

CEREBROVASCULAR ABNORMALITIES

**A book-atlas of macroscopic
and microscopic aspects**

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The cerebrovascular development

The aortic arches and the great vessels of the neck and of the brain

According to Shapiro (2012), there are two guiding principles which underlie most of the vascular evolutionary adaptation that occurs as the nervous system complexity increases. **The first** one is represented by the development of transversely oriented vessels which are connected by longitudinal ones.

This developmental pattern diminishes the hemodynamic need for segmental vessels at every level and enables some of these vessels to regress.

The second is that as new cerebral territories emerge in evolution, there is a progressive recruitment of existing vascular networks in order to supply the emerging territories (Lasjaunias et al., 2006; Shapiro, 2012b).

The stages of development

The stages are based on the internal and/or the external morphological development, and they are correlated with the gestational, or the postovulatory age (Padgett, 1948; O'Rahilly and Muller, 1986).

The embryonic period covers the first eight weeks of development and is divided in 23 stages. **The foetal period** begins after the embryonic one, in the moment when the embryo reaches 30 mm in length and becomes possible the identification of all the adult features.

The dura mater and the arachnoid membrane develop from the mesoderm, while the pia mater originates from the mesoderm and the neural crest.

Within the outer layer of the dura mater there can be found the dural venous sinuses (Mcdonald and Johns, 1999).

The major veins which connect the area of the cerebral cortex with the dural venous sinuses, as well as the main cerebral arteries, pertain to the arachnoid. The deepest layer is represented by a separate envelope which is located in direct contact with the surface of the neural tube. This is the structure from which originates the pia mater, that contains a vascular plexus which gives rise to all the penetrating arteries and all the arterioles, veins and venules within the brain. At this point there can be discussed two different components of the vascularization of the brain. These are represented by intrinsic blood vessels (the pial and the cerebral vascular plexuses) and extrinsic blood vessels (the subarachnoid and the dural blood vessels) (Duckett, 1971).

All the blood vessels have the appearance of angioblastic channels which proliferate.

Up to dimensions of approximately 40 mm, the walls of the arteries and those of the veins are composed of a single layer of endothelial cells.

Within the pial plexus, the arteries have a more superficial location than the veins, while in the subarachnoid space the situation is reversed, in that the veins are positioned more superficially than the arteries.

The extrinsic vascular plexus in the meninges precedes in its development the intrinsic one within the brain.

In humans, the vasculogenesis begins on the embryonic day 18(E18) in the splanchnopleuric mesoderm of the embryonic disk (Larsen, 1997). A series of inducing factors which are secreted by the underlying endoderm cause some cells of this primitive spongy mesoderm to differentiate into angioblasts, which develop into flattened endothelial cells (Larsen, 1997).

The endothelial cells join together in order to form small vesicular structures called angiocysts, which in turn join up to form long tubes, or vessels that are called angioblastic cords (Larsen, 1997).

However, the characteristic branching pattern of the blood vessels in each region is determined by cues from the underlying endoderm and its extracellular matrix (Larsen, 1997).

According to Dungan and Heiserman (1996) and Larsen (1997), between E21 and E25, the endocardial heart tubes fuse into a primitive heart, and the aortic sac becomes connected to the dorsal aorta.

Subsequently, the embryonic folding carries the endocardial tubes into the ventral thorax where they fuse to form a single primitive heart tube, and the paired dorsal aortae attached to the cranial ends of the tubes are pulled ventrally to form a pair of dorsoventral loops which represent the first aortic arch arteries (Dungan and Heiserman, 1996; Larsen, 1997).

During the fourth and fifth embryonic weeks, four additional pairs of aortic arches develop, they connecting the aortic sac at the superior end of the truncus arteriosus to the dorsal aortae (Larsen, 1997).

According to Larsen (1997), the dorsal aortae remain separate in the region of the aortic arches, but during the fourth week they fuse together from the fourth thoracic segment to the fourth lumbar segment in order to form a single midline descending aorta.

By E32, there had been formed five pairs of aortic arches (Dungan and Heiserman, 1996) which course around to vascularize five branchial arches.

In humans, the fifth branchial arch either never develops at all, or it appears briefly and then regresses, thus explaining the absence of the aortic arch 5 (Larsen 1997).

Consequently, not all the arches are present together at any one time (Padget 1948).

