

REVIEW

Morphological aspects of the vasculogenesis and angiogenesis during prenatal edification of the circle of Willis: a review

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Abstract

In the literature, there are many articles reporting anatomical variations of circle of Willis (CoW), defined as those changes that lead to the inability of this anastomotic structure to maintain adequate brain flow. Because there is such a wide variation in the configuration of the CoW, its anatomical variations affect the hemodynamics of blood flow, thus contributing to the development of aneurysms or stroke. As such, we consider that a good knowledge of the embryological development of the constituent arteries of the CoW can shed some light on the causes of the appearance of its anatomical variants. Reviewing literature, we will present the embryological development of the constituting arteries of the CoW and will begin with vasculogenesis and angiogenesis of the vascular system as a whole. Then, we will focus on the embryological development of the internal carotid artery (ICA) and its branches because, starting with the embryological day 24, these arteries are the first vessels that begin to develop to provide the necessary blood for the primitive brain. As the hindbrain increases its volume, a larger amount of nutrients is needed. Because a larger amount of blood is required to be provided by the primitive ICAs, there is a need for arterial capacity development and thus the posterior circulation begin to take shape. At this stage, the posterior circulation consists of a plexiform arterial network that receives blood from the carotid artery through the carotid–vertebrobasilar anastomoses. At the 5–8 mm embryonic stage, these anastomoses begin to regress, and the basilar artery and vertebral arteries become independent of the ICA. We are pointing out on the process of regression of these primitive vessels, emphasizing the fact that their persistence represents the starting point for the appearance of anatomic anomalies of the CoW, which are identified in the adult individuals. In this review, we also present and illustrate some developmental abnormalities of the anterior and posterior parts of the CoW.

Keywords: embryology, circle of Willis, internal carotid artery, anatomical variant.

Introduction

The circle of Willis (CoW) or *circulus arteriosus cerebri* is an anastomotic arterial structure lying at the base of the brain, around the optic chiasm and other structures of the interpeduncular fossa. In English literature, this anatomical structure is often called the arterial “circle” or “ring” that connects both sides of the anterior circulation to each other and both of them to the vertebrobasilar system [1].

There are other studies in which the CoW is not considered a circle, but an arterial “polygon” with a variable number of sides depending on the author. Many authors describe the CoW as a heptagon, consisting of anterior side – anterior communicating artery (AComA), two anterolateral sides

– left and right anterior cerebral arteries (ACAs), two posterolateral sides – left and right posterior communicating arteries (PComAs), two posterior sides – left and right posterior cerebral arteries (PCAs) [2]. Others consider it an eight-sided polygon (octagon), made of left and right internal carotid arteries (ICAs) in their supraclinoid segments, left and right horizontal or pre-communicating segments (A1) of the ACAs, AComA, left and right PCAs, and the tip of the basilar artery (BA) [3].

There are also researchers who consider it a nine-sided polygon (nonagon) (Figure 1), consisting of the following: one anterior side – AComA, two anterolateral sides – left and right ACAs, two lateral sides – left and right proximal segments of the ICAs, two posterolateral sides –

left and right PComAs, two posterior sides – proximal segments of the left and right of PCAs [4].

Finally, there is the concept that a complete CoW consists of 10 arterial sides (decagon), as the followings: two ICAs, two ACAs, one AComA, two PComAs, two PCAs and one BA [5].

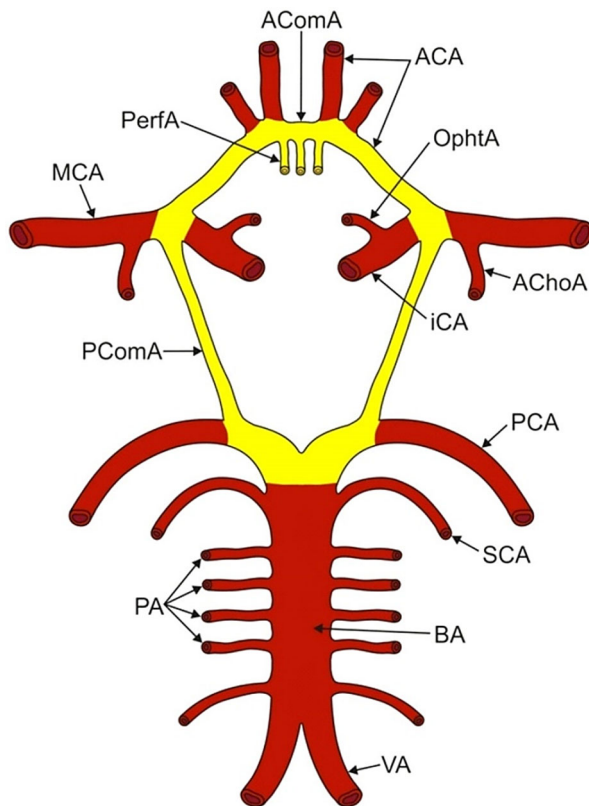


Figure 1 – Diagram illustrating the constituent arteries of the CoW as a nonagon (yellow color). ACA: Anterior cerebral artery; AChoA: Anterior choroidal artery; AComA: Anterior communicating artery; BA: Basilar artery; CoW: Circle of Willis; iCA: Internal carotid artery; MCA: Middle cerebral artery; OphtA: Ophthalmic artery; PA: Pontine arteries; PCA: Posterior cerebral artery; PComA: Posterior communicating artery; PerfA: Perforating arteries; SCA: Superior cerebellar artery; VA: Vertebral artery.

