.[12,13] Endothelial cells form vascular cords that canalize and become interconnected in a plexular network that extends into the embryo, building the cardiovascular system, the first organ system of the embryo.[4,5,12,13] This process is under the control of, among others, the vascular endothelial growth factor VEGF and its receptor VEGFR2.[13] Vasculogenesis proceeds cranially and invades the meninx primitiva to form a vascular meshwork around the primitive cephalic central nervous system.[14] The vascular lumen forms by vacuolization of the endothelial cords (a truly intracellular lumen). These primordial vessels connect together to form an indistinct meshwork without clear preferential channels (hence its name of primary head *plexus*)[3] and it is impossible at the beginning to differentiate between arteries and veins.[3] This early process was not studied in human embryos but in chick embryos between the stages of 9 and 16 somites; this would correspond to day 28 in human, that is, just before and at the time of the closure of the neuropores (for developmental staging, see Ref.[15]).

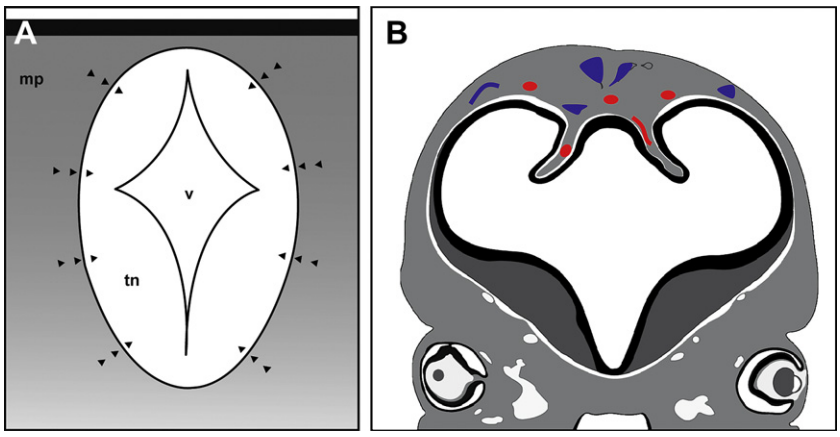

Fig. 2. Week 5. The neural tube is embedded into a dense connective tissue, the meninx primitiva (mp) (*A, B*) that contains vascular loops (*B*) connected to the dorsal aortae and cardinal veins. They are forming the primordial brain vascular meshwork, from which oxygen and nutrients diffuse to the neural tissue.

Over the next day or so, an active proliferation of endothelial channels takes place between the cranial ectoderm and the neural surface. This proliferation starts early around the forebrain and the midbrain, and later around the hindbrain; it also proceeds from the ventral aspect of the brain vesicles to its dorsal aspect.[3] At the same time the meninx primitiva begins to undergo the dramatic changes that will result in the formation of the calvarium, dura, and fluid-filled leptomeninges, to the development of the choroid plexuses and to the opening of the fourth ventricular outlets. The perineural vascular meshwork follows this meningeal reorganization.[3] The deeper vascular endothelium that covers the wall of the neural tube flattens and takes the appearance of a capillary network. The superficial vascular layer takes the appearance of larger and more continuous channels that form clear connections with the paired dorsal aorta and cardinal veins, and will eventually become the major brain arteries and veins. Between these deep and superficial vascular layers, a few communications persist and become the branches of the arteries and the tributaries of the veins[3]: arterial supply and venous drainage channels become selected from this initial meningeal meshwork as they respond to the evolving and species-specific needs and morphology of the developing brain.

The morphogenetic alterations that result in the adult pattern of brain arteries has been described in great detail by Padget,[7] while the morphogenesis of the veins has been mostly described by both Streeter[3] and Padget.[16,17]

MORPHOGENESIS OF THE BRAIN ARTERIES

Padget[7] studied the development of the cerebral arteries by using a method of graphic reconstruction from 22 sectioned embryos of the Carnegie Collection ranging in age from 24 to 52 days (4–43 mm). Her outstanding contribution therefore rests on a relatively limited number of specimens. Based on the evolution of the cardiovascular system, especially the aortic and pulmonary arches, Padget identified, defined, and illustrated 7 steps or stages in the development of the brain arteries, from an early undifferentiated pattern to the essentially adult pattern.

At stage 1, the primitive carotid artery supplies the forebrain as well as the hindbrain through the transient carotid-vertebrobasilar connections (4–5 mm, 28–29-day embryo).

The internal carotid artery (ICA) can already be recognized at this stage. The ICA supplies the 3 forebrain, midbrain, and hindbrain vesicles. Rostrally when reaching the forebrain, it divides into an anterior olfactory branch (future anterior cerebral artery, ACA) that passes dorsal to the optic vesicle, and a posterior branch that resolves into a plexus around the midbrain without reaching the hindbrain. The ICA also connects with the contralateral ICA behind the Rathke pouch, so forming the posterior segment of the future circle of Willis.

More proximally, the hindbrain instead is fed by 3 presegmental and 1 intersegmental arterial channels. Two originate from the proximal ICA: the trigeminal artery at the level of the trigeminal ganglion, and the otic artery at the level of the otic vesicle. Two originate from the paired dorsal aorta: the hypoglossal artery along the hypoglossal nerve, and the proatlantal artery (first intersegmental cervical C1 artery) along the first cervical nerve (**Fig. 3**). These trunks supply the paired ventral bilateral longitudinal neural arteries that feed the hindbrain on either side at this stage

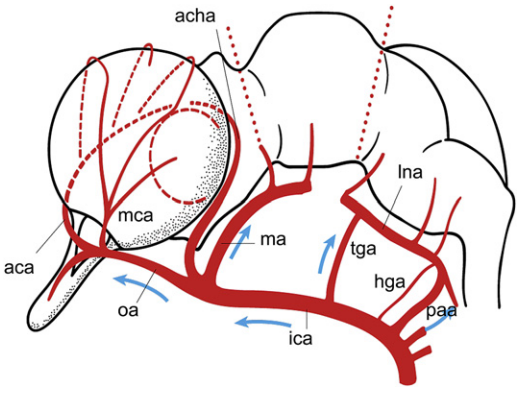

Fig. 3. Week 5. Within the primordial vascular meshwork, the ICA can be recognized. It supplies the forebrain and the midbrain via its terminal branches, the olfactory artery (oa) and the mesencephalic artery (ma). The olfactory gives off the early ACA cranially and the ACHA caudally around the neck of the growing hemisphere; the MCA appears as a lateral branch of the ACA. More caudally, the ICA and the primitive aorta send three branches that supply the hindbrain via the longitudinal neural artery (lna); these branches are named after their accompanying nerves/location: craniocaudally the trigeminal (tga), hypoglossal (hga) and proatlantal (paa) arteries.

(**Fig. 4**A). The trunks eventually regress, after the bilateral longitudinal neural arteries have fused on the midline, and connected cranially with the caudal division of the ICA and caudally with the longitudinal paravertebral anastomosis that will become the vertebral artery. The channels actually exist for a very short time of 4, at most 8 days (for the trigeminal and proatlantal arteries) before vanishing at about stage 3.[7] Uncommonly they may persist and be functional as anatomic variants/malformations in clinical settings.

At stage 2 the posterior communicating artery forms (*5–6 mm, 29-day embryo)*.

The caudal divisions of the ICAs extend caudally and join the bilateral longitudinal neural arteries to form the true posterior communicating arteries (PCOMs). Consequently, the trigeminal arteries are dwindling at their carotid origin, as well as the hypoglossal arteries. The longitudinal neural arteries tend to unite along the midline to form the basilar artery (BA) (see **Fig. 4**B). At this stage they still remain largely dependent on the proatlantal (first intersegmental) arteries for their caudal supply.

At stage 3 the forebrain arteries can be recognized; the basilar and vertebral arteries are completed (*7–12 mm, 32 days)*.

Within the primitive meshwork, the trunk of the ACA develops rostrally around the neck of the growing hemispheric vesicle, and the early stem of the future middle cerebral artery (MCA) extends laterally from it (see **Fig. 5**). Behind the neck of the growing hemisphere, the primitive anterior choroidal artery (ACHA) courses toward the diencephalon; it is now the largest branch of the ICA. The ICA also provides a primitive dorsal ophthalmic artery. Caudally, from the caudal end of the PCOM 2 dorsal branches emerge, 1 posterior choroidal artery (PCHA) toward the diencephalon and 1 mesencephalic artery toward the midbrain (**Fig. 6**A). The BA has further evolved by midline fusion of the longitudinal neural arteries; the trigeminal artery may still be found at this stage, but it is usually interrupted already.[7] The vertebral artery (VA) is now forming as a longitudinal paravertebral anastomosis between the intersegmental cervical arteries from C7 to C1[7]; (see also Fig. 1 in Ref.[18]). Over the rhombencephalon the anterior superior cerebellar artery (ASCA) becomes distinguishable.

At stage 4 the mature pattern becomes apparent (*12–14 mm, 35 days)*.

The anterior division of the ICA now provides clearly recognizable although still plexiform branches: the ACA with a medial branch that approaches the midline to form the anterior communicating artery (ACOM), the early MCA, dorsal and ventral primitive ophthalmic branches, the prominent ACHA, as well as the PCHA and the mesencephalic arteries. The BA and the VA show further development, and early rhombencephalic branches can be recognized.

At stage 5, which can be called the choroid stage, the adult pattern has become obvious (*16–18 mm, 40-day embryo)*.

Klosovskii[1] stressed the role the choroid plexuses play in supporting the early brain tissue. During weeks 5 to 7, these projections of the meninx primitiva develop into the fourth, third, and lateral ventricles (**Fig. 5**A, B).[19,20] Because they become extremely active from a metabolic point of view, they induce a clear selection of their arterial feeders: the ACA anteriorly,[7,21] the ACHA inferiorly, and the PCHA posteriorly (see **Fig. 5**C). (Although the adult ACA is separated from the tela choroidea by the callosal and hippocampal commissures, it is originally a choroidal artery. Its subfornical branch still reaches the foramen of Monro in the human fetus,[7,16] the adult chimpanzee,[22] and in injected adult human anatomic specimens [personal data]). The MCA grows as a lateral branch, primarily striatal at this stage, of the proximal ACA. The mesencephalic artery also is now prominent and forms a rich plexiform network over the tectal plate. This specific pattern at this stage—choroidal arteries including the ACA, and mesencephalic arteries—corresponds to the anatomy of the

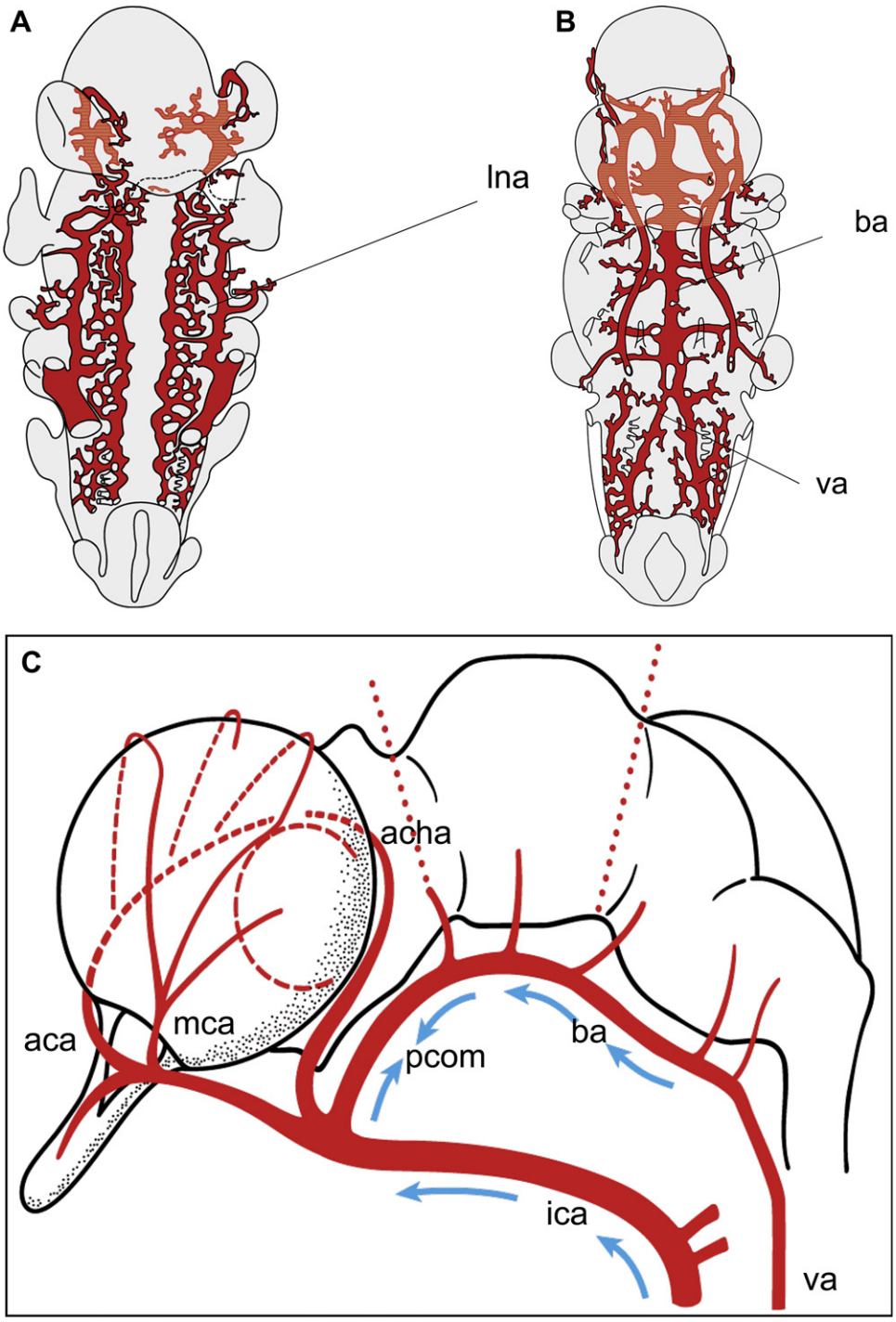

Fig. 4. Week 5. The paired longitudinal neural arteries (lna) extend along either sides of the hindbrain; at this stage, all brain arteries are plexular (*A*). They tend to unite by fusion along the midline, to form the BA (*B*). Simultaneously they become connected cranially with the mesencephalic artery via the PCOMs, and caudally with the forming intersegmental anastomotic VAs (*C*). This new blood supply results in the regression of the trigeminal, hypoglossal and proatlantal arteries.