The first pair of aortic arches regresses completely, except for small remnants which might give rise to portions of the maxillary arteries (Okahara et al., 2002). On E29, the second pair of arches also regresses, except for a small remnant which gives rise to a portion of the stapedia artery (Okahara et al., 2002).

Padget (1948 and 1957) had described seven stages for the arterial development and eight for the development of the venous system.

The carotid arteries form as a result of the involution of three separate arterial segments: the first two aortic arches and the segment of the dorsal aorta which connects the third and the fourth branchial arch arteries, called the ductus caroticus (Dungan and Heiserman, 1996).

At E24, the primordial posterior circulation can be found under the appearance of a plexus of vessels which can be observed along the ventral surface of the rhombencephalon;

subsequently, these vessels coalesce in order to form the bilateral longitudinal neural arteries, which are the predecessors of the basilar artery (BA) (Dungan and Heiserman, 1996; Danaila, 2001; Lasjaunias et al., 2006; Raybaud, 2010).

E28 (when the embryo has a length of 4 - 5 mm) is related more to the dural and the arachnoid vascular development.

The internal carotid arteries can be identified ventrally as paired branches of the dorsal aorta, which spread from the level of the third aortic arch towards the cephalic extremity.

Cranially, the internal carotid arteries (ICAs) divide into a caudal branch which goes in a dorsal direction and a cranial branch which continues in the direction of the cephalic extremity. According to Padget (1948 and 1957), the cranial branch bends around the optic vesicle and then ends within the olfactory area. It had been named primitive olfactory artery, and it gives rise to the middle cerebral artery (MCA), the anterior cerebral artery (ACA) and the anterior choroidal artery (AChA).

The caudal branch forms a plexus on the mesencephalon, which will give rise later to the posterior communicating artery (PcoA), while the smaller ventral branch, which is known under the name of the primitive maxillary artery, vascularizes the optic vesicle.

A major dorsal branch is represented by the primitive trigeminal artery, which merges with the paired bilateral longitudinal neural arteries. (Padget, 1948 and 1957).

These arteries, which are positioned dorsal to the carotid system, are applied directly on the ventral surface of the neural tube.

They give rise to a plexus-like system of channels which covers the ventral and the lateral surfaces of the neural tube.

Between the neural arteries and the carotid artery there are also several more proximal anastomoses, such as the primitive otic artery, the hypoglossal artery, as well as the first intersegmental cervical artery. The latter, which is the most proximally located one, vascularizes the longitudinal neural artery (Padget, 1948 and 1957).

In general, these arterial communications will retrogress during the embryonic stage XVII. Whenever they persist, the vertebral arteries will remain hypoplastic. If they persist after birth, the previously mentioned arteries are designated as persistent, or primitive.

The most frequently encountered persistent anastomosis is represented by the trigeminal artery, which is present in 0.1 - 0.7% of the population, followed by the hypoglossal artery, which is encountered in 0.25% of the individuals.

The rest of them are very rare, and they don't have any clinical importance.

In adults, the **primitive trigeminal artery** originates from the internal carotid artery (ICA), in the proximity of the junction between the petrous segment and the cavernous one, after which it travels together with the roots of the fifth cranial nerve over the petrous crest, or through it, in order to merge with the basilar artery in the area between the superior cerebellar artery and the anterior inferior cerebellar artery.

The **primitive otic artery** connects the petrous segment of the carotid artery with the caudal basilar artery, through the internal auditory meatus.

The **persistent hypoglossal artery** originates from the proximal portion of the cervical segment of the internal carotid artery, after which it travels through the anterior condylar foramen (the hypoglossal canal) in order to give rise to the basilar artery. Usually, in such cases there can't be found any vertebral arteries.

More rarely encountered is the **proatlantal intersegmental artery**, which merges with the vertebral artery in the superior area of the posterior arch of the atlas.

The hypoglossal artery, as well as the proatlantal artery, can also originate from the external carotid artery (ECA).

Together, these anastomoses provide the primary blood supply to the rhombencephalon between E24 and E29.

By E29, the distal portion of the internal carotid artery (ICA) has divided into cranial and caudal branches (Dungan and Heiserman, 1996).

The caudal branch forms the posterior communicating artery (PCoA), the P1 segment of the posterior cerebral artery (PCA), and a part of the basilar artery (BA) (Gillian, 1972).