However, no matter how many sides are given to this arterial “polygon”, the most significant is the fact that the anatomy of CoW is known to vary significantly.

In the recent years, there are more and more articles reporting numerous anatomical variants of CoW, defined as those morphological changes that lead to the inability of this anastomotic structure to maintain an adequate brain flow. The published anatomical variants of CoW are the lack of some of the vessels that make up this structure, the presence of additional arteries, the abnormal origin of some of its arteries as they are found to be obviously different to the right and to the left of this structure, the presence of a smaller diameter of an artery compared to the contralateral artery, etc. However, it is important to note that studies conducted so far, based on autopsy or on imaging data, show that a normal CoW occurs in only 16.6% and 42.8% of the population [6, 7], so in less than half of the studied cases.

Because there is such a wide variation in the configuration of CoW, anatomical variations affect the

hemodynamics of blood flow especially during cardiac surgery with extracorporeal circulation [8], in the occlusion of one of its major cerebral arteries, during subarachnoid hemorrhage or during neurosurgical interventions or in other intracerebral disorders [9].

In these conditions, we consider that a good knowledge of the embryology of the CoW can shed some light on the development of the anatomical variants of its constituent arteries.

Early formation of human embryonic vasculature

Embryonic vasculogenesis and some factors influencing this process

The embryological development of the constituting arteries of CoW cannot be understood without a good knowledge of the development of the vascular system as a whole.

Now, it is well known that the development of the vascular system of the embryo takes place before the heart begins to beat [10].

The process of embryonic vasculature development consists of two main stages: vasculogenesis (*i.e.*, *de novo* blood vessel formation from individual precursor cells) and angiogenesis (*i.e.*, development of new vessels from pre-existing ones).

Blood vessels formation starts on the embryonic day 17 (E17) at the level of the extraembryonic splanchnic mesoderm in the yolk sac wall from a primitive multipotent precursor cell called hemangioblast. These cells proliferate and form aggregates of cells called hemangioblastic aggregates, which in turn will give rise to two cell lines, namely: hematopoietic stem cells (HSCs) and endothelial precursor cells, which are the first cells to differentiate into a functional phenotype in the embryo. The two cell lines form together blood islands [11].

Vasculogenesis and hematopoiesis take place under the action of regulatory substances. As the formation of mesodermal precursors is needed, these cells appear under the action of several cooperating signals that induce mesodermal cells to form blood vessels. The most important signals are the bone morphogenetic protein 4 (BMP4) and fibroblast growth factor 2 (FGF2), which have roles in mesoderm formation. Evidence of their significance in vasculogenesis was obtained from experimental studies when it was found that the mesoderm fails to develop in the absence of BMP4 and in the case of FGF2 receptor (FGFR2) inactivation [12].

Once multipotent mesodermal cells have formed, they will be directed to differentiation into endothelial cell lineages by soluble signals derived from adjacent endodermal endothelial cells. One such soluble effector is Indian hedgehog (IHH), which has a role for vascular induction and its effector can be BMP4. However, some studies have shown that in BMP4-null mutant mouse embryos can be identified an aberrant vasculogenesis and hematopoiesis thus proving the role of BMP4 in these two processes [12].

On the embryonic day 18 (E18), from primitive HSCs will emerge erythropoietic cells and some pluripotent progenitor cells of future megakaryocytes and primitive

macrophages, and this process is called hematopoiesis or hemopoiesis [11].

If hematopoiesis initially begins in the yolk sac and the extraembryonic mesoderm, later it moves into the liver, where HSCs will develop and will then colonize the bone marrow and other lymphatic organs [11].

Also, on E18, vasculogenesis begins in the splanchnic mesoderm of the embryonic disc and afterwards in the paraxial mesoderm, thus proving that this process is correlated with that of hematopoiesis. Firstly, primitive hemangioblasts surrounding primitive HSCs undergo *de novo* differentiation into the endothelial progenitor cells (EPCs), and then differentiate themselves into embryonic endothelial cells (EECs). The later create small vesicular structures through the process called vasculogenesis. These small structures lengthen and interconnect, leading to the appearance of the primary vascular network that invades embryonic tissues to form the arterial, venous and lymphatic channels. At the end of week 3, this vascular network completely vascularizes yolk sac, connecting stalk, and chorionic villi [11, 13].

On E18, blood vessels also begin to develop from the intraembryonic splanchnic mesoderm. Unlike the formation of blood vessels in the extraembryonic splanchnic mesoderm, the formation of blood vessels in the intraembryonic splanchnic mesoderm is not a simultaneous event with hematopoiesis. Endothelial precursor cells differentiate into EECs, which later will establish small vessel networks that will join together, then will grow and invade other tissues to form primary embryonic vascularization. Subsequently, this primitive vascularization expands and remodels by angiogenesis [11].