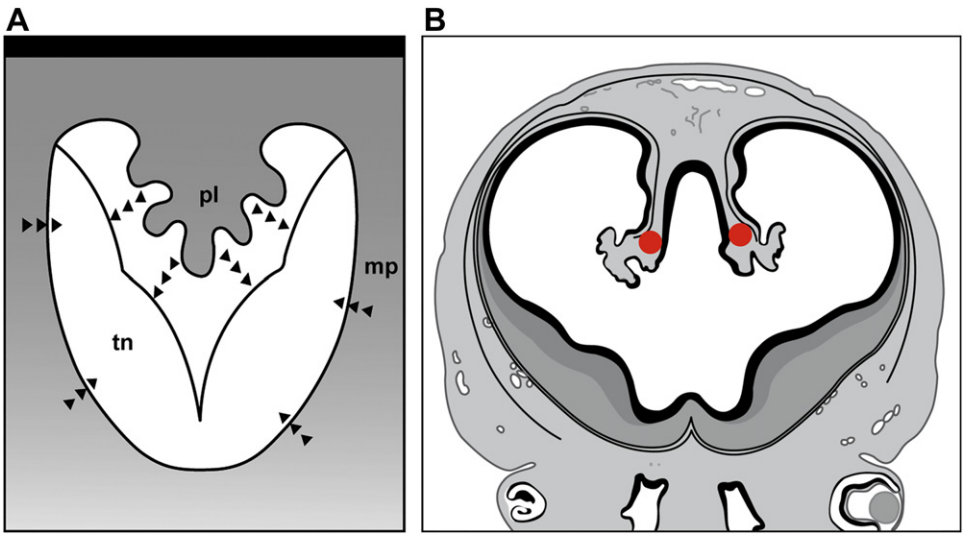

Fig. 5. Week 6. The meninx primitiva forms the choroid plexuses (pl), intraventricular meningeal extensions that allow the growing neural tissue to be supplied by the ventricular CSF in addition to the peripheral meninge (*A*, *B*). The choroid plexuses are large, well vascularized structures loaded with glycogen and they strongly determine the prominence of their feeding arteries: ACA, ACHA, PCHA, from which the whole brain vasculature originates.

arterial feeders of the vein of Galen arteriovenous malformations.[6]

At stages 6 (20–24 mm, 44 days) and 7 (40 mm, 52 days), the mature pattern is completed with the circle of Willis and the capture by the posterior hemispheres of the vertebrobasilar blood supply.

A completed, still plexiform ACOM sends a branch to the anterior corpus callosum. A prominent perforant (intracerebral) artery, the recurrent artery of Heubner is already apparent as well, coursing from the ACA toward the medial striatum. The MCA, striatal also at this stage, is fully developed. Dorsal branches of the mesencephalic arteries have extended across the dorsal meninges to the inferior and medial-posterior portion of the now significantly expanded cerebral hemispheres, forming the cortical territory of the posterior cerebral artery (PCA) at the expense of the ACHA (**Fig. 6**). In addition, this new mesencephalic-PCA territory typically is not supplied by the ICA any more but via the VAs and BA instead: the now huge cerebral hemispheres have captured part of the vertebrobasilar blood supply. Besides the ASCA, the anterior inferior and posterior inferior cerebellar arteries (AICA and PICA) have become more apparent in the plexus that still covers the caudal hindbrain (**Fig. 6**).

In summary, the arterial system of the brain evolves within and from an initially undifferentiated vascular meshwork, always in a precisely adapted response to the evolving metabolic requirements of the expanding neural tissue.[3] Initially, the ICA feeds the fore- and the midbrain through its anterior and posterior terminal divisions, while the hindbrain is fed by presegmental/intersegmental branches from the ICA and the paired aorta: these transient branches regress with the development of the final PCOM and vertebral arteries. Over the brain surface, specific arterial channels differentiate, which at the early stages correspond to the growing zone (neck) of the cerebral hemispheric vesicles and to the differentiation of the choroid plexuses: the ACA anteriorly, the ACHA posteriorly; together with the PCHA, they later supply the prosencephalic tela choroidea and its glycogen-loaded plexular formations. The MCA emerges as a lateral branch of the ACA, together with the other nonchoroidal parenchymal branches of the ACA, ACHA, and (captured) PCA when the intrinsic intraparenchymal vasculature develops at the late embryonic and early fetal period. In a different way because of different local conditions, the vasculature of the midbrain and hindbrain evolve according to the same hemodynamic (ie, metabolic) rules. The conditions in which the initial meshwork consolidates into discrete arteries explain most of the many variants and morphologic abnormalities that can be observed in later life. As the metabolically defined territories are species-specific and essentially constant, distal arterial distribution is fairly constant and most variations are found in the proximal segments of the feeders, where different hemodynamic "solutions" may become selected in the initial meshwork (resulting in a "variations on a theme" anatomy).

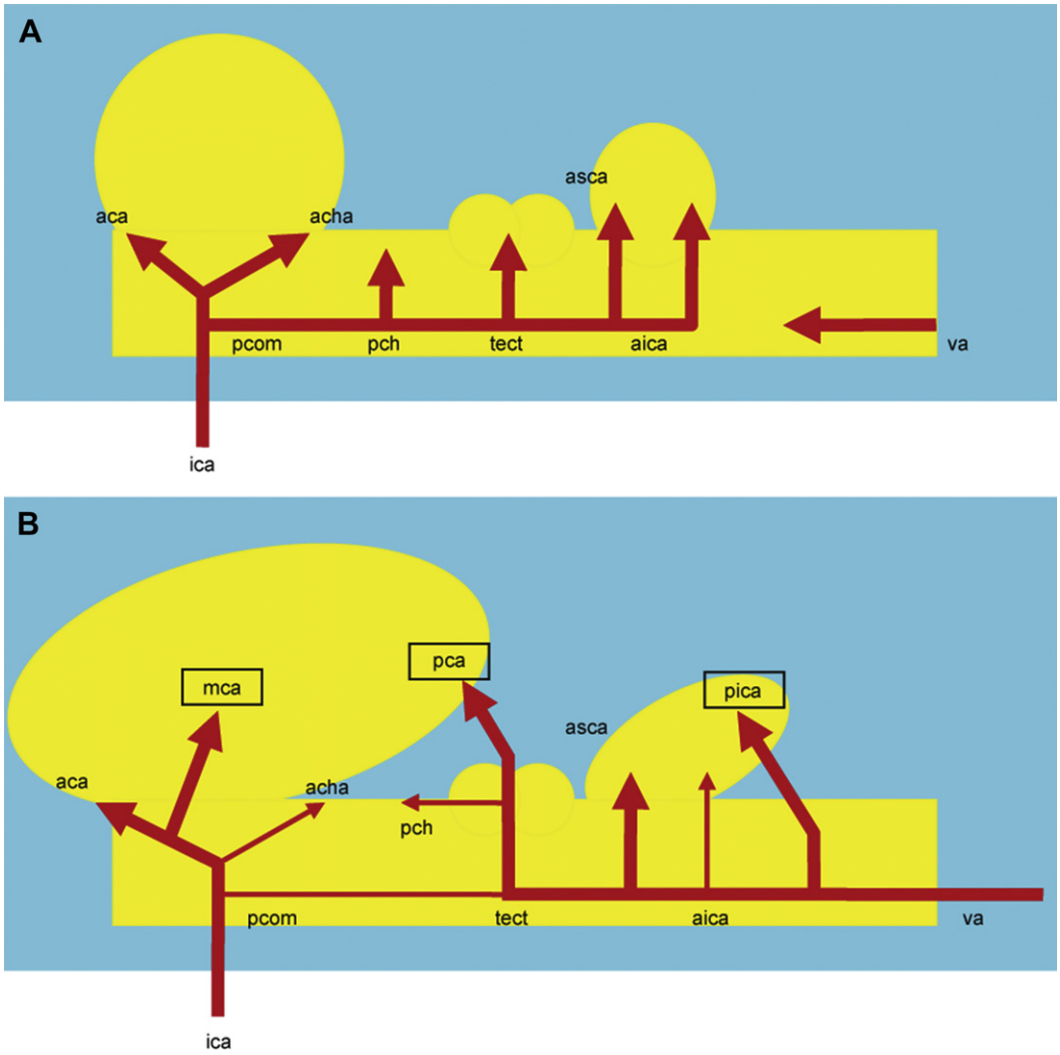

Fig. 6. Weeks 7–8. The initial arterial vasculature responds to the segmentation of the brain into the telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon (*A*). However the hugely expanding cerebral hemispheres and the cerebellum capture the territories of normally more caudal arteries: the PCA, branch of the mesencephalic arteries for the cerebral hemispheres, and the PICA, initially a branch of the medulla oblongata, for the cerebellum (*B*) (to do that arteries must cross the meningeal spaces, which is possible because at this stage the dorsal meninx primitiva is still compact). This also results in the capture of the vertebral blood by the cerebral cortex.

ANGIOGENESIS: THE INTRINSIC VASCULARITY OF THE BRAIN

The 2 main steps in the development of the forebrain (using it as a model of the whole brain) are firstly the cellular proliferation (in the germinal matrices or neuroepithelia) and migration, and then the energy-avid intracortical organization. Cellular proliferation and migration mainly occur before week 20, while cerebral connectivity becomes significant in the last trimester of gestation until well after birth. Accordingly, the brain vasculature develops in 2 separate episodes: the first, within the periventricular germinal zone, mostly before week 20, fading progressively toward the end of gestation, and the second in the cortical plate, mostly after week 27.

Two discrete kinds of germinal matrices exist in the forebrain. One overlays the central gray matter (ganglionic eminence), and is designated the striatal neuroepithelium and subventricular zone by Bayer and Altman.[20] In addition to glial cells, it provides mostly GABAergic cells, both to the underlying basal ganglia (local migration) and distantly to the cerebral cortex (tangential migration). The other germinal matrix sits in the depth

of the future white matter (cerebral pallium, or mantle), but not under the corpus callosum. Depending on its location it is designated the frontal, parietal, posterior, temporal neuroepithelium and subventricular zone by Bayer and Altman.[20] This matrix provides both the radial glia and the glutamatergic pyramidal neurons to the cortical plate. The germinal matrices attenuate during the last trimester and disappear around term. These matrices remain prominent in the depth of the frontal lobes and over the caudate heads later than in the posterior parts of the hemisphere.

Around the time of its closure, the rostral neural tube is composed of an undifferentiated stratified epithelium surrounding a ventricular lumen. In the 2 following weeks, the development of the ventral ganglionic gray matter (subpallium) antecedes the development of the dorsal cortex (pallium). A laterobasal thickening corresponding to the development of the basal ganglia appears as early as week 6[20]; its results from the migration of mostly GABAergic neurons from the ganglionic germinal zone (ganglionic neuroepithelium) to the ventral periphery according to an outside-in process (the peripheral cells are the oldest). At about that time, a preplate made of primitive neurons (it is also called the plexiform layer or the marginal zone) also appears at the periphery of the dorsal pallium[20,23]; however, a true cortical plate does not appear until the eighth week.[20,23] There are 2 types of neuronal migrations to the cortex, radial and tangential. The migration of the excitatory pyramidal neurons from the germinal zone of the pallium (cortical neuroepithelium) develops radially in an inside-out fashion, the older neurons sitting in the deep layers and the younger ones in the superficial layers. Most of the migration of the cortical pyramidal neurons takes place between week 8 and week 17, and is nearly achieved at 20 weeks, but late cortical neurons migrate from the subventricular germinal zone until term time.[24] The migration of the inhibitory cortical interneurons develops tangentially (parallel to the surface of the brain) from the ganglionic neuroepithelium toward their final destination in the cortex.[25]

The long-range connectivity mostly develops after 25 weeks, and keeps increasing until about 2 years after birth. The synaptic activity that goes with it induces a shift from anaerobic to aerobic cortical metabolism, which is supported by a shift of the angiogenetic activity from the (fading) germinal zone to the cortical plate between 20 and 25 weeks. It is also reflected by a corresponding increase in cortical blood flow.[26]

Angiogenesis, both arterial and venous, develops from the surface network.