The posterior communicating artery quickly takes over as the main blood supply to the rhombencephalon, while the trigeminal artery recedes over the course of a few days (E29 - E32). As a result, the caudal branch annexes the midbrain and the hindbrain vesicles into its circulation territory (Dungan and Heiserman, 1996; Shapiro, 2012).

The cranial branch, which is also called the olfactory artery, provides the blood supply for the large, developing forebrain vesicle and it is the predecessor of the anterior cerebral artery (ACA), the first and the phylogenetically oldest artery of the telencephalon (Dungan and Heiserman, 1996). In addition to becoming the anterior cerebral artery, this blood vessel subsequently gives birth to multiple branches for the rapidly growing telencephalon, including the anterior choroidal artery (ACHA), the middle cerebral artery (MCA), and the anterior communicating artery (ACoA) (Dungan and Heiserman, 1996; Okahara et al., 2002; Shapiro, 2012).

In short, the third pair of aortic arches develops into the common carotid arteries (CCAs) and in the internal carotid arteries (ICAs).

The fourth and the sixth pairs of aortic arches undergo an asymmetric remodelling, in order to supply the blood to the upper extremities, to the dorsal aorta, as well as to the lungs (Dungan and Heiserman, 1996; Larsen, 1997).

The fourth aortic arch on the left side remains in continuity with the aortic sac and with the midline fused dorsal aorta in order to form the definitive adult aortic arch, whereas the fourth aortic arch on the right side loses its connection with the fused midline aorta and, together with a portion of the right dorsal aorta, forms the proximal right subclavian artery.

Finally, the sixth pair of aortic arches contributes to the building-up of the pulmonary arteries and of the ductus arteriosus (Dungan and Heiserman, 1996; Larsen, 1997).

At 5 weeks, the choroid plexus begins to differentiate within discrete regions of the central canal / ventricular system (Lasjaunias et al., 2006). The future anterior choroidal artery is derived from a branch vessel which extends from the cranial ramus to feed the plexus of the telencephalic vesicle (Larsen, 1997). Another branch originating from the caudal ramus, the posterior choroidal artery, supplies the blood for the choroid plexuses of the diencephalon and of the mesencephalon (Larsen, 1997).

Finally, the choroid plexus of the future fourth ventricle is supplied by a dominant feeder which branches from the basilar artery or from the longitudinal neural arteries, and it ultimately becomes the posterior inferior cerebellar artery (PICA) (Dungan and Heiserman, 1996; Larsen, 1997; Raybaud, 2010).

During the period between weeks 5 and 7 begins the shaping up of the basilar artery through the fusion of the longitudinal neural arteries.

Thus, the bilateral longitudinal neural arteries fuse at the level of the ventral rhombencephalon in order to form the midline basilar artery. More caudally, at the level of the spinal cord, these vessels merge to form the anterior spinal artery (Lasjaunias et al., 2006; Shapiro, 2012).

This process of fusion of the arterial and of the venous channels in a single final vessel, which is the common mechanism for the cerebrovascular development, had been called by Streeter (1915) anastomotic progression or circumfluent anastomosis.

The basilar artery and the primitive posterior communicating artery have the following distinct branches: diencephalic, mesencephalic (the posterior communicating artery and a branch which corresponds to the posterior choroidal artery), and metencephalic (the primordial superior cerebellar artery).

The cervical segmental branches between the internal carotid artery and the vertebral artery are still present, but the higher anastomoses disappear in this developmental stage (Padget, 1948; 1957; O'Rahilly and Muller, 1986).

According to Larsen (1997), the vertebral arteries (VA) appear as longitudinal anastomoses between the cervical intersegmental arteries located lateral to the spinal cord and then join the proximal end of the basilar artery with the longitudinal neural arterial system (Larsen, 1997). Subsequently, the vertebrobasilar arterial system begins to meet the demands of the brainstem and of the cerebellum and progressively annexes this vascular territory from the posterior communicating artery (Lasjaunias et al., 2006; Raybaud, 2010).

The basilar artery provides numerous branches for the metencephalon and for the myelencephalon. In this developmental period also become evident the larger trunks of the three main cerebellar arteries, the superior cerebellar artery being the most developed one. All the intersegmental connections disappear, and the vertebral artery, which originates from the subclavian artery, provides segmental arteries for each level of the cervical spinal cord (Padget, 1948; 1957).