Some cells of the splanchnic mesoderm differentiate into EPCs or angioblasts under the influence of inducing substances secreted by the underlying endoderm. Then, the angioblasts evolve into flattened endothelial cells and join together to form small vesicular structures, which, in their turn, unite into long endothelial cords or primitive vessels. This process is called vasculogenesis and its result consists in establishing the initial configuration of the embryonic circulatory system due to the development of these endothelial cords through the intraembryonic mesoderm and their later coalescence to form a large network of primitive vessels.

This network grows and expands through the embryo due to four main processes: (i) the continuous formation, migration and coalescence of EPCs into endothelial cords; (ii) angiogenesis, that represents the processes of budding and sprouting of new vessels from the existing endothelial cords; (iii) vascular intussusception or nonsprouting angiogenesis, in which existing vessels are divided in order to produce additional vessels; (iv) inserting new EPCs into the walls of the existing vessels [11].

Embryonic angiogenesis and some factors influencing this process

Expansion by angiogenesis occurs by sprouting from existing vessels or by intussusception, defined as the splitting process of the existing vessels.

Sprouting of new vessels represents the main mechanism of angiogenesis and it is induced by both hypoxia/ischemia and growth factors from the microenvironment. With the

formation of small vessels, the impedance to blood flow decreases in the larger arteries, thus allowing the blood flow-induced remodeling of the arteries that provide blood to that area [14].

During angiogenesis, the growing blood vessels follow a certain gradient generated by vascular endothelial growth factor (VEGF) on the target tissues/regions where a vascular bed needs to be built. The level of oxygenation mediates angiogenesis by alternating VEGF levels and there is an inverse correlation between these two elements. Thus, under hypoxic conditions, VEGF level increases and stimulates angiogenesis, but under hyperoxic conditions, VEGF level decreases and angiogenesis suspend. However, once a vessel becomes well developed, VEGF presence is no longer needed [11].

On the other hand, the Notch signaling pathway is a conserved intercellular signaling mechanism, being essential for proper embryonic development. This pathway often plays a crucial role on the precursor cells when they must follow one of their many pathways.

Notch is a transmembrane receptor protein involved in the regulation of cell differentiation in many developing systems. Notch signaling also regulates cell proliferation and cell death. During embryogenesis, it acts as an inhibitor to the vascular system development, preventing the blood vessels from budding by reducing the level of VEGF receptors in endothelial cells [15].

Formation of the CoW during human embryonic development

Aortic arches and their morphological changes during the embryo development

The development of the circulatory system for blood supply to the future brain begins with the formation of the six pairs of arteries of the primitive pharyngeal arches in the embryonic stage of 1.3 mm, which are subsequently subjected to changes during embryonic development [14].

In fact, in the human embryo, at about three to four weeks of development, six pairs of outpouchings of mesoderm appears on both sides of the developing pharynx, corresponding to the pharyngeal arches, which are named as followings: the first, the second, the third, the fourth, the fifth, and the sixth pharyngeal arches. The fifth arch never forms in 50% of the embryos or, if it is formed, it is for a short period because it will soon degenerate [16].

Each pharyngeal arch has a cartilaginous core, a muscular component, an artery and a cranial nerve, all of these structures being surrounded by the mesenchyme. The arteries of the pharyngeal arches are known as the aortic arches and are labeled as following: the 1st, the 2nd, the 3rd, the 4th, the 5th, and respectively the 6th aortic arch [17].

The development of the aortic arches and cranio-cerebral vascularization begins around the 24th day of embryonic life (E24), with the appearance of the first aortic arch. It should be noted that the aortic arches are short vessels that connect the ventral aorta with the dorsal aortae on each side.

From day 26 until day 29 of the embryonic development (E26–E29), the 2nd, the 3rd, 4th, and the 6th aortic arches develop through vasculogenesis and angiogenesis in their

protective pharyngeal arches, incorporating endothelial precursor cells, which migrate from the surrounding mesoderm.

Thus, in week 5 of the embryonic development, the arteries of the aortic arches develop ventrally from the aortic sac, which is an expansion of the cranial end of the truncus arteriosus. Dorsally, these arteries connect to the left and right dorsal aortae. In evolution, the pairs of the first two aortic arches (the 1st and the 2nd) regress as the next arches are formed. The 2nd pair of aortic arches appear in the 2nd pharyngeal arches until E26 and then develop to connect the aortic sac to the dorsal aortae. Simultaneously, the 1st pair of aortic arches regresses completely, except for small remnants, which can participate in the development of some portions of the future maxillary arteries. On the embryonic day 28 (E28), as the 1st pair of aortic arches regresses, the 3rd and the 4th pairs of aortic arches develop. Finally, on the E29, the 6th pair of aortic arches is formed, but the 2nd pair of aortic arches regresses, except for small remnants that give rise to some parts of the stapedia artery, which supplies blood to the primordium of the stapes bone in the developing ear [11].