Angiogenesis is the process by which vessels form by budding from preexisting vessels. In the brain, it proceeds from the surface capillary layer of the leptomeningeal vascular meshwork. These endothelial surface capillaries form buds that approach the external basal lamina and the marginal glia of the cortex, and develop numerous filopodia that penetrate into the brain tissue.[1,9] A tip cell leads the progression, ahead of a strand of stalk cells that proliferate and form a vascular lumen while pushing the tip cell forward. Adjacent vessels form horizontal connections in the germinal zone so that a flow with incoming (''arterial'') and outgoing (''venous'') blood is constituted (**Fig. 7**A,

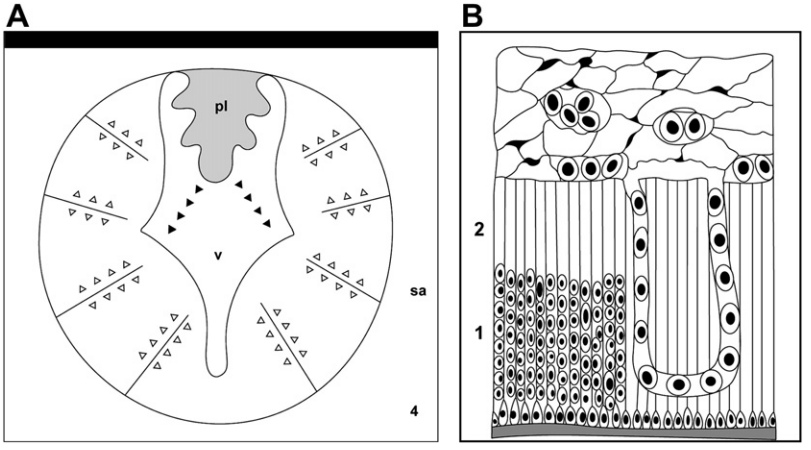

Fig. 7. Week 6 onward. When the neural tissue becomes too thick to be fed by extrinsic diffusion alone and while the germinal matrix develops, the intrinsic vascularization appears (*A*), while the meninx primitiva becomes the subarachnoid space (sa). Intrinsic vessels form by angiogenesis: capillaries grow from the surface and extend toward the periventricular germinal zone where they connect together to form primitive arterio-venous loops (*B*). The cortex itself is not significantly vascularized until well after mid gestation.

B). Oxygen concentration obviously is a potent regulator of angiogenesis. From the genetic point of view, *VEGF-A* (vascular epithelial growth factor) is the main actor in the angiogenetic process through the receptor *VEGFR-2* and the coreceptor *Neuropilin-1*; *VEGF-A* is highly expressed in the subventricular zone first, then later in the neurons of the cortical plate, then after vascular remodeling is completed, in the glial cells.[14] *VEGFR-2* is expressed in the endothelial cells of the perineural vascular plexus and in the capillary sprouts.[14] The *Dll4*/*Notch* signaling pathway further regulates the number/density of vessels within the parenchyma, as well as the *Slit2*/*Robo4* signaling pathway: both prevent endothelial stalk cells from acquiring the tip cell phenotype.[14] *Integrins* are cell adhesion receptors involved in cell-to-cell and cell-to-matrix interaction; they help to regulate angiogenesis by maintaining the endothelial cell communication with the neuroepithelium.[14] *Wnt7a* and *Wnt7b* also appear to be critical in the regulation of central nervous system (CNS) angiogenesis, and their expression is required in the neuroepithelium during the angiogenetic process.[14] After migration into the CNS, the blood vessels need maturation, remodeling, and pruning, together with the recruitment of vascular smooth muscle cells (VSMC): this involves the *Pdgfb*/*Pdgfr*β pathway.[14] The *TGF*β signaling pathway is important for endothelial cell proliferation and differentiation, and for recruitment of VSMC; it involves *endoglins* and *alk1,* whose mutations cause hereditary hemorrhagic telangiectasia (HHT).[14] A last pathway crucial to CNS angiogenesis is the *Angiopoietin*/*Tie2* signaling pathway: deficient mice present with immature vessels lacking branching, organization in large and small vessels, and VSMC.[14] Finally, a last interesting point to mention is that the tip cells of the endothelial channels behave like the growth cones of the axons: in the processes of remodeling and vessel navigation, they respond to the influence of the same guidance molecules. For example, *ephrinB2* (arterial) and *EphB4* (venous) are repulsive and are required for establishing and maintaining the arterial-venous interface; *netrins* are mostly repulsive (mostly attractant for axons); *Slit*/*Robo* are involved also, as mentioned above, as well as the *Semaphorin3E-PlexinD1* signaling pathways (see Ref.[27] for review).

Intrinsic vascularity develops from ventral (*ganglionic*) *to dorsal* (*pallial*) *and in the germinal zone long before the cortex*.

From a morphologic point of view, endothelial cell proliferate, canalize, approach, and connect with the neighboring channels to form simple arteriovenous loops into the deep germinal matrix first, and much later in the cortex: early branching does not appear in the cortical layers until week 20.[1,9] At the early stages the vessels are not yet differentiated, their arterial or venous function being determined by the direction of the blood flow only (see **Fig. 7**). However, the vascular pattern becomes more elaborate as the cerebral mantle thickness and complexity increase, with a multiplication of intermediate small-caliber arteriovenous connections that become true capillaries (<2 red cells), and enlarging feeding and draining trunks (up to 10 red cells) that behave like true arterioles and venules.[28] Only in the germinal zone do the primitive ''sinusoid'' capillaries remain undifferentiated until the germinal zone disappears at term. Because the perforators originate from the surface to feed the most active layer in the deep ventricular zone first, all arterial perforators are transcerebral.[28–30]

- At 5 weeks, intrinsic vessels are seen entering the medulla and pons to ramify in the ventricular zone; this process becomes more prominent at 6 weeks, with other vessels entering the cerebellar rudiment as well as the rhombencephalic tela choroidea.[29] In the following weeks the vasculature of the cerebellum expands to the territory of the 3 future cerebellar arteries.[29] The development of the cerebellar cortex is significantly different in its modalities from the development of the cerebrum; however, to the best of the author's knowledge, no specific description of the cerebellar angiogenesis is found in the literature.
- The early vascularization of the midbrain develops in a similar fashion, very dense from the early stage (5 weeks), first in the ventricular area, and later more diffusely.[29] The vasculature of the diencephalon is also dense. Both start ventrally from the PCOMs, with longer feeders extending to the dorsal diencephalon (tela choroidea), and from the midbrain further toward the posterior and medial part of the cerebral hemispheres after 9 weeks,[29] thus establishing the distal hemispheric territory of the PCA. At the same time, these distal branches of the PCOMs become supplied by the vertebrobasilar arteries.
- In the telencephalon, the first striatal branches appear at 5 weeks and become more numerous at week 6. These branches develop from the olfactory artery, future ACA (forming the artery of Heubner), and from the stem of the future MCA.[29] The ACHA also gives branches to the basal diencephalon as well as to the

posteromedial part of the hemisphere: the later contribution, however, regresses as that of the PCA expands, so that the ACHA comes to supply mostly the choroid plexus of the forebrain (and the temporal uncus).[29]

- The cortex itself does not demonstrate any endothelial structure at 5 weeks.[29] At 6 weeks a few endothelial strands without apparent lumen and without apparent connection with the surface network have been noted,[29] suggesting that endothelial channels could originate de novo also in the parenchyma. By week 7 these channels seem to establish links with the leptomeningeal plexus while becoming canalized.[29] By 12 to 15 weeks, radial, likely arterial vessels connected to the meningeal plexus course toward the germinal zone where they form a subventricular plexus, still without giving off any ramification to the cortical plate.[28–30] Only by 20 weeks do horizontal intracortical branches start to arise in the deep cortical layers, with few recurrent branches directed to the more superficial cortex.[30] These horizontal branches and their associated recurrent collaterals become more numerous from 20 to 27 weeks while new horizontal branches develop in the superficial layers of the cortex.[30] From 27 weeks to term, new superficial radial branches develop from the superficial network.[30] After birth the cortical vasculature becomes much denser, especially in the intermediate cortical layers.[30] It seems that in response to the predominantly peripheral brain growth, shorter vessels develop in between the longer ones[28]; in the rat brain this has been described as forming a system of hexagonally packed vascular supply units that would provide and maintain an even distribution of the perfusion.[31]

Similar findings were reported, obtained by using microradiography (radiopaque vascular injections) in brain specimens of neonates ranging in age from 23 to 40 weeks' gestation. An abundant arteriolar network fed by the transcerebral arterial perforators was demonstrated in the ventricular and subventricular zone in preterms from 23 to 30 weeks. After 34 weeks this deep network progressively fades away to disappear toward the time of term. Note that the absence of any centrifugal arterial pattern and of any deep arterial border zone is specifically mentioned in the anatomic literature of the last decades,[28,32] especially when using stereoscopic analysis.[28]

The vascular fate (*arteries, capillaries, veins*) *depends primarily on flow*.

In the early fetal period all vessels are simple endothelial channels, and it is impossible to identify morphologically what is arterial, capillary, or venous. Because of their very simple hollow structure they are designated as ''sinusoid'' channels or ''sinusoid'' capillaries (this undifferentiated appearance is reproduced in undifferentiated tumors such as the glioblastoma multiforme). The arterial versus venous function is defined by the direction of flow only, not by the vascular structure. In addition, the arterial or venous fate of the vessels may change over time depending on the local metabolic conditions. However, most horizontal connections between the perforators are likely to represent the early capillary network.

- By tracking the course of the perforators, Allsopp and Gamble[29] were able to identify transcerebral perforators from the germinal zone that seemed to connect with the venous plexus on the brain surface in a 5-week embryo, suggesting that the pattern of transcerebral medullary vein could be present early in the development. In the same developmental period they also noted vessels lining the third ventricular ependyma, possibly forming early subependymal collectors.[29]
- Kuban and Gilles[28] noted that while all channels in the germinal zone are sinusoid capillaries devoid of media and adventitia, larger channels with the characteristics of veins are identified at 27 weeks at the interface between the germinal tissue and the caudate, as well as at the angles of the lateral ventricles, so forming the early subependymal veins.
- A muscularis appears at midgestation (20 weeks) in the striatal vessels, giving them their arterial appearance. Development of this muscularis extends from the pial vessels toward the putamen (24 weeks) and the caudate (26 weeks), but does not extend into the germinal tissue.[28]
- The extrastriatal parenchymal vessels remain sinusoid channels without a muscularis until the end of the gestation. At 24 weeks, they are relatively small (10–25 μm); they may divide into 5- to 15-μm capillaries, or converge to form 20- to 40-μm vessels at the ventricular surface, presumably venous. Toward the end of gestation, transcerebral trunks measure 20 to 40 μm and the collecting vessels 50 to 120 μm[28]: a clear arteriovenous differentiation in the pallium therefore appears in the last weeks of gestation only.[28]

For all observers, the arterial, venous, or capillary fate of the primary vessels appears to depend mainly on the flow. Still, specific signaling molecules have been identified that label the channels as arterial or venous at very early stages (see Ref.[13] for review): *ephrin-B2*, *neuropilin-1*, *notch3*, *Dll4*, and *gridlock* for arteries; *EphB4*, receptor for ephrin-B2, and *neuropilin-2* for veins. However, experiments in which the flow pattern was artificially modified could reverse the arterial or venous character of the channels, and even change the expression of the markers, suggesting that it is the hemodynamics that plays the major role in arteriovenous specification and patterning of the intrinsic brain vessels.[13]

The cranial neural crest cells give the forebrain arteries their identity.

A last point that should be mentioned regarding the brain arteries concerns the origin of their smooth muscle cells and pericytes (cells that mediate vasoconstriction and form part of the blood-brain barrier). Like that of the meninx primitiva, this origin is different in the cord, hindbrain, and midbrain vessels on the one hand, and in the forebrain vessels on the other hand. In the caudal parts of the brain and in the cord the arterial media and the pericytes derive from the mesoderm like the endothelial cells. By contrast, in the forebrain they originate from the neural crest (or mesectoderm[33]). The forebrain itself originates from the anterior neural plate, which forms an expansion of the neural tube rostral to and beyond the anterior end of the notochord. As mentioned earlier, the skeleton of the face and anterior skull base (maxillary, nasal, orbital regions, paranasal sinuses) as well as the coverings of the brain (meninges, calvarium, scalp, dermis) cannot have a somitic origin, and instead are produced by the neural crest. As the anterior neural plate itself is also devoid of neural crest, the midfacial skeleton and the coverings of the forebrain are made by neural crest cells that migrate from the posterior diencephalic and the mesencephalic portions of the neural tube.[33] In a similar way, the same groups of neural crest cells form the muscular media and the pericytes of the forebrain arteries as well.[34] The limit between the neural crest-associated forebrain arteries and the classic endothelium-associated mid- and hindbrain arteries is clearly demarcated at the level of the circle of Willis.[34] Such a difference in origin might explain why arterial pathologies may be different in the forebrain from the more posterior segments: not only Stürge-Weber disease or meningo-angiomatosis,[34] but also Moya-Moya disease and syndromes that characteristically affect the arterial supply to the forebrain only.