The final and the most tenuous structure of the posterior circulation is the one which supplies the blood for the territory of the posterior cerebral artery, which is, both developmentally and phylogenetically, among the newest of the cerebral blood vessels.

At 9 weeks, the arteries have reached the adult form. The increase in the dimensions of the cerebral hemispheres leads to the broadening of the posterior cerebral artery, while the dimensional growth of the cerebellum leads to the enlargement of the dimensions of the posterior inferior cerebellar artery (PICA) and of the anterior cerebellar artery (AICA).

The embryology of the cerebral venous system

During the process of development, the vascular plexuses are constantly adjusted to the surrounding spaces and depending on their specific functions. The veins which drain the embryonic encephalic parenchyma, or those which provide services to an increasingly larger volumes of tissues, are subjected to a continuous compression.

Frequently, they have to cross long distances through the arachnoid and through the dura mater to reach the dural sinuses in order to be able to continue to perform their function also during the last developmental stages, when their stretching is unavoidable (Danaila, 2016).

The final distribution of the veins is the result of the hemodynamic demands of the tissues from which each vein derives, as well as of the global hemodynamic balance (Lasjaunias and Berenstein, 1987).

With the formation of the neural tube, the amniotic fluid enters the lumen through the neuropores. Simultaneously with this occurrence, it is also established the primordial structure of the heart and of the blood vessels. From this moment on begins the closure of the neural tube and the extension, dorsal to the aorta, of the endothelial buds which spread towards the neural tube (Danaila, 2016).

According to Streeter (1918), the vascular channels appear to be intimately associated with the welding of the neural fold, without being differentiated in arteries, veins and capillaries, and in the absence of the circulation which is not present yet.

Initially, the venous system appears between E26 and E28 in the form of a transient midline vessel within the hindbrain region (Scher, 2012).

According to Bracard et al. (1996), there are eight embryological stages through which takes place the development of the encephalic veins. However, at the 28th day it is not possible to differentiate the arteries from the veins. The first embryonic venous structure is the vena capitis medialis, which is located on the wall of the neural tube, medial to the roots of the cranial nerves at level of the cells which will form the majority of the future pial arteries and veins (Padget, 1948; 1957).

According to Larsen (1997) and Raybaud (2010), by E32, bilateral venous channels called the anterior cardinal veins emerge and provide the first definitive drainage system from the dural capillary plexuses.

During the 5 millimetres stage (the 30th day), the primitive network of the head disappears, and in its place will emerge the primitive venous network, which is known as the “primitive sinus of the head”, and is included within a mesenchymal tissue (the future dura mater) (Padget, 1948; 1957). This sinus is located medial to the sprouts of the fifth, the tenth, the eleventh and the twelfth cranial nerves, and lateral to the outline of the future seventh, eighth and ninth cranial nerves.

It drains a venous capillary network located lateral to the encephalic vesicles through three dural plexuses; the cranial or the anterior dural plexus, which drains both the telencephalon and the mesencephalon, the middle dural plexus, which drains the metencephalic region (including the future cerebellum), and the posterior or the caudal plexus, which drains the myelencephalic region (Padget, 1948; 1957; Bracard et al., 1996; Scher, 2012).

The primary head veins which drain these plexuses are tributaries of the anterior cardinal veins, and these will become later the internal jugular veins (Raybaud, 2010).

Other associated veins which develop in this period include the primitive maxillary vein and the ventral pharyngeal vein, which will become later the lingual, the facial, and the external jugular veins (Scher, 2012).

Consequently, on the 32nd day, that is, during the first stage of the venous development, the pattern of the successive regression and formation of the new venous channels begins through the emergence of the vena capitis medialis, which is replaced afterwards by the vena capitis lateralis (the primitive sinus, or vein, of the head) and which is located lateral to the otic vesicle and medial to the fifth, the tenth and the twelfth cranial nerves. Caudally, it merges with the cranial vein. This is the first venous drainage structure of the brain (Macdonald and Johns, 1999).

Between E35 and E37, the anterior dural plexus becomes associated with a primitive marginal sinus and begins to transform into the future superior sagittal and transverse sinuses (Larsen, 1997; Raybaud, 2010; Scher, 2012).

Thus, each of the cerebral dural plexuses drains a “primitive marginal sinus” from the dorsomedial surface of each telencephalic vesicle.