Embryological divisions of the ICA

From the 3rd aortic arch, in the E24, the common carotid artery (CCA) and the initial portion of the ICAs begin to form [14]. Thus, the segments of dorsal aortae that connect the 3rd and 4th pairs of aortic arches disappear from both sides of the body. The cranial extensions of the dorsal aortae that ensure the irrigation of the head receive blood entirely through the 3rd pair of aortic arches. Therefore, the 3rd pair of aortic arches gives rise to the right and left CCAs and at the proximal portions of the right and left ICAs. The distal portions of the left and right ICAs are derived from the cranial extensions of the right and left dorsal aortae [11]. The right and left external carotid arteries (ECAs) sprout from the right and respectively left CCAs and also receive some contributions from the first two aortic arches. The stapedia arteries, which represent some remnants of the 2nd pair of aortic arches, contribute to the formation of the right and left internal maxillary artery and of the right and left middle meningeal arteries, which are the branches of the ECAs [18].

The two paired dorsal aortae remain separate in the region of the aortic arches, but fuse below the level of the fourth thoracic segment to form a single median dorsal aorta.

At the 4 mm stage (E28), the ICA, which is already formed as a cranial extension of the paired dorsal aortae, divides itself into the rostral (anterior) and caudal (posterior) branches (Figure 2). Its anterior (rostral) branches irrigate the optic and olfactory regions through the primitive arteries, and the posterior (caudal) division will become the future PComA, which will ensure the origin of the PCA and posterior choroidal artery (PChoA) [19].

Embryological development of the vertebrobasilar system

During the early stages of brain development, ICA provides most of the blood needed to the developing brain through several branches.

The BA initially develops as two dorsal longitudinal

vascular plexuses originating in the 3rd and 4th arches, during week 5 of gestational age. In these early stages of embryonic development, the posterior circulation is based almost entirely on the blood supply that comes from the anterior circulation through the carotid–vertebrobasilar anastomoses [14], represented by a number of primitive vessels that connect the two parallel neural longitudinal channels, the future developing BA, with ICA [18].

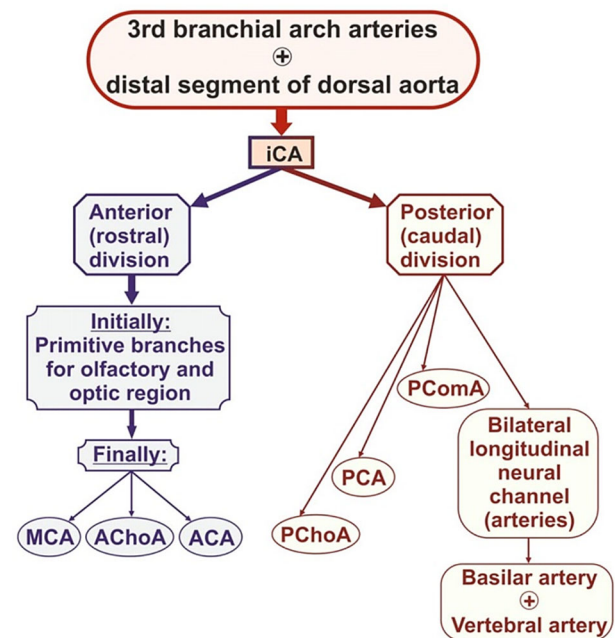


Figure 2 – Schematic representation of brain arteries having their embryologic origin from iCA. ACA: Anterior cerebral artery; AChoA: Anterior choroidal artery; iCA: Internal carotid artery; MCA: Middle cerebral artery; PCA: Posterior cerebral artery; PChoA: Posterior choroidal artery; PComA: Posterior communicating artery.

More than a century ago [20, 21], there were already some suggestions that there are some segmental vessels in the embryonic hindbrain area that act as carotid–basilar anastomoses during the human embryo development.

Now, it is well known that at 4 mm stage of embryonic development, each ICA anastomoses with the longitudinal neural artery (LNA) on the same side, the future vertebrobasilar artery, through four primitive vessels, *i.e.*, trigeminal artery (TA), otic artery (OtA), hypoglossal artery (HA) and intersegmental proatlantal artery (ProA) [14].

However, when the embryo reaches 12 mm and PComA, BA and vertebral artery (VA) are already formed, these primitive anastomotic vessels, being transient ones, usually disappear. The primitive otic artery (pOtA) regresses first and the same regression will later affect the primitive hypoglossal artery (pHA). Intersegmental primitive trigeminal artery (pTA) and primitive proatlantal artery (pProA) persist for another short period of time. Occasionally, these primitive arteries persist in postnatal life, being defined as the vestige of the corresponding primitive embryonic vessel, which provided carotid–basilar anastomoses in embryonic life [19, 22, 23].

The lifespan of the pTA, the pOtA and the pHA is about a week, and if the PComA develops and connects with the BA, these three presegmental arteries regress. Unlike pTA, pOA, and pHA, the pProA persists until the

VAs are fully developed. A segment of the pProA becomes embedded in the V3 segment of the VA and in the distal portions of the occipital artery (OccA) [14].

At the 4–5 mm embryonic stage, bilateral LNAs (arrows) are also supplied by the cervical intersegmental arteries (CIA). At the 5–8 mm embryonic stage, the vascular communications between ICA and bilateral LNAs regress (pTA, pOtA, pHA, pProA, and CIA) and bilateral LNAs fuse and form the BA on the midline [19]. Also, the PComA replaces the tentorial artery as a source of collateral supply between the anterior and posterior circulation [14, 22, 24, 25].