MORPHOGENESIS OF THE BRAIN VENOUS SYSTEM

Unlike the arterial supply (from the periphery to the ventricle), there is dual venous drainage of the brain: the deep white matter veins drain into the subependymal venous system toward the vein of Galen, while the cortex and superficial white matter veins drain into the superficial, meningeal venous system. As for the arteries, the shaping of the venous system follows chronologically the development of the brain metabolism.

Before the intrinsic vasculature develops, the venous drainage is strictly meningeal and choroidal; transient vein of Markowski.

As Streeter described it, the vascular system in weeks 5 and 6 is confined to the meninx primitiva.[3] The pericerebral meshwork divides into a deep (future pial) layer over the brain surface and a superficial (future dural) layer. The deep layer is a simple capillary layer. In the superficial layer channels become continuous and connect with the paired aorta and the cardinal veins, to form early arterial and venous trunks. Connections between the superficial layer and the deep capillary layer become the arterial feeders and the venous draining channels (early form of bridging veins).

During weeks 6 to 8, the tela choroidea becomes specialized and, to better support the brain tissue, develops the intraventricular choroid plexus.[1,6,7,20] Specific feeding and draining channels develop accordingly. The feeding channels are the ACA, ACHA, and PCHA (see earlier discussion). The venous drainage has been shown to run successively through a ventral diencephalic vein toward the primitive transverse sinus and then, more importantly, through prominent bilateral dorsal choroid veins.[17] The main collector of the superior choroid veins is a single, median dorsal vein called the vena mediana prosencephali or median prosencephalic vein (**Fig. 8**). First described by Markowski in 1911,[8] then by Hochstetter in 1938,[35] it was later described by Padget who called it the "primitive internal cerebral vein," recognizing however that such a term was confusing, as both the tributaries and the course of this single median meningeal vein are different from those of the later true, paired, choroidal internal cerebral veins.[17] The vein of Markowski is a single, median, dorsal prosencephalic vein that is not contained within the tela choroidea, but instead stretches as a true bridging vein across the would-be arachnoid space to the dorsal dura. It originates at the level of the paraphysis where it receives both superior choroid veins, and runs dorsally to the dorsal interhemispheric marginal venous sinus.[8,17,35] (The paraphysis is a transient evagination at the anterior fold of the

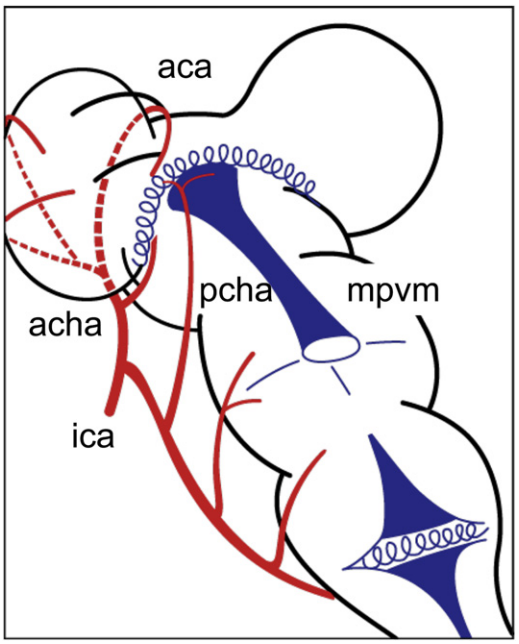

Fig. 8. Weeks 6–11. The choroid stage. The ACA cranially, the ACHA caudally encircle the neck of the hemispheres toward the tela choroidea and the plexuses, together with the PCHA, branch of the midbrain arteries. The tela choroidea and plexuses are drained by a single, median dorsal bridging vein (median prosencephalic vein of Markowski) (mpvm) that antecedes the development of the internal cerebral veins and vein of Galen.

tela choroidea, located between the interventricular foramina of Monro.) The vein of Markowski is a specific drainage vein of the choroid plexuses, found as soon as the choroid arteries are identified (week 6). It regresses and disappears after week 11, at the end of the choroid stage, replaced by the vein of Galen when the subependymal drainage appears following the development of the intrinsic vasculature of the marginal zones.[35]

The subependymal venous system develops de novo from subependymal anastomoses extending to the tela choroidea.

As mentioned above, at the early stages all intrinsic vessels develop centripetally by sprouting from the initial surface capillary meshwork and extend to the metabolically active germinal zone, where they form simple vascular loops in which some trunks act as arteries and others as veins. Therefore in principle, and apparently at the beginning at least (5 weeks),[29] the veins draining the germinal zone empty into the surface meningeal veins and are therefore true transcerebral veins (see **Fig. 7**B). The shift of the dorsal drainage from a purely choroid one into the vein of Markowski to a common choroid and parenchymal drainage through the vein of Galen around week 11 means that it is about that time that connections have become established between the veins draining the germinal zone and those in the tela choroidea, providing the subependymal veins with a dorsal outlet. The first deep vein noted to join the Galenic system is a vein of the anterior nucleus of the thalamus that is seen joining the superior choroid vein at the foramen of Monro about week 9.[17] But to the best of the author's knowledge, no description is found in the literature of how the vasculature of the germinal zone secondarily forms subependymal collectors, nor how these collectors connect to the dorsal dural veins.

For the former question, it is logical to assume that as the deep vasculature of the germinal zone forms a richly interconnected capillary network, draining channels may become selected within that network that would flow under the ventricular surface. Although the process is not specifically analyzed, the location of such channels, at the interface between the germinal tissue and the caudate (for the ganglionic eminence) and under the ependyma (for the pallium) has been described, though only at 26 to 27 weeks, a relatively late stage.[28,32] For the second question, on how the subependymal veins become connected to the system of the vein of Galen, there is no description either. It is logical again to assume that the venous anastomoses may extend from the deep white matter neuroepithelium to the neuroepithelium of the basal ganglia, and from there to the veins of the tela choroidea. As a matter of fact, Padget mentioned the vein of the anterior nucleus of the thalamus as being the first to do so at 9 weeks, joining the superior choroid vein at the level of the foramen of Monro, presumably via the insertion line of the tela choroidea on the surface of the thalamus. This pattern for the veins in the tela choroidea of draining both the choroid and the basal ganglia (and by anastomotic extension the deep white matter) is similar to there being a common arterial supply to both the choroid structures and the deep gray nuclei; however, no arterial anastomosis with the white matter arteries has ever been convincingly documented,[28,32] while the subependymal system drains both the gray and the white matters. In any case, the importance of the drainage from the dorsal thalamus and dorsal basal ganglia would explain the prominence of the intrachoroidal channels that become the internal cerebral veins and therefore, the importance of the vein of Galen and straight sinus. On the contrary, the contribution of the choroid plexus becomes relatively small and can not maintain the patency of the vein of Markowski.

The intracerebral venous anatomy is affected by the cerebral development.

Anatomically, the intracerebral veins can now be differentiated into 3 groups (**Fig. 9**)[36,37]:

- Deep medullary veins and dorsal nuclear veins draining into the subependymal system
- Cortical-subcortical medullary veins and ventral nuclear veins draining into the leptomeningeal system
- A few transcerebral veins connecting the surface network with the subependymal network; although their existence has been controversial,[16] it is now well documented.[16,38,39]

It can be inferred from the embryology that the first veins to develop are the transcerebral veins, which are followed by the subependymal veins, then by the cortical-subcortical veins. Indeed, as the first vascular trunks originate from the brain surface capillaries and form loops in the marginal zone about week 6, the trunks that function as veins return to the surface and therefore form true transcerebral veins.[16,29] The drainage of the deep vascular network forms later: at least some drainage toward the vein of Galen is attested at about 9 to 11 weeks.[17,35] Last to develop, the cortical venous drainage likely becomes apparent in the third trimester only, as the cortical metabolism and vascularization do not become significant until 27 weeks.[28] In injected specimens of premature neonatal brains, a dense periventricular venous network contrasting with a sparse drainage of the cortical ribbon has been documented (26 and 29 weeks), as well as the relatively early presence of transcerebral veins (25 weeks)[32]; at term, the venous channels appeared much more evenly distributed from the depth to the surface.[32] In adult brains studied in a similar fashion, the venous density appears much higher in the cortex, the subcortical white matter, and the basal ganglia than in the periventricular white matter.[36,37] Because of the precedence in development of the transcerebral veins and of their relative rarity in mature brains, it has been hypothesized that most of them would attenuate or

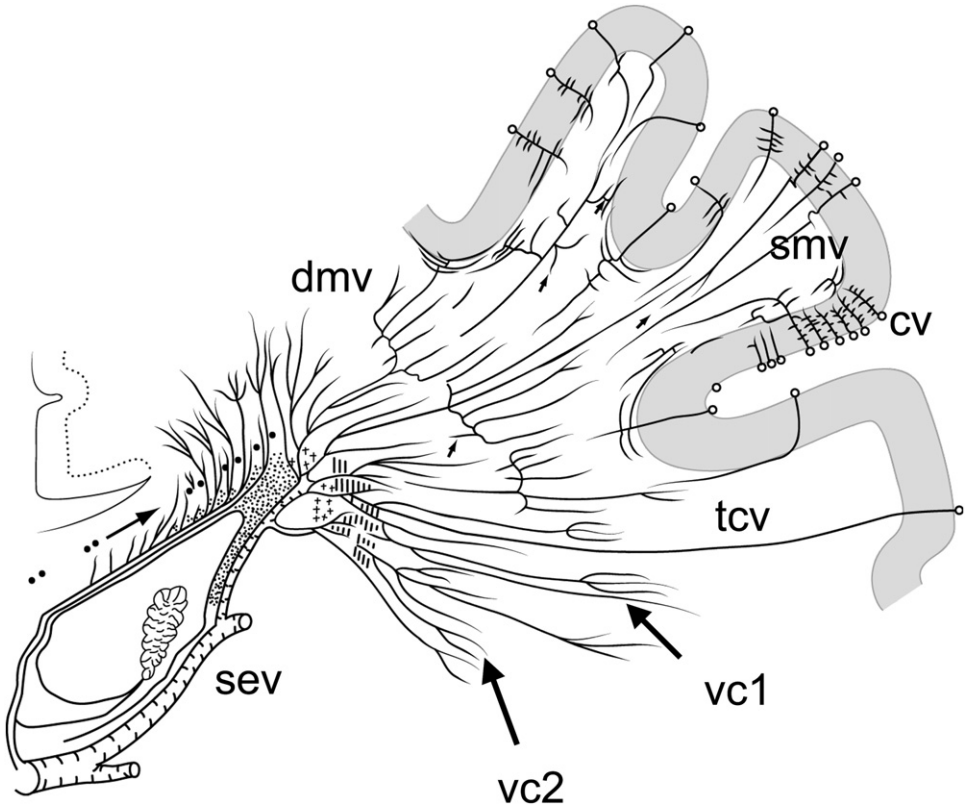

Fig. 9. The organization of the intrinsic venous sytem. The superficial medullary (smv) and cortical veins (cv) drain toward the surface. Deep medullary veins (dmv) converge toward the ventricles, forming larger collectors that join the subependymal veins (sev). There are two main confluence zones, one in the centrum semi-ovale (vc1), one in the subventricular zone (vc2), that seem to be determined by the development of the white matter. (*Data from* Okudera T, Huang YP, Fukusumi A, et al. Micro-angiographical studies of the medullary venous system of the cerebral hemispheres. Neuropathology 1999;19:93–111.[37])

become discontinuous during the period of mostly peripheral expansion of the hemispheres.[37]

Analyzing the collaterals of the medullary veins, Okudera and colleagues[37] made the observation that the mode of branching of the veins and the location of the venous confluence zones reflected in some way the organization of the white matter, especially its predominantly peripheral expansion during the second half of gestation (see **Fig. 9**). These investigators also noticed that certain bundles at least could be identified by the location of the lines of confluence: optic radiations and arcuate subcortical fibers.[37]

The morphogenesis of the extracerebral venous system is affected by the morphologic development of both the brain and the skull.

The development of the extracerebral veins is complex,[3,16,17] evolving according to the increasing cerebral vascularity, the changes in the skull base in large part, and the changes in the brain morphology itself reflected by the changes in the calvarium. The development has been divided into 7 stages by Padget,[17] covering the period between just after the closure of the neural tube and the time when the adult pattern is clearly established, that is, between the early fifth week to the 11th to 12th week. However, the fact that the venous arrangement continues to evolve until after birth must be stressed.[16]

Simply put, the early brain is surrounded by a vascular plexus that drains itself in a pair of ventrolateral channels, the primary head sinuses (**Fig. 10**). The growth of the otic vesicles interrupts the flow in the ventral primary head sinus and results in the development of dorsal collateral channels that may be dural and, depending on the local conditions and especially the increasing vascularity of the brain, pial. In addition, the expansion of the brain vesicles pushes the meninges and the venous channels they contain toward the periphery, so that the flow is transferred from some channels in the plexus to adjacent ones that are better protected, typically at the edges of the brain vesicles: between the cerebral hemispheres and the vault (forming the superior sagittal sinus), between the cerebral hemispheres, the cerebellum, and the vault (forming the transverse sinuses), and between the cerebral hemispheres and the tentorium (forming the straight sinus). In fetuses, sinuses may still be found anywhere within the falx or the tentorium, which therefore retain their plexular pattern.[40] However, as dural venous sinuses with a triangular section are more likely to resist pressure from the surrounding cerebrospinal fluid than sinuses with parallel walls, they are the ones that remain patent throughout adult life.