The entirety of this dural venous network becomes more lateral relative to the outline of the cranial nerves, first to the tenth and the eleventh, and then the fifth cranial nerves.

This lateralization of the dural venous network represents the first step in the development of the future cerebral venous sinuses (Bracard et al., 1996).

In short, beginning with the 33rd day, the anterior venous plexus has a primitive marginal sinus on the dorsal surface of the cerebral hemisphere. This contributes to the formation of the superior sagittal sinus and of the transverse sinus. A telencephalic vein, which enters the anterior portion of the plexus, will eventually become a tentorial sinus.

In this stage it also becomes visible a diencephalic vein which, in its lateral trajectory outside the pial plexus, crosses the arachnoid membrane and goes to the anterior dural plexus (Macdonald and Johns, 1999).

Below the telencephalic vesicle also begins to emerge a vein which will be subsequently identified as the superficial middle cerebral vein.

It is worth mentioning that at a similar time, within the hindbrain, the posterior dural plexus joins the primary head vein where the latter drains into the anterior cranial vein (i.e., the primitive internal jugular vein). Thus, the stem of the posterior dural plexus will constitute the caudal end of the future sigmoid sinus (Larsen, 1997; Raybaud, 2010; Scher 2012).

By E43 and E52, the middle and the posterior dural plexuses form a secondary anastomosis, with a change in the venous drainage towards a new, dorsally located channel.

During this period takes place the development of the pons and of the cerebellum.

The development of the anastomosis between the various plexuses tends to diminish the role of the primitive sinus of the head, which regresses.

The resulting dorsolateral longitudinal venous channel represents the primitive transverse sinus (the anastomosis between the cranial and the middle dural plexuses) and the sigmoid sinus (the anastomosis between the middle and the caudal dural plexuses) (Padget, 1957; Bracard et al., 1996; Danaila, 2016). During this period, the venous blood from the neural tube is not always drained exclusively through the superficial veins.

Thus, the primitive marginal sinus also receives veins from the telencephalon. The telencephalic vein gives rise to the middle superficial cerebral vein, which empties in the tentorial sinus, that is, in the future sphenoparietal sinus.

The diencephalic vein and the ventral mesencephalic vein empty into the cranial dural plexus. The ventral mesencephalic vein empties temporarily in the remnant of the middle dural plexus, which is known under the name of the preotic sinus, before the complete development of the sigmoid sinus. The ventral myelencephalic vein empties into the caudal dural sinus.

This shift in drainage is the first functional indication of the existence of the transverse and the sigmoid sinuses, with the transverse sinus representing the most cranial portion of the anastomosis and the sigmoid sinus representing the caudal portion (Scher, 2012).

Therefore, at this stage there are not yet present any deep veins because the outline of the straight sinus, which appears on the 50th day, drains only the choroid plexus (Padget, 1957).

Between E50 and E52, progressive changes continue to occur in the development of the cranial sinuses, with the transverse sinus becoming more definitive, with the first indication of a sagittal sinus in both its inferior and superior locations (Padget, 1957; Bracard et al., 1996; Mirzadeh and Spetzler, 2015; Danaila, 2016).

Despite these ongoing changes, the development of the venous system continues to lag behind that of the arterial system, with the sigmoid sinus being the only definitive sinus by the end of the embryonic period.

The superior sagittal sinus emerges more definitively at E60, as the cerebral hemispheres enlarge.

According to Raybaud (2010), the primitive straight sinus and the primitive great cerebral vein of Galen also begin to develop at this time, thus providing internal cerebral drainage.

In short, the primitive marginal sinus merges with its contralateral homologue in order to form the superior and the inferior sagittal sinuses (Padget, 1948; 1957).

The tentorial sinus drains the deep telencephalic vein, the future deep central vein, as well as the ventral and the dorsal diencephalic veins.

The tentorial system is the preponderant telencephalic and diencephalic drainage route.

The primitive internal cerebral veins, which emerge during this stage, only have a role for the drainage of the choroid area.

The cranial dural plexus disappears, but it can be observed the development of the primitive transverse sinus, which drains the superior sagittal sinus and the tentorial sinus, as well as the mesencephalic veins (Padget, 1948; 1957).