At the 7–12 mm stage, the VA is formed from transverse anastomoses between the CIA starting with pProA and proceeding down to the 6th CIA (which eventually forms the VA origin from the subclavian artery) [14]. Later, the CIA develop into the paired VAs [19], and the ACA, anterior choroidal artery (AChoA), and middle cerebral artery (MCA) develop from their ipsilateral ICA (Figure 2) [22].

Embryological development of the MCA

In the embryonic stage of 11–12 mm (35 days), the development of MCA appears as small vascular sprouts, originating on the anterior division of the primitive ICA, but in the proximity of the origin of ACAs. Even though at this stage MCAs are still plexiform vessels and not true arteries, both of them are the major sources of blood for the cerebral hemispheres [14].

In the 16–18 mm stage, the MCAs become more prominent, their plexiform appearances disappear as two arteries are formed, and their branches enter further into the cerebral hemispheres [14].

Embryological development of the ACA complex

Initially, the terminal end of the developing cranial segment of ICA is represented by the primitive olfactory artery (pOlfA) that will later become the ACA (Figure 2), but at a later embryological stage, the rostral (anterior) division of the ICA will also give rise to the MCA, and the AChoA. At the same time, the caudal (posterior) segment of ICA will produce the PCA (*i.e.*, the fetal variant). Also, at this stage, the superior cerebellar artery (SCA), a branch of the future BA, is the only source of blood for the primitive cerebellum (Figure 2) [4, 14].

The ACA, as a continuation of the pOlfA, extends upward and backward between the developing cerebral hemispheres. The pOlfA will regress later but some remnants will remain to supply a small artery branch to the nasal cavity and to the anterior perforated substance [3].

The pOlfAs have both medial and lateral branches, which are called medial olfactory artery (mOlfA) and lateral olfactory artery (lOlfA), respectively.

The mOlfA will become ACA, and from the lOlfA will gradually develop the MCA, the recurrent artery of Heubner, the AChoA, and lateral striatum artery. Possible variations of the environment during these evolutionary stages lead to the appearance of several anatomical variants involving ACA [26].

Left and right developing ACAs continue to grow medially to each other, leading to the formation of a reticular anastomosis between them [22]. On embryonic day 44 (E44), *i.e.*, 24 mm embryos, the reticular vessels from this area fuse to form a single trunk, which, during the

fetal period, already has the shape of the future AComA, but it has a large diameter, comparable to that of the ACA. The development of the cerebellar arteries occurs later, corresponding to a delayed development of the cerebellum compared to the brain [22].

The embryology of the ophthalmic artery (OphA) is closely related to the development of the ACA.

In the 5–6 mm embryonic stage, the optic cup and the optic stalk begin to form [28]. The primitive dorsal ophthalmic artery (pDOphA) also begins to develop. It has its origin at the junction of the cranial (anterior) and caudal (posterior) division of the primitive ICA, namely at the level of the origin of the future PComA [27]. In the embryonic stage of 7–12 mm, there are already two primitive OphAs. The pDOphA supplies the capillary plexus to the optic cup, and primitive ventral ophthalmic artery (pVOphA) appears as being opposite to the AChoA. The blood supply to the optic tissue is still plexiform at this stage.

In the 12–14 mm embryo, pDOphA has two optic branches and these are the common temporal ciliary artery (future lateral ciliary artery) and a hyaloid artery (future central retinal artery). Also, pVOphA provides the common nasal ciliary artery that will become the future medial posterior ciliary artery [28].

From the embryonic stage of 16–18 mm to the embryonic stage of 40 mm, a series of anastomoses and arterial regressions occur, so that the proximal portions of the primitive OphAs evolve into the adult form of the OphA, and the distal parts of the pDOphA and the pVOphA become the permanent branches of the OphA [27, 28].

In the 40 mm embryonic stage, the OphA reaches an approximately adult configuration [27, 28].

Developmental abnormalities of the CoW

Anatomical variants of the anterior part of the CoW

Some studies have identified a high percentage (about 35%) of anatomical variations of AComAs and considered them as the consequences of all those different processes it undergoes during its development [29]. Most often, this vessel can be dilated and equal in size to ACA and this morphological feature is defined as the embryonic shape (Figures 3 and 5), but many other patterns can be identified, such as: absence (Figure 4), which is also quite common, duplication/fenestration (Figure 6), triplication, a “X”, “Y”, “N”, or an “H” shape, a plexiform aspect, etc. [30]. Nedelcu *et al.* reported a complex vascular anatomy of the CoW, consisting in a partially duplicated AComA associated with an aberrant origin of the right fronto-orbital artery in the left ACA and an accessory branch emerging from the same source and concluded that these anomalies could be the cause for epileptic seizures [31]. There are also numerous anatomical variations that are identified for the A1 segment of the ACA. The most common anatomical variant found at this level was hypoplasia (Figures 4, 5 and 7), which appears in approximately one third of cases, followed by absence, fusion of the two ACAs (or azygos artery) (Figure 8), fenestration (Figure 6) [30, 32]. Sometimes, the entire anterior artery complex may be affected, such as AComA duplication associated with ACA triplication, but these abnormal morphologies can lead to an aneurysm of the AComA [33].