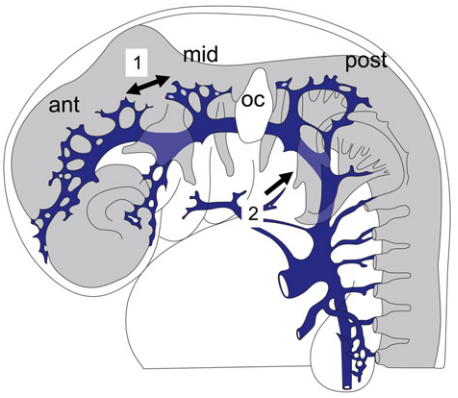

Fig. 10. Week 6, early. Early venous drainage system. Three venous plexuses (ant, mid, post) drain the neural tube via three venous stems into a ventrolateral primary head sinus. This head sinus also receives a maxillary vein cranially. It passes ventral to the otic capsule (oc). The major event is the growth of the otic capsule that will induce a dorsal collateralization, notably between the anterior and middle plexuses (**1**). The head sinus also passes medial to the trigeminal ganglion and vagus nerve (**2**).

At the time of closure of the neuropores, the first endothelial channels surround the brain, but blood is not yet circulating.[3] Shortly after, however, as described earlier, the meningeal stratification begins, together with a corresponding stratification of the vascular meshwork into a "pial" meshwork of capillary on the neural surface, a "dural" meshwork of larger vessels connected to the paired aorta and the cardinal veins, and an intermediate layer of "arachnoid" connections between the 2, which allows for the formation of arteriovenous loops.

This corresponds to *Padget stage 2* (*early week 5; 5 mm)*. The carotid artery then supplies the forebrain and midbrain rostrally through its terminal anterior olfactory and posterior mesencephalic branches, and more caudally the hindbrain and the longitudinal neural arteries through the carotid-vertebrobasilar anastomoses. Schematically on each side, the venous plexuses that surround the laterodorsal aspect of the brain are drained by 3 venous stems into a lateroventral channel: the primary head sinus, which is continuous caudally with the cardinal veins. The venous plexuses are divided into 3 groups: the anterior plexus covers the forebrain and the midbrain (not unlike the rostral territory of the ICA at this stage), the middle plexus covers the metencephalon, and the posterior plexus covers the myelencephalon. The plexuses are drained by 3 corresponding venous stems: the anterior stem runs just rostral to the trigeminal ganglion, the middle stem between the trigeminal ganglion and the otic

vesicle, and the posterior stem caudal to the vagus nerve. The primary head sinus receives the primitive maxillary vein, a rostral tributary that also drains the optic vesicle, then the anterior stem; it passes medial to the trigeminal ganglion (in the location of the future cavernous sinus) and receives the middle stem; then it passes lateral to the otic vesicle and surrounds the vagus nerve (by way of a lateral anastomosis), and receives the posterior stem while becoming the cardinal vein (see **Fig. 10**).

At *stage 3* (*week 6, 10 mm*) the main brain arteries are forming: the ACA, MCA, ACHA, PCOM, BA, and early VA. The anterior venous plexus expands over the forebrain and midbrain; it receives an early telencephalic (actually striatal) vein and caudally establishes dorsal anastomoses with the middle plexus (eventually this anastomosis will be the transverse sinus) (**Fig. 11**). The primary head sinus has now migrated through its lateral anastomosis in a position lateral to the vagus nerve (see **Fig. 11**) (the medial channel will remain as the inferior petrosal sinus) and, as a consequence, the cardinal vein can now be called a true internal jugular vein. This vein evolves further at *stage 4* (*week 7, 10–16 mm)*, when pial-arachnoid and dural channels are better individualized with now obvious telencephalic, diencephalic, mesencephalic, mesencephalic, and myelencephalic pial veins, mostly on the ventral aspect of the brain. This architecture reflects the early vascularization of the germinal matrix and the early development of the basal structures (especially the striatum).

Stage 5 (*late week 7 to early week 8, 16–21 mm*) corresponds to the development of the choroid plexuses and therefore of the choroid arteries (ACA, ACHA, PCHA). The first drainage of the choroid plexuses of the forebrain is through the ventral pial diencephalic vein. The telencephalic vein is now fully individualized; as it is still partly intradural, it is called the tentorial sinus (**Fig. 12**). Because of the continuous expansion of the otic vesicle (now the otocyst) a large dural anastomosis develops between the middle and the posterior plexuses; together, the anastomosis and the posterior stem form the sigmoid sinus (see **Fig. 12**). As a consequence; the stem of the middle dural plexus is dwindling but remains connected to the anterior segment of the primary head sinus; together they form the pro-otic sinus, the future cavernous sinus. The channels of the anterior part of the anterior plexus gather in between the growing hemispheres to form the sagittal plexus, and over the midbrain, between the forebrain and the hindbrain, to form the tentorial plexus.

Stage 6 (*week 8, 18–26 mm*) is the full-fledged choroid stage. The choroid plexuses of the forebrain are now drained by a specific choroid vein, the median prosencephalic vein of Markowski (identified as the ‘‘primitive internal cerebral’’ vein by Padget, who however mentions how such a name can be confusing[17]) (**Fig. 13**). This vein posteriorly defines the early straight sinus within the tentorial plexus, which suggests that the vein of Galen would integrate at least part of the vein of Markowski.[35] The continuous expansion of the otocyst completely effaces the corresponding segment of the primary head sinus, and its flow of blood instead is conveyed by the now achieved collateral that with the stem of the posterior plexus forms the sigmoid sinus (see **Fig. 13**). The stem of

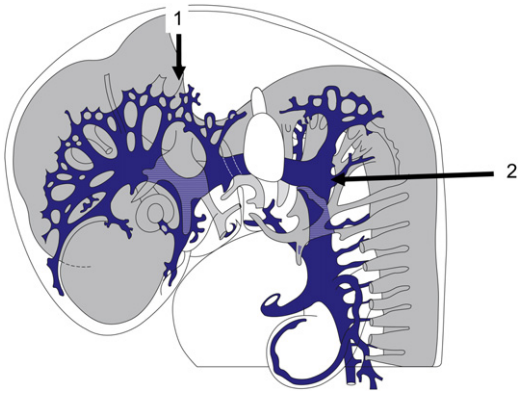

Fig. 11. Week 7. The dorsal collateralization develops (**1**). Via a lateral anastomosis, the primary head sinus passes lateral to the vagus nerve: by this translation, it becomes the jugular vein (**2**).

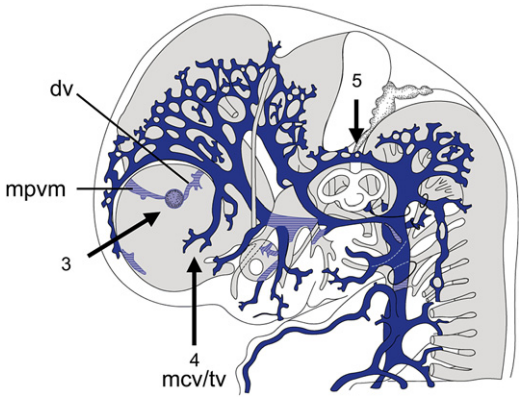

Fig. 12. Week 8. The choroid plexus develops (**3**), drained ventrally (diencephalic vein, dv) and soon dorsally (vein of Markowski, mpvm). A telencephalic vein drains the lateral aspect of the hemisphere (future middle cerebral vein and tentorial sinus) (mcv/tv) (**4**). The growth of the otic vesicle progressively obliterates the primary head sinus and a collateral develop dorsal to the otic vesicle between the middle and the posterior plexuses (**5**).

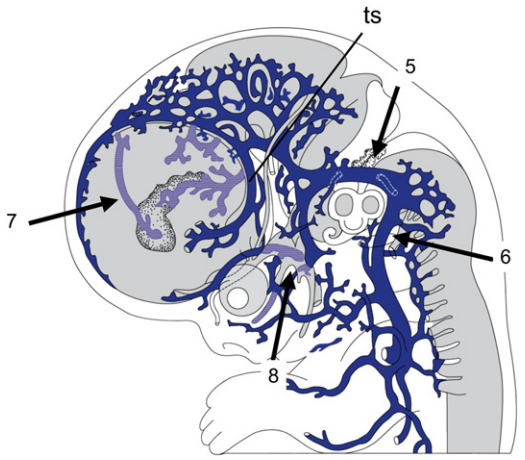

Fig. 13. Week 9. The primary head sinus has become obliterated by the otic capsule, and replaced by a dorsal collateral (**5**); together with the posterior stem (**6**), this collateral forms the complete sigmoid sinus. The initial anastomosis between the anterior and middle plexuses now is pushed caudally by the growth of the hemispheres and forms the transverse sinus (ts). The vein of Markowski is now the main choroidal vein (**7**). The middle stem forms the pro-otic sinus (**8**); it drains anteriorly into the remaining anterior segment of the primary head sinus.

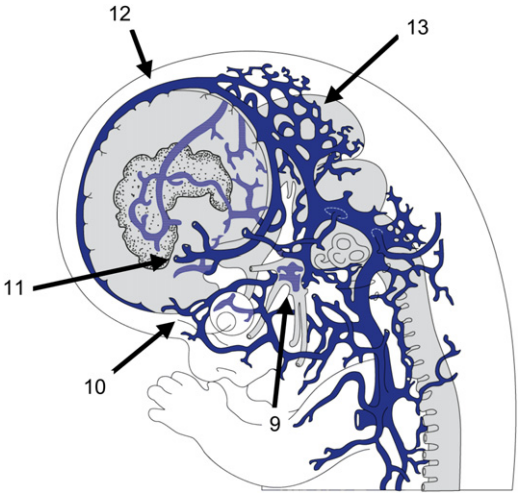

Fig. 14. Month 3, early. The anterior portion of the pro-otic sinus medial to the trigeminal ganglion forms the cavernous sinus (**9**). It receives the facial/maxillary vein and the superior ophtlamic vein (**10**). The middle cerebral vein is well apparent (**11**). The consolidation of the dorsal dural plexuses forms the superior sagittal sinus (**12**). More posteriorly, the tentorial plexus is still primitive (**13**).

the middle plexus joins the primary head sinus in front of the otocyst and forms the pro-otic sinus (see **Fig. 13**). The pro-otic sinus remains connected cranially to the primitive maxillary vein and the primitive supraorbital vein, and thus forms the primitive cavernous sinus. At the same time the stem of the anterior plexus that drained the forebrain regresses and disappears while on the contrary, the tentorial sinus expands, prolonging the now apparent middle cerebral vein toward the primitive transverse sinus (which itself has evolved from the initial dorsal anastomosis between the anterior and the middle plexuses, at stage 3). More pial tributaries become apparent ventrally and dorsally on the brain as the vascularity of the germinal matrices increases.

At *stage 7* (*week 9, 40 mm*) the main features of the mature brain venous system are apparent. This stage is still the choroid one, with a prominent single median prosencephalic vein of Markowski. The primitive maxillary vein now has evolved to form the superior ophthalmic vein; it is drained by the still pro-otic sinus, located medial to the trigeminal ganglion and forming the cavernous sinus (**Fig. 14**). Due to the hemispheric expansion, the superior sagittal sinus has resulted from the "concentration" of the sagittal plexus and the tentorial sinus has elongated, becoming parallel to the transverse sinus. Finally, the veins of the superficial tissues that were initially drained by the intracranial plexus and secondarily became tributaries of the external jugular system become embedded in the chondrification of the occipital bone and form the anterior, lateral, and posterior condylar, the mastoid, and the occipital emissary veins.[16,17,41,42] Because the vascularization of the scalp develops much later than that of the meninges, no emissary vein exists at the level of the calvarium except, inconstantly, in the parietal squamae.[16,17]

At the last developmental stage, identified by Padget as *stage 7a* (*third month, 12 weeks, 60–80 mm)*, the expansion of the brain has further accentuated the mature appearance of the venous system. Posteriorly the remains of the conglomerate of channels that formed the tentorial plexus result in the usually variable, asymmetric, plexular appearance of the torcular (**Fig. 15**). The anterior expansion pulls the partly arachnoid, partly dural middle cerebral vein-tentorial sinus toward the edge of the lesser wing of the sphenoid (see **Fig. 15**), where it is often confused with the so-called sphenoparietal sinus of Breschet. Dorsally, with the expansion of the intrinsic vasculature into the intensely active germinal zones, the subependymal system now is drained by the (true, paired, final) internal cerebral veins via the final vein of Galen into the now well-established straight sinus (see **Fig. 15**). The internal cerebral veins are joined dorsally by the basal veins (of Rosenthal), a relatively new anastomotic channel that links, from ventral to dorsal, a tributary of the telencephalic vein, part of the ventral diencephalic

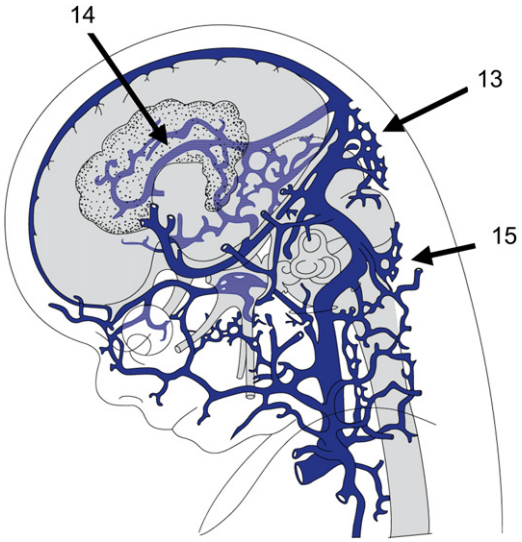

Fig. 15. Month 3, late. Condensation of the tentorial plexus results in the plexular appearance of the torcular (**13**). Shortly after the shift from the choroid stage to the intrinsic vasculature stage, the final internal cerebral veins are formed together with the final vein of Galen and straight sinus (**14**). The posterior dural plexus persists until after term (**15**).