From the middle dural plexus remains only the preotic sinus, the future superior petrosal sinus (Streeter, 1918), which, due to the disappearance of the cranial dural sinus drains the supraorbital veins and the primitive maxillary veins. This venous confluence, which is located medial to the V, is the outline for the developing cavernous sinus.

The inferior petrosal sinus appears, and it empties, together with the ventral mesencephalic vein, into the sigmoid sinus. The latero-mesencephalic venous affluences of the primitive transverse sinus become organized in the tentorial plexus, this being the basis for the formation of the posterior confluence of the sinuses (the torcular herophili).

Consequently, by E52, the pro-otic sinus will develop from the original trunk of the middle dural plexus and from the contiguous middle component of the primitive sinus of the head. This is incorporated in the diploic layer of the membranous bone at the level of the petrosphenoidal junction, where it remains a potentially collateral area. The lateral end of the pro-otic sinus merges with the sigmoid sinus at the lateral end of the superior petrosal sinus. The medial end leaves the cavernous sinus ventral, medial and anterior to the trigeminal ganglion, while the superior petrosal sinus begins from its dorsal, posterior and lateral portion, often without any proximal connection with the cavernous sinus.

The cavernous sinus is formed from the secondary plexus which is derived from the primary head vein and is located between the otic and the basioccipital cartilages. This plexus will form the inferior petrosal sinus which empties through the primordial hindbrain channel into the internal jugular vein. In this way, the medial part of the pro-otic sinus contributes to the formation of the cavernous sinus and of the inferior petrosal sinus, while its lateral part gives birth to the meningeal sinuses of the middle line, to some portions of the sphenoparietal sinus and to the veins located lateral to the trigeminal ganglion, all these becoming evident during the period between 9 and 12 weeks.

At the beginning, the tentorium is oriented vertically, and subsequently, concomitantly with the pronounced growth of the hemispheres, it becomes horizontal.

The transverse sinus, which is located on the same line with the internal jugular vein, is driven posteriorly at an angle of 90 degrees and elongated in an anterior-posterior direction by the cerebral hemispheres whose dimensions are continuously growing.

The tentorial plexus forms the medial end of the transverse sinuses, after which it merges with the marginal sinus in the area where the superior sagittal sinus meets the torcular herophili.

Caudally, in the area where the primitive myelencephalic vein comes in contact with the primitive sinus of the head, it will arise, medial to the otic vesicle, a trabecular venous channel which covers the sixth cranial nerve and merges with the pro-otic sinus.

This will become the inferior petrosal sinus. The cranial extension of this trabecular channel leads to the formation, medial to the internal carotid artery, of the cavernous sinus.

The early neighbourhood relationships of the cavernous sinus, which is located medial to the trigeminal ganglion and lateral to the carotid artery, persist also in the adult life. Here it can also be found an internal vein and a straight sinus.

The cavernous sinus, which had arisen from the venous plexus of the medial end of the pro-otic sinus, is connected transversally with the one located on the opposite side through the intracavernous sinuses and through the basilar plexus. The medial portion, which in adult passes alongside the lesser wing of the sphenoid bone, forms the sphenoparietal sinus.

A large part of the cerebellar drainage tends to persist in being collected through the superior petrosal vein. The posterior cerebellar veins develop and empty into the falcine sinus located within the tentorium, which, in turn, empty into the medial transverse sinus (Padget, 1956; Mullan et al., 1996). A group of superior vermian veins empty into the galenic venous system through the tentorial plexus (Macdonald and Johns, 1999).

During this phase of the development of the embryo, the transverse sinus reaches its definitive position within the cerebellar tentorium. The tentorial sinus becomes separated from the sphenoidal sinus, while the superior petrosal sinus becomes pre- and supraotic (Padget, 1948; 1957).

Cranial to the primary fissure, the drainage of the anterior lobe is directed towards the galenic venous confluent.

Matsushima et al. (1989) had ascertained that, besides the drainage of the torcular region, of the paratorcular area and of the middle portion of the transverse sinus, there are also tentorial sinuses which drain the vermian veins and the posterior hemispheric veins into the galenic and the petrosal venous confluents. This fact had also been reported by Picard et al. (1990). In the conception of the above mentioned authors, the tentorial sinus interconnects the supratentorial and the subtentorial veins.