However, the complete development of ACA and of

ACoMA marks the final achievement of adult CoW in the embryonic stage of 6–7 weeks [14].

Anatomical variants of the posterior part of the CoW

The posterior part of the CoW is formed at an earlier stage, when the fetal PCA transforms itself into the PCA. The adult PCA connects with the BA because some branches of the fetal PCA fuse medially to form the distal portion of the BA, and the PChoA is incorporated into adult PCA.

Finally, the major components of CoW are almost complete, with the PCA taking up most of the blood from the posterior circulation, leaving the PComA as an embryological remnant in most cases [22].

Anatomical variants of CoW are more common in its

posterior part [34, 35], some authors reporting that almost two thirds of the brain they analyzed presented anatomical variations of the posterior circulation [36].

These anatomical variants can appear either in the form of unilateral or bilateral hypoplasia/atresia of the PComAs (Figures 4–9), and as unilateral or bilateral absence of the PComAs (Figure 8) or of the PCA, or as the fetal variant of the PComA (Figures 7, 8, and 10). However, in a previous article, we found out that 5.12% of all CoW studied by us on fresh autopsied brains presented bilateral hypoplasia of the PComAs [37]. We also published a unique constellation of anatomical variants of CoW consisting in the association of hypoplasia of the right ACA, bilateral hypoplasia of the right and the left PComAs [38].

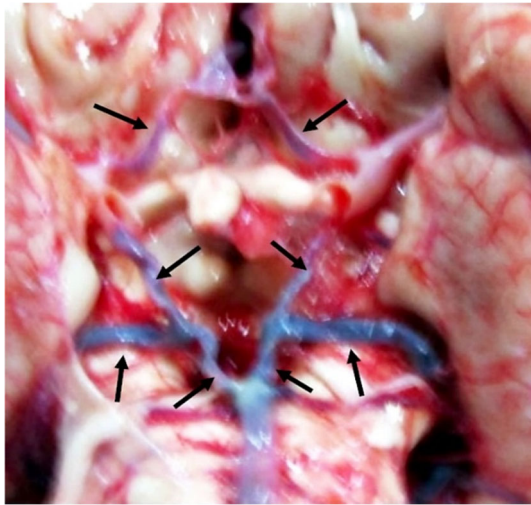


Figure 3 – F, 66 years old. Macroscopic view of the CoW on fresh autopsied brain: fetal configuration of the CoW with all its component arteries (black arrows) having the same caliber, which is a feature similar with that identified at the 40-mm stage (eight weeks) of embryonic development (authors' collection). CoW: Circle of Willis; F: Female.

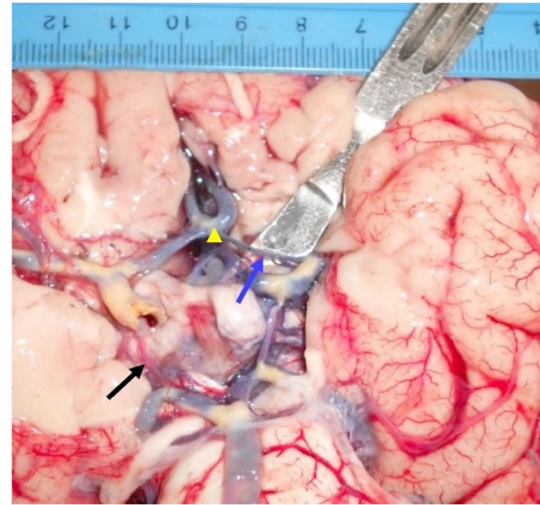


Figure 5 – F, 70 years old. Macroscopic autopsic image of the CoW: ACoMA with embryonic shape (yellow arrowhead), hypoplastic left ACA (black arrow), and atresia of right PComA (green arrow) (authors' collection). ACA: Anterior cerebral artery; ACoMA: Anterior communicating artery; CoW: Circle of Willis; F: Female; PComA: Posterior communicating artery.

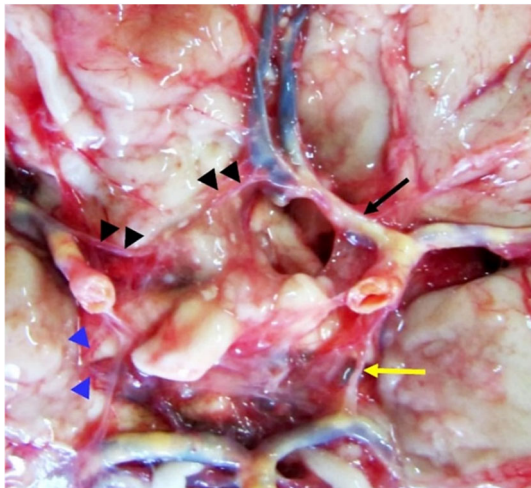


Figure 4 – M, 86 years old. Macroscopic view of the CoW on fresh autopsied brain: left ACA splits in two A2 segments, absence of ACoMA, atresia A1 of right ACA (black arrowheads), atresia right PComA (yellow arrow), and hypoplastic left PComA (yellow arrow) (authors' collection). ACA: Anterior cerebral artery; ACoMA: Anterior communicating artery; CoW: Circle of Willis; M: Male; PComA: Posterior communicating artery.