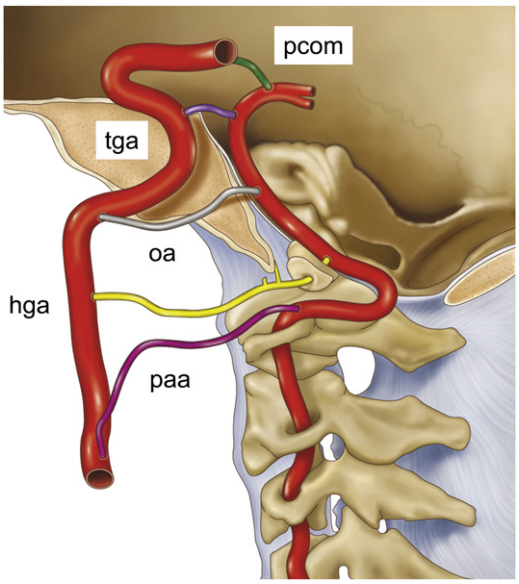

Fig. 16. Persistent vestigial arteries: trigeminal, between the proximal carotid siphon and mid BA (tga); otic, between the proximal intrapetrous segment and the inferior third of the BA via the IAM (it probably doesn't actually exist) (oa); hypoglossal, between the extracranial IAC and the intracranial VA at the origin of the PICA (hga); proatlantal, between the extracranial ICA and the occipitovertebral segment of the VA (paa).

vein, the mesencephalic vein, and the dorsal diencephalic vein.[17,43] The possible drainage pathways of the basal vein result from this multisegmental structure: mainly but not only posterior toward the vein of Galen via the dorsal diencephalic vein; laterally to the superior petrosal sinus via the mesencephalic vein[17,43] and to the superior petrosal sinus via the ventral diencephalic-peduncular segment; anteriorly to the cavernous sinus-sphenoparietal sinus or the tentorial sinuses-transverse sinus via the telencephalic segment.[43]

VARIANTS, DOUBTS, AND MALFORMATIONS

Persistent Vestigial Carotid-Vertebrobasilar Anastomoses

These are occasional angiographic findings, identified as the persistent trigeminal, otic, hypoglossal, and pro-atlantal arteries, felt to reflect the homonymous embryonal (rather than fetal) arterial supply to the hindbrain (see **Fig. 3; Fig. 16**). It should be remembered that this embryonal (not fetal) pattern concerns tiny capillaries, lasts a few days only, and was identified in a very small number of specimens. This is likely the oldest brain vascular abnormality that can be clinically observed, as this arterial arrangement occurs immediately after the closure of the neural tube. The persistent vestigial arteries can hardly be called malformations as they have essentially no impact on the life. These arteries are commonly found in association with vascular diseases, mostly aneurysms, but this association is biased by the fact that the pathology leads to the vascular investigation. No explanation is found in the literature for their persistence. Usually a normally transient embryonal vessel may persist in development when a flow is abnormally maintained in its lumen; because this vestigial vessel is maintained and hemodynamically significant, the normal later-appearing vessels are typically altered. However, in this instance it is hard to assume that it is an initial hemodynamic disorder that would have induced the abnormality: those embryonic arteries are present at a stage when flow is quantitatively close to zero, occurring in purely endothelial channels that can become reversibly either arterial or venous.[3,17] So it is more logical to assume that the persistence of the embryonal vessels is due to either a defect of the inhibition processes, or a defect of induction of the normally later-appearing vascular changes (eg, PCOM connection, VA connection).

The *persistent trigeminal artery* (*PTA*) (the most common vestigial artery observed, which usually regresses at week 5, before stage 3) has been extensively described.[44–52] The PTA extends from the ICA when it enters the cavernous sinus, to the midportion of the basilar BA; it may originate

more proximally on ICA, however, and might then be misinterpreted as an otic artery. The PTA is said to be medial when it runs into the sella and perforates the dura in a groove lateral to the clivus, or sometimes apparently through the dorsum sellae itself[46]; and it is said be lateral when it runs together with the sensory roots of the trigeminal nerve and exits at the Meckel's cave, below the petroclinoid ligament. PTAs have also been classified in different types depending on the territory they supply.[44] Saltzman type I is when it supplies the upper BA with the paired ASCAs and PCAs; the proximal BA is typically hypoplastic and the ipsilateral PCOM is missing. Saltzman type II is when it supplies the BAs with the ASCAs only, both PCAs being supplied by the ICAs through the PCOMs; the first segment (basilar) of the PCAs is then missing. A third type, called PTA variant (or Saltzman III) is when the trigeminal artery joins a remnant of the primitive paired longitudinal neural artery and supplies one ipsilateral cerebellar artery only, mostly AICA, sometimes PICA or ASCA, without joining the BA.

Multiple associations have been mentioned: arterial aneurysms obviously, either because of unusual weakness points in the arterial system, or flow related but possibly also because of a diagnostic bias[53]; arteriovenous malformations, with the same possible explanation as the aneurysms; mechanical complications, mostly tic douloureux but also pituitary disorders and oculomotor deficits; and even such a bizarre association as a hemangioblastoma.[54]

The *persistent otic artery* (*POA*) has been exceedingly rarely reported, with apparently only 8 cases published with this diagnosis.[45,48,55–58] In fact its very existence is denied by many. To be a real otic artery, it must arise from the lateralmost portion of the petrous segment of the ICA (proximal to the caroticotympanic artery), travel through the internal auditory meatus, and join the BAs at its caudal end. Apparently, none of the rarely reported cases displayed those features convincingly.[56] This finding makes one wonder whether such an anastomosis actually exists even in the embryo (apparently only described by Padget as "remnants of highly transitory presegmental branches" from 1 illustrated specimen, and possibly 2 more not illustrated, at stage 1 only, in early week 5[7]).

The *persistent hypoglossal artery* (*PHA*) is the second most common persistent vestigial artery, though much less common than PTA. It is normally short-lived, regressing before stage 2, in week 5. The vessel leaves the ICA at the C1 to C3 level, enters the skull through the anterior condylar (hypoglossal) canal where it courses posteromedially to form the terminal segment of the VA that gives off the PICA and the BA itself, as typically both VAs are absent or hypoplastic, the contralateral one terminating in the contralateral PICA.[50,59–63]

The last is the *persistent pro-atlantal intersegmental artery* (*PPIA*), which corresponds to the first spinal intersegmental artery. In the embryo it is, besides the trigeminal artery, the most important vessel to supply the longitudinal neural arteries. The PPIA disappears at stage 3, in week 6, when the VA becomes functional.[7,64–66] Even in normal anatomy, it persists as the horizontal segment of the vertebral artery that passes between the occipital bone and C1, and as portions of the occipital artery.[67] The abnormally persistent vestigial artery actually is the proximal segment that extends from the extracranial ICA (initially the primitive aorta) to this horizontal interoccipito-atlantal segment. The origin is usually in the lower segment of the ICA (type I PPIA); it less commonly originates from the external carotid artery (ECA) (type II PPIA), and rarely from the common carotid artery (CCA). (A distinction also is made sometimes between the type I as a true proatlantal artery and type II as a simple persistent primitive first cervical intersegmental artery,[66] but the consequences of this distinction are not clear.) A PPIA may rarely be bilateral.[65] The VAs commonly are absent or hypoplastic, uni- or bilaterally. Other major associated vascular abnormalities may affect the aortic arch,[66] the CCA and its bifurcation,[66] or the ECA.[64]

Segmental agenesis/hypoplasia of the vertebrobasilar junction. The agenesis or hypoplasia of the terminal segments of the vertebral arteries may represent the reverse situation from the persistent lower vestigial arteries. This situation is extremely common when it is unilateral, but it is extremely rarely bilateral.[68] A globally hypoplastic VA may supply an ipsilateral PICA only, and the missing segment is then between the PICA and the BA, or the VA is totally absent and the PICA is supplied by the BA. It may be speculated that this would correspond to a failure to form the distal hypoglossal artery for the former and the proatlantal/intersegmental artery for the latter.

Variations of the Leptomeningeal Segments of the Brain Arteries

It is beyond the scope of this review to present the variations and malformations of the extradural ICA (for reviews, see Refs.[69,70]) or VA. The many variations of the cisternal segments of the brain arteries have been associated with an increased incidence of aneurysms.

The circle of Willis is extremely variable. It is composed of the ACOM, proximal ACA, the end of the carotid siphon (segment 8 of the ICA for Gailloud and colleagues[70]), the PCOM, the proximal PCA and

the BA bifurcation. This BA bifurcation may be classic, between the PCAs, or more caudal at the level of the ASCA. Asymmetry and hypoplasia of one or several segments of the circle of Willis are extremely common and likely reflect the hemodynamic balance of a specific individual. This balance may even change over time, and the circle of Willis may be accordingly remodeled.[71] One proximal ACA may be larger than the other one, and supply the ipsilateral hemisphere and most of the contralateral one. One PCOM may be large and supply the distal PCA territory; this carotid origin of the PCA is erroneously described as a "fetal" PCA—if anything, it would be an "embryonal" PCA. It is as a rule associated with a hypoplasia of the proximal (basilar) segment of the PCA, and often with a hypoplastic A1 segment of the ipsilateral ACA. A PCA with carotid origin (ACHA is identified) should not be confused with the hyperplastic ACHA (then a usual tiny ACHA is not identified): this is the retention of the early embryonic pattern of distribution (see later discussion).

Fenestration of the different segments may occur, reflecting the original plexiform arrangement from which the arterial trunks became selected by preferential flow.

Whereas hypoplasia of any of the various segments of the circle of Willis is common, complete aplasia is less common and may suggest a true malformation rather than an anatomic variant. Complete aplasia certainly may compromise collateral flow in case of disease (or even of positional arterial compression); it also may alter the even distribution of the perfusion pressure in normal conditions.

The anterior cerebral artery. The azygos ACA describes a condition in which the first segments of the ACA join each other on the midline to form a single median trunk that runs for some distance before sending branches to both cerebral hemispheres. It can be considered a midline fusion of normally paired trunks, or as an extended form of ACOM. It is a primarily vascular abnormality, which is different from the azygos ACA seen in holoprosencephalies, when a single ACA attached to a single telencephalic vesicle. Another, more common variation of the ACA is the bihemispheric pattern in which one ACA supplies both hemispheres, using the ACOM as a bifurcation, while the contralateral A1 segment is hypoplastic.

In the rare case of persistent primitive olfactory artery (PPOA), the ACA runs ventrally along the olfactory bulb into the anterior cranial fossa before turning back abruptly (hairpin turn) to join its distal cortical territory, or form the ethmoidal artery.[72] This could be thought to simply represent an extreme form of variation within the primordial network. However, it is associated with the absence of the striatal artery of Heubner (presumably compensated for by striatal branches of the MCA) and also by the absence of an ACOM[72]; this latter feature can be considered a true malformation.

The last malformation is the infraoptic origin of the ACA,[73] which has also been called carotid-anterior cerebral artery anastomosis (**Fig. 17**).[74,75] The ACA originates, oddly, at the level of the ophthalmic artery (or even proximal to it[76]) and runs under the optic nerve (or may pierce it, or the chiasm[76]) to join its distal territory at the level of the ACOM. It may be strictly infraoptic or, together with a "normal" A1, form a ring about the optic nerve.[73,76] This malformation seems to result from the initially plexular ACA together with the complex development of the primitive maxillary, transient ventral, and dorsal ophthalmic arteries (for review see Ref.[73]).