Caudal to the primary fissure, the venous drainage is oriented towards the posterior venous confluent. De Miguel et al. (1996) had demonstrated on the serial sections of the foetus in the 70 mm stage that the vein which drains the choroid plexus of the fourth ventricle empties posteriorly into the foetal tentorial venous plexus. This vein receives branches which arrive from the posterior primitive region of the cerebellum, thus providing the venous drainage for the cerebellar hemispheres.

The processes which underlie the cerebrovascular development explain the variant anatomy as a developmental vestige, such as the persistent carotid-vertebrobasilar anastomoses which had failed to regress (Raybaud, 2010). The most common persistent anastomosis is the normal posterior communicating artery (Dungan and Heiserman, 1996). The persistent trigeminal artery, the persistent hypoglossal artery, the otic and the proatlantal intersegmental arteries (the persistent first cervical intersegmental artery) are rare, with an incidence rate between 0.1% and 1.2% (Yilmaz et al., 1995).

There are also many other variations in the vascular anatomy within each region of the cerebral circulation.

For example, there are several variants of the anterior cerebral artery / anterior communicating artery complex. The unpaired arrangement, called the azygos anterior cerebral artery, consists of the single arterial trunk distal to the anterior communicating

artery which supplies the blood for both hemispheres. The incidence of the azygos anterior cerebral artery ranges between 0 and 5% of the individuals (Calzolari et al., 1991).

The bihemispheric anterior cerebral artery consists of a pericallosal artery which supplies the blood to the medial portions of both hemispheres, with the ACA on the opposite side being hypoplastic and supplying only the callosomarginal branches. This variation is found in 2 to 7% of anatomic specimens (Permuter and Rhoton, 1978).

The triplicated anterior cerebral artery (the median artery of the corpus callosum) has several names, including the medial ACA, the third A2 artery, or the accessory anterior cerebral artery (Okahara et al., 2002). This vessel is thought to be derived from the embryonic median artery of the corpus callosum, a branch of the anterior communicating artery (Okahara et al., 2002). It supplies the blood to the corpus callosum, to the septal nuclei, to the septum pellucidum, to the rostral fornix, and to a part of the frontal lobes.

The variations in the basilar artery are due to differences in the extent or the completeness of the fusion, which occurs in a caudal to rostral direction (Lasjaunias et al., 2006). Therefore, a short basilar artery is the result of a lack of fusion of the caudal segment, whereas an unfused or an unzipped upper BA results from the lack of fusion of the rostral segment. The incomplete fusion at the level of the midsegments results in a fenestrated configuration (Okahara et al., 2002).

The molecular determinants of the cerebrovascular development

As early as 1986, it had been discovered that the central nervous system produces proangiogenic factors, which include the fibroblast growth factor-1 (Risau, 1986) and the vascular endothelial growth factor-A (VEGF-A) (Eichmann et al., 1993; Flame et al., 1995).

It had been ascertained that the expression of the vascular endothelial growth factor-A was developmentally regulated in the neural tube (Ogunshola et al., 2000; Hogan et al., 2004). The genetic ablation of the VEGF-A in the neural tube had resulted not only in a reduced vessel density and branching, but also in defects in the neural tube itself (Haig et al., 2003; Raab et al., 2004).

According to Bautch and James (2009), a big number of signalling pathways which are important in the vascular development were also co-opted by the developing nervous system.

These pathways include the VEGF/VEGF receptors, the semaphorins/plexin receptors, the neuropilins (co-receptors of both the VEGF and the plexin receptors), the netrins/UNC receptors/DCC receptors, and the slit/Robo receptors (Bautch and James, 2009).

Haigh et al. (2003) had concluded that defects which were seen with the global VEGF-A deletion were due to a direct effect on the endothelial cells.

However, this finding has been contradicted by the results of other studies which had reported that the VEGF signalling is important for the neuronal survival and function (Carmelit, 2003; Ward and Lamanna, 2004; Lambrechts and Carmelit, 2006).

It is now well-established that when embryonic bodies which had been genetically ablated for the VEGF receptor flk-1 were grafted into quail hosts, these were defective regarding the angioblast migration and the perineural vascular plexus contribution, this fact suggesting the existence of a role which is played by the VEGF signalling in the formation of the perineural vascular plexus (Ambler et al., 2003).

Conversely, transplants of mouse neural tube into the quail embryos had led to the ectopic formation of a quail-derived perineural vascular plexus around the graft, thus being revealed the fact that the neural tube was the source of the patterning signals for