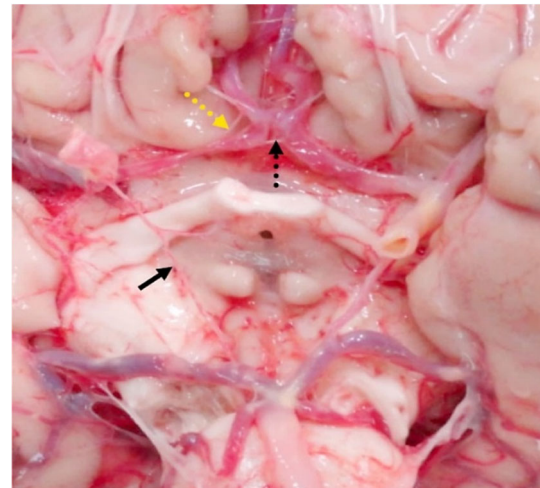


Figure 6 – M, 65 years old. Macroscopic view of the CoW on fresh autopsied brain: fenestration of ACoMA (black discontinuous arrow), fenestration of right ACA (yellow discontinuous arrow), atresia of right PComA (black arrow) (authors' collection). ACA: Anterior cerebral artery; ACoMA: Anterior communicating artery; CoW: Circle of Willis; M: Male; PComA: Posterior communicating artery.

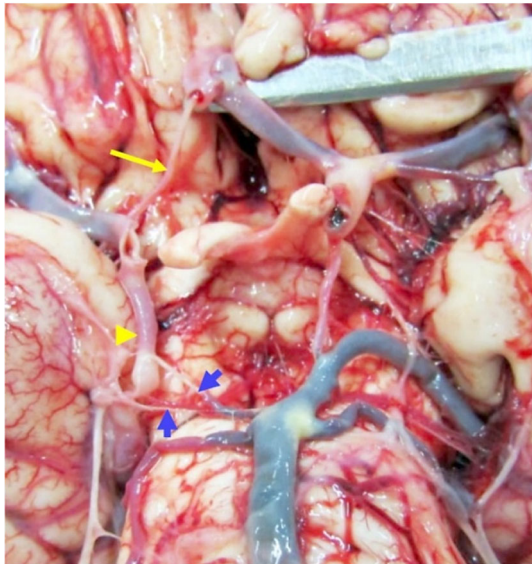


Figure 7 – F, 81 years old. Macroscopic view of the CoW on fresh autopsied brain: hypoplastic right ACA (yellow arrow), right fetal PComA (yellow arrowhead), and hypoplastic and double PCA on the right side (dark blue arrows) (authors' collection). ACA: Anterior cerebral artery; CoW: Circle of Willis; F: Female; PCA: Posterior cerebral artery; PComA: Posterior communicating artery.

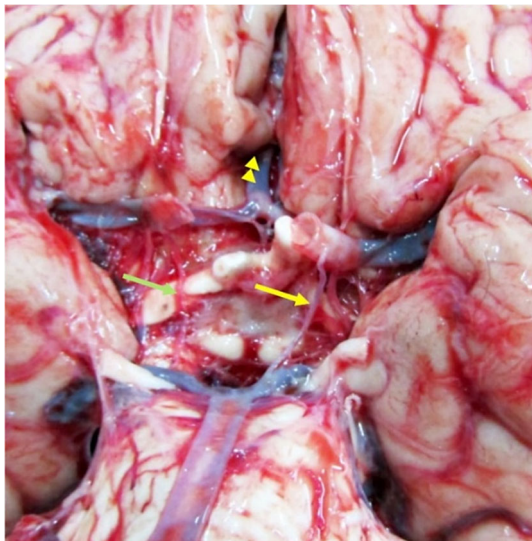


Figure 8 – M, 52 years old. Macroscopic view of the CoW on fresh autopsied brain: absence of AComA due to joining of the two AI segments of the ACA, having as a result the formation of a single trunk or azygos ACA (two yellow arrowheads), associated with hypoplastic left PComA (yellow arrow) and absence of right PComA (green arrow) (authors' collection). ACA: Anterior cerebral artery; AComA: Anterior communicating artery; CoW: Circle of Willis; M: Male; PComA: Posterior communicating artery.

Anatomical variants of the CoW as a whole

During embryogenesis, the vertebrobasilar and the carotid systems will connect to each other, so that at the base of the brain a unique vascular system will be formed, called the arterial CoW. It not only joins the two systems together, but through its transverse bridges it connects the arteries from the right part of CoW with those from its left part [2].

The American neuroembryologist Dorcas Hager Padgett

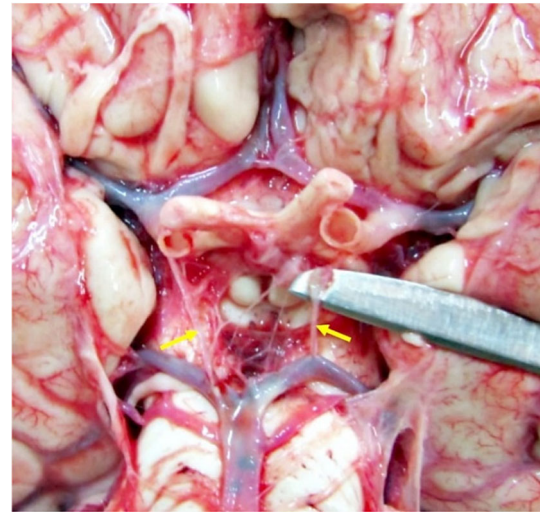


Figure 9 – F, 79 years old. Macroscopic view of the CoW on fresh autopsied brain: bilateral hypoplastic PComAs (yellow arrows) (authors' collection). CoW: Circle of Willis; F: Female; PComAs: Posterior communicating arteries.

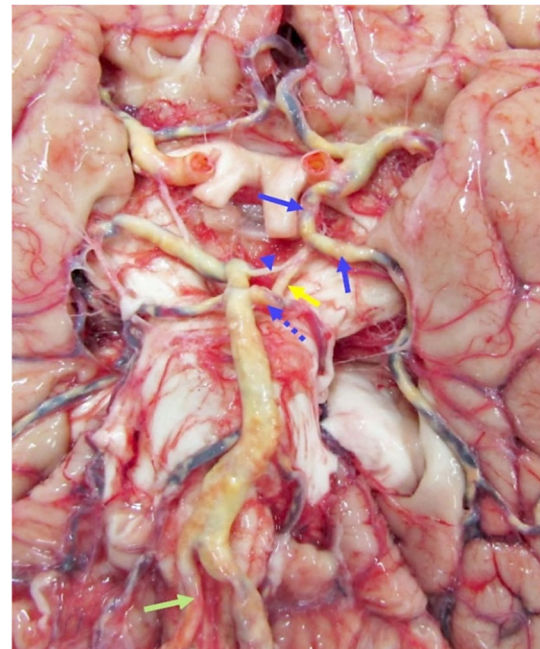


Figure 10 – F, 81 years old. Macroscopic view of the CoW on fresh autopsied brain: partial fetal PComA (black arrows), left hypoplastic PI segment of PCA (black arrowhead) joining with a fetal abnormal arterial branch (yellow arrow) that unite fetal PComA with left SCA (discontinuous arrow), associated with hypoplastic right VA (green arrow) (authors' collection). CoW: Circle of Willis; F: Female; PCA: Posterior cerebral artery; PComA: Posterior communicating artery; SCA: Superior cerebellar artery; VA: Vertebral artery.

was the first researcher to accurately describe and illustrate the embryonic development of human brain vascularization by studying the CoW of 19 human embryos from the world-renowned *Carnegie Collection* – Carnegie stages (CS). She provided an accurate description of CoW development due to identification of various anatomical variations in this age group, including incompletely closed CoW in CS 18 and CS 19 embryos, but closed CoW in embryos with CS over 19 [39].

Recently, in 2016, Takakuwa *et al.* [1] analyzed 20 CoW taken from Japanese human embryos using three-dimensional reconstruction of serial histological sections. They identified a significantly higher number of unclosed CoW in CS 20, 21, 22, and 23, mainly in the anterior part of the CoW because of the absence of the AComA due to a deficiency of fusion between right and left ACAs. However, these authors also noted hypoplasia/atresia of right or left PComAs or of the P1 segment of the PCA, suggesting that these arterial variations occur in the embryonic period, thus influencing the development and growth of the brain by affecting the correct vascularization.

However, this study showed a different fact from Padgett's study, namely that their Japanese embryological CoW was completely closed only in the CS 23, so one or even two CSs later than the CS reported by the article from 1948. This can be determined by the changes in people's lifestyle in the 21st century compared with the 20th century, or to the mother's lack of certain minerals or vitamins in her diet, or it can be the result of an ethnic type of embryonic evolution.

CoW as a whole can be symmetrical, but many times an asymmetrical one can be found on angiograms or at autopsy of neurological deceased patients. This asymmetry is related with anatomical variants of some of its constituting arteries to which an aneurysm or a stroke can be associated (Figures 4–7).

But the most important fact is that adult individuals with anatomical variants of CoW are prone to develop cerebrovascular disease with a poor prognosis. In a previous study, we found out that the causes of death of such patients were correlated with cerebrovascular diseases (*i.e.*, cerebral infarction and hematomas/hemorrhages) in almost two thirds of them, cerebral aneurysm in a small number of cases, but the cause of death was also related to other non-neurological causes, such as myocardial infarct, pneumonia, lung cancer with multiple metastases or pulmonary tuberculosis associated with cerebral dissemination [40].

It is worth to mention that the appearance of anatomical variants of the constituent arteries of the CoW is not a unique event during embryonic development. Such anatomical variants appear at the level of any artery in the human body. Up to date there have been published numerous such cases discovered in adulthood, either in