The middle cerebral artery. Three types of abnormality can be observed to affect the MCA: fenestration, duplication, and accessory MCA. Although they have fed much controversy, these abnormalities seem relatively simple to understand from an embryologic point of view. A fenestration is a focal remnant of the plexular pattern that is the rule at the beginning of the development; it is no different from the fenestrations of other brain arteries. The simplest definition of the other MCA variants is that of Teal and colleagues[77]:

- The duplicated MCA is the early origin from the ICA of one of the MCA trunks.
- The accessory MCA originates from the ACA; it can be considered a cortical extension of the medial striatal artery of Heubner into the cortical territory of the MCA.[78–80]

From the early vascular embryogenesis, it is known that 2 forebrain arteries initially emerge from the ICA around the neck of the hemispheric

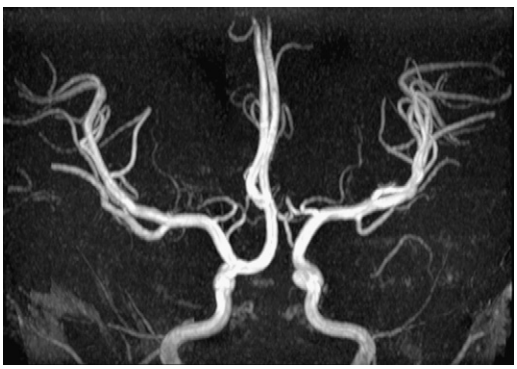

Fig. 17. Infraoptic ACA (or carotid-ACA anastomosis). The right ACA originates from the ICA at the level of the ophthalmic artery and runs medially under the optic nerve toward the ACOM.

vesicle and toward the tela choroidea: the ACA anteriorly (primitive olfactory at this stage) and the ACHA posteriorly. Both the artery of Heubner and the MCA develop as basal striatal branches of the primitive ACA. Normally, only the MCA is to develop later laterodorsal branches toward the cerebral mantle, but it is not abnormal for the artery of Heubner to do so. Typically and logically, the cortical branches of the artery of Heubner supply the frontobasal cortex adjacent to the medial striatum, and the more proximal (ie, caudal) duplicate MCA supplies the temporal territory of the MCA.[81]

The anterior choroidal artery. One of the 2 oldest and prominent brain arteries in the embryo, the ACHA in the mature brain territory is typically restricted to: (1) a temporal choroid branch to the choroid glomus, where it is in balance with the posterolateral choroidal artery; (2) deep perforators to the optic tract, posterior limb of the internal capsule and deep white matter, and variable portions of the adjacent medial globus pallidus and lateral thalamus, in balance with the MCA and PCA territories; (3) anterior hippocampal, parahippocampal, and uncal cortices with the amygdala, again in balance with the PCA through multiple surface anastomoses.

Embryologically, the inferior temporo-occipital and medially the occipital cortices should have belonged to the ACHA; however, they became supplied by the PCA. The rare cases of hypertrophic ACHA are cases in which this artery supplies the whole hemispheric territory of the PCA. Cases of ''duplicate'' PCAs are cases in which the ACHA supplies the inferior temporal cortex and the PCA supplies the medial temporo-occipital cortex.

The posterior cerebral artery is the most variable. Very commonly, it may originate hemodynamically from the carotid arteries (''embryonic'' pattern) or from the BAs (classic pattern), or differently on each side. Uncommonly, it may leave part or all of its forebrain territory to the ACHA (see above).

The vertebrobasilar system. The BAs results from the midline fusion of the paired longitudinal neural arteries. The fusion is said to be craniocaudal by most investigators,[82–85] in reference to Goldstein and colleagues[83] and Padget,[7] but also caudocranial[86] in reference to Goldstein and colleagues.[83] The author was unable to find any comment in Padget about a craniocaudal or caudacranial progression of the fusion: the only comment is that at stage 2 and from a single specimen, the fusion islands would be present in all parts of the BA but more in the caudal end.[7] The fusion has been subdivided into 2 processes, which have been named a ''longitudinal'' fusion (midline fusion of the 2 longitudinal neural arteries) and an ''axial'' fusion (fusion of the initially discrete craniocaudal segments of the BA: trigeminal segment first, joined by a carotid segment and by a vertebral segment).[85]

- The so-called longitudinal nonfusion[82] is usually segmental and is commonly designated fenestration of the BA: only a small segment of the artery is duplicated. The BA is the most common fenestrated site among the cerebral arteries. Fenestrations are usually, but not always located in the caudal part of the artery. Fenestrations reflect the description by Padget at stage 2 of multiple midline fusion areas (or ''islands'') that become secondarily continuous.[7] Intraluminal septations are likely mild forms of fenestrations.[87] Complete or near-complete nonfusion (or extreme fenestration) of the BA is exceptional but can be observed in clinical settings,[83–85] mostly in association with pituitary duplication (**Fig. 18**).[84,86]
- In the so-called axial nonfusion, the 3 segments that are constitutive of the BAs remain discontinuous: a caudal ''vertebral'' segment that supplies the PICAs only; an intermediate ''trigeminal'' segment that supplies the AICA, ASCA, and the pontine perforators; and a cranial ''carotid'' segment that supplies the PCAs.[85] Accordingly, the PTA Saltzman type II, or the bilateral terminal segmental agenesis of the vertebral arteries[68] are variants of this so-called axial nonfusion. Of note, the 2 processes can be mingled when only the proximal/caudal/vertebral, or only the distal/cranial/carotid segments remain unfused on the midline.

(It should be mentioned that these terms are confusing. The ''longitudinal'' nonfusion would be better named ''midline [or median] nonfusion'' [holoprosencephaly often is described as a *midline fusion* of the hemispheres, with *midline fusion* of the thalami, of the caudates]. The longitudinal discontinuity between the caudal, middle, and cranial segments of the BAs could then be named ''longitudinal nonfusion.'')

Finally, the lateromedullary duplication of the terminal VA is caused by the persistence of a normal, typically transient parallel anastomotic artery that runs parallel to the terminal vertebral artery between CN VII and CN XI.[7]

The Aneurysm of the Vein of Galen as a Model

The development of the endovascular approach to treat intracranial arteriovenous malformations and fistulae in the last decades has generated much

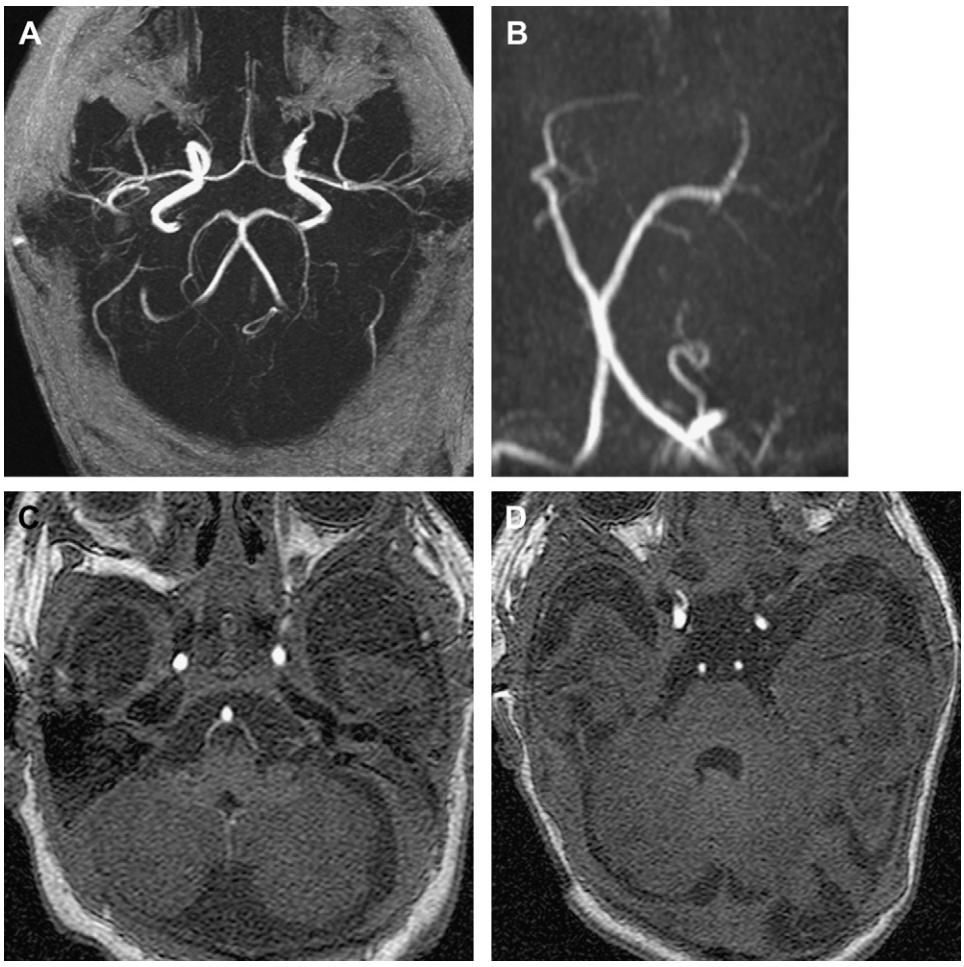

Fig. 18. Midline non-fusion of the BA. Patient with cleft palate, nasal dermoid and pituitary duplication. The BA is divided except for its low ponto-medullary segment. The PCOMs are absent (*A*). The left PICA has a low origin (*B*). AICAs originate at the level of the ponto-medullary sulcus, where the BA is fused (*C*). BA is widely divided at the pontine level (*D*).

interest in the so-called vein of Galen aneurysms (for review, see Refs.[6,88]). This renewed interest in the vascular anatomy of the malformation has cast new light on the embryology.

The first point to consider is the malformation is supplied by the ACA, ACHA, and PCHA anteriorly, and the dorsal midbrain arterial plexus more posteriorly (**Fig. 19**). The choroid afferents point to the tela choroidea; the normal drainage of the tela choroidea is through the paired internal cerebral veins toward the vein of Galen: a double drainage pattern therefore could be expected. Instead, the venous sac is always single. Therefore it could be identified not as a vein of Galen, but as the dorsal prosencephalic vein (of Markowski)[8,35] (see **Figs. 8, 12,** and **19**) (described by Padget as the primitive internal cerebral vein[17]). This vein is not identified before week 8, and not after week 11. This finding brought a better understanding of the malformation. As a purely choroidal vein, it fits the purely choroidal arterial pattern of the malformation. It also fits the dorsal midbrain arterial supply, which is described as dense at this stage of development.[7,29] Anatomically, it points to an extraparenchymal, that is, a meningeal fistula in what is going to be the velum interpositum and the ambient cistern. It can therefore be related to the congenital dural arteriovenous fistulae that involve the torcular and transverse sinus; embryologically the tentorial plexus and meningeal arteries often contribute to the fistulae of the vein of Galen aneurysm.[6]

Chronologically, the malformation points to the choroid stage of Klosovskii,[1] the relatively short period in which the meninges and choroid plexuses represent the main structures feeding the neural tissue, with specific and well-defined arteries and veins. This period extends roughly (there is much overlap) from week 8 to week 11. It is therefore logical

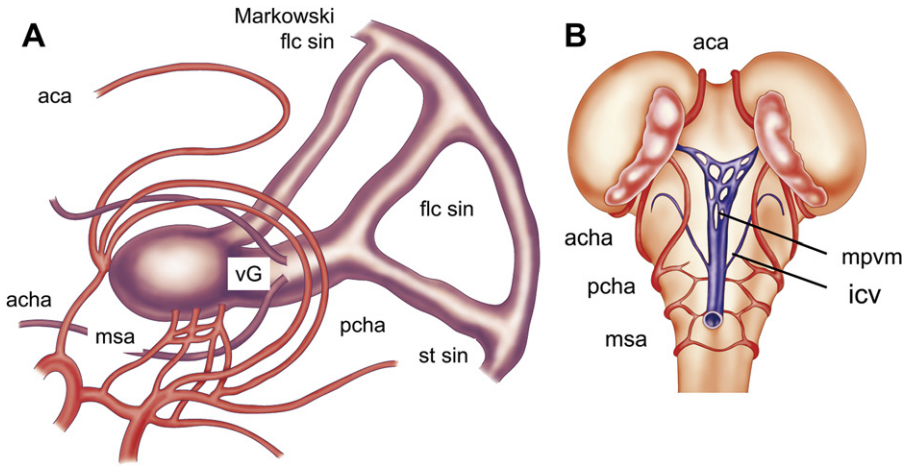

Fig. 19. Vein of Galen aneurysm. The fistulae are extracerebral, in the wall of the venous sac. They are fed by the originally choroidal arteries anteriorly (ACA, ACHA, PCHA) and by the dorsal midbrain arteries posteriorly. The venous sac is single, midline. It may be drained dorsally toward the straight sinus (vein of Galen pattern), or toward a falcine sinus (vein of Markowski pattern), or both (*A*). On the whole, the vascular pattern of the malformation reflects the anatomy at the choroidal stage (*B*).

to assume that the hitting event that generated the fistula(e) occurred about week 8, and that the high flow in the fistula(e) prevents the regression of the vein. However, in medical environments where fetal ultrasound is performed at 12, 22, and 32 weeks, aneurysms of the vein of Galen are commonly reported in the last trimester, and apparently never before 22 weeks.[89] This means that it may be well compensated for over a long time, and the decompensation may be related to the rapid increase of cortical vascularization in the last trimester. Alternatively, it could be that the vein of Markowski does not really disappear and that it could be hemodynamically "reactivated" by the fistula.

The second point concerns the morphogenesis of the vein of Galen. It is implicit from the description of Padget that the "primitive internal cerebral vein" (truly the vein of Markowski according to the accompanying description)[17] is continuous with the straight sinus, meaning that it shares common portions with the final vein of Galen. This point is mentioned also by Hochstetter, who states that the vein of Galen forms from the caudalmost part of the vein of Markowski, after regression of its rostral part.[35] So a bridging vein drained by the future straight sinus would have 2 successive tributaries, one anterior (from the choroid plexuses to the vein of Markowski) and one posterior (tributaries of the true internal cerebral and basal veins to the vein of Galen). This is not illogical, and would explain why many vein of Galen aneurysms drain "normally" into a normally located straight sinus (complemented or not by a falcine sinus), and further, why some present with normally located internal cerebral veins draining into the aneurysmal sac (see **Fig. 19**).[90,91] However, it is not always so, and there are examples of "vein-of-Galen aneurysms without a vein of Galen" in which the malformation is drained directly into a falcine sinus toward the superior sagittal sinus and then, via another falcine sinus, toward the straight sinus (falcine loop) (**Fig. 20**).[6] Such cases suggest that rather than a partly common Markowski-Galen vein, a separate vein of Markowski may occur that cannot connect with a true vein of Galen. This suggestion is consistent with the general variability of the bridging venous pattern. The clinical implication is that the organization of the venous drainage of the brain may be dramatically different in different patients presenting with a vein of Galen malformation.

It should mentioned that a separate drainage via a falcine sinus, common in the fetus,[40] does persist in atretic parietal cephaloceles[92] (**Fig. 21**) because the path to the straight sinus is interrupted by the dysraphic cleft. It may even also be observed incidentally as an apparently normal variant (**Fig. 22**).

Developmental Venous Anomalies

The so-called venous angiomas have been known for a long time from angiography (caput medusae with dilated transcerebral venous stem).[93] Huang and colleagues[36] proposed the more precise anatomic name of medullary venous malformation, correlating them with the normal intrinsic venous anatomy.[94] The term DVA for *developmental venous anomaly* was introduced by Lasjaunias

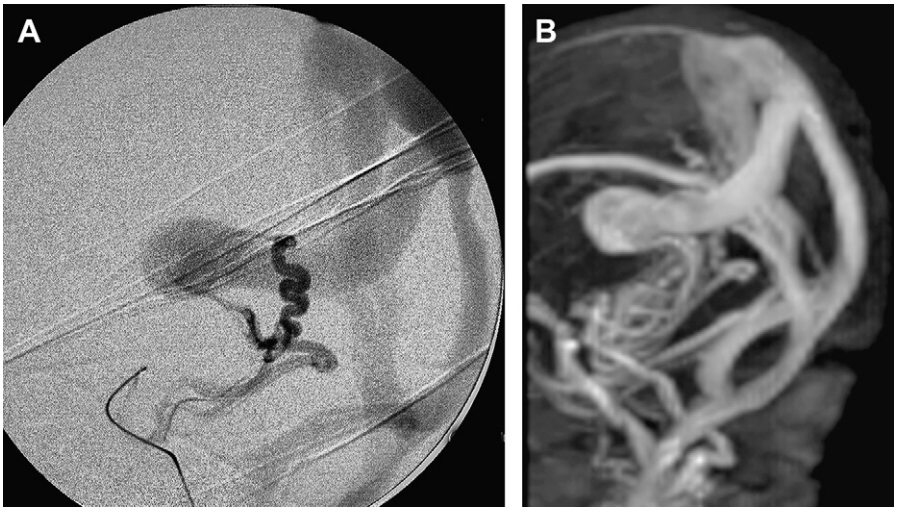

Fig. 20. Vein of Galen aneurysm, falcine loop. On the angiogram the aneurysm drains into a falcine sinus, presumably according to the vein of Markowski pattern, toward the superior sagittal sinus, then through another falcine sinus anteriorly and to the straight sinus. No vein corresponding to the vein of Galen is interposed between the venous sac and the straight sinus (*A*). Similar MR angiographic pattern in another patient; the straight sinus appears to be fed primarily by the falcine loop and inferior sagittal sinus (*B*).

and colleagues[95] in 1986 to stress the fact that in their view, this venous abnormality was not a pathologic condition, only an extreme but normal variant of the brain drainage pattern; besides the white matter, this enlarged vein may be located also in the basal ganglia, thalamus, or brainstem. Thanks to the wide use of brain computed tomography and magnetic resonance imaging, it has become clear that they are the most common vascular malformation found in the brain; however, their significance is still uncertain (for review, see Refs.[96–98]).

The anatomy of DVAs reproduces the normal mature venous parenchymal anatomy.[36,93–100] The histology of DVA is consistent with that of a normal vein. A DVA is composed of a convergent array of collectors that may be subcortical or periventricular (umbrella-like or jellyfish-like, hence caput medusae), and of a single collector that may be subcortical, deep paraventricular, or transcerebral, in any combination.[99] A DVA drains a larger territory than would be expected from any normal collector, and its size is proportionate to the size of the portion of brain tissue it drains. The lesion is considered congenital (ie, developmental) because locally, the area that it drains is devoid of its normal veins.[97,100] However, how this would happen is uncertain.

- An early arrest of venous development has been suggested, that would result in the retention of an assumedly embryonal/fetal

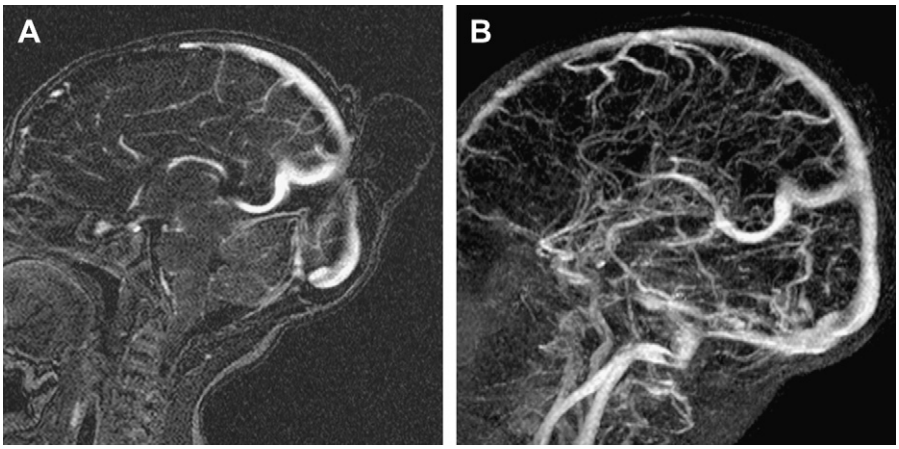

Fig. 21. Parietal cephalocele. The dysraphic cleft separates the diencephalic veins from the tentorium and as a consequence the internal cerebral veins drain into a likely retained vein of Markowski. Source image (*A*) and MIP (*B*).

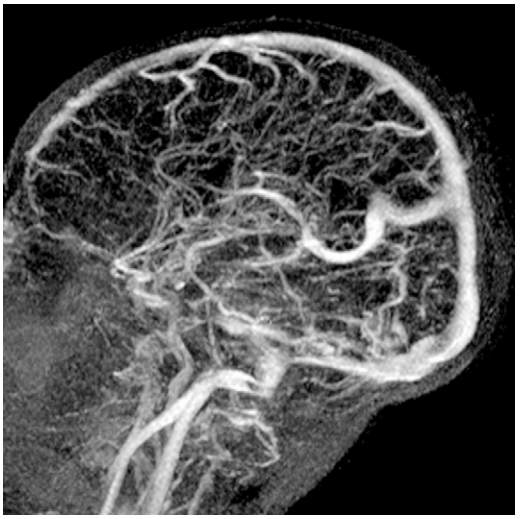

Fig. 22. Incidental finding in a child investigated for arrested hydrocephalus. A pattern similar to that of Fig. 21 is observed: venous curve around the splenium, perhaps longer and wider than usual (retained vein of Markowski?), falcine sinus, no straight sinus. No associated malformation.

pattern.[96–99] Yet, the anatomy of the malformation reproduces the normal anatomy, not any intermediate pattern.[28,32] Also, if one looks at the principles that rule the arteriovenous differentiation, nothing is likely to arrest the development of a vein: the venous anatomy passively adapts to the arterial hemodynamics, and flow may even change the fate of a channel from artery to vein.[13] At the early stages of gestation, until 20 weeks in the basal ganglia[28] and close to term in the cortex,[28] all vessels are histologically undifferentiated, and only their size and branching pattern (dividing vs converging) tells what they are.[28] Early perforators form simple arteriovenous loops that go to the paraventricular germinal zone, so all the early veins are transcerebral, which is not the case for DVAs. Furthermore, the cortical-subcortical region does not show any vascularization until midgestation (first cortical collaterals) and is not significant before the last trimester. Therefore, in any case, a developmental arrest as the cause of DVA would occur late, and from the data of embryology, it is hard to conceive when and how it would happen.

- A second somewhat related suggestion was made that DVA would result, again as an embryonal/fetal structure, from the reactivation of dormant embryonal sinusoid channels as an adaptation to a lesion affecting the surrounding veins.[94]
- The last hypothesis is that the DVA would have simply been a preexisting medullary vein that would have been used as a collateral channel to compensate for the loss of adjacent veins; it would therefore be an acquired lesion.[97–99]

However, circumstantial evidence suggests the likelihood of a truly developmental, dysplastic lesion. DVAs may be part of more diffuse vascular pathologic entities such as the Blue Rubber Bleb Nevus (BRBN) syndrome, possibly HHT (personal data), sinus pericranii, head and neck superficial venous[101] or venolymphatic[98] malformations. DVAs are known for being associated with cavernomas, typically developed in the caput medusae[98]; it is assumed that some microbleeds from the DVA would induce a neoangiogenesis, but the possibility that both the cavernoma and the DVA would be expressions of the same defect cannot be ruled out. Besides, because the morphogenetic paths are few, DVAs might represent a single, common morphologic end result of various pathogenetic processes. By comparison, polymicrogyria may be clearly familial or genetic on the one hand and obviously environmental on the other hand (fetal cytomegalovirus infection), besides being, most of the time, idiopathic.

Or else DVA might be a capillary disease. All real vascular malformations of the brain involve the capillary bed: arteriovenous malformation or fistula (no interposed capillaries) and telangiectasia (ectatic capillaries), possibly related to cavernomas or angiomas. The arterial "malformations" described above are deviations from the classic anatomic pattern but the arteries themselves are not malformed. The capillary is the primordial vessel that only secondarily becomes differentiated into arteries and veins. It may be speculated that the dilated DVA could result from a hypertrophic malformed capillary bed, for which there are some supportive facts. Some diffuse enhancement may be demonstrated within the field of the DVA, which has been assumed to reflect a venous restriction[96] but might as well be a primary lesion. Hemodynamic studies have demonstrated increased cerebral blood volume in the field of drainage of the DVA[102]; it is assumed to be related to the same venous restriction, but it might reflect an abnormal capillary bed also. De novo development of a telangiectasia or a cavernoma in the caput medusae is well documented, spontaneously[103–106] or after radiotherapy (**Fig. 23**).[107] There are several reports linking DVAs with the development of "arterialized DVAs" and AVMs.[97,108–110] All these secondary, clinically

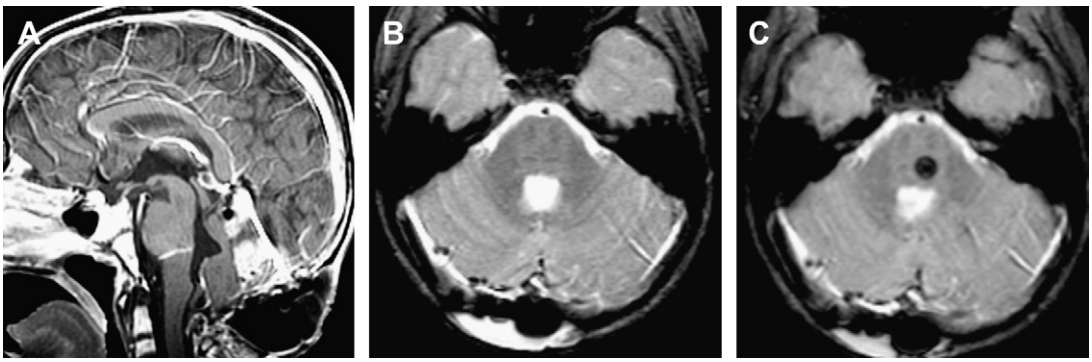

Fig. 23. Medulloblastoma. DVA crosses the brainstem at the lower pons (*A*); otherwise normal axial GET2* appearance of the pons (*B*). Three months later axial GET2* demonstrates the image of a cavernoma adjacent to the DVA (*C*).

significant lesions are assumed to be induced by the DVA, but they might as well represent evolutive forms of a capillary disorder. All this, of course, is speculative and does not say why the (hypothetically) abnormal capillary territory of the DVA would be devoid of normal venous drainage. However, a similarity can be found with Stürge-Weber disease, in which the extensive superficial angioma drains through DVA-like channels toward the subependymal vessels only, without any superficial drainage. Classic embryology does not explain this either.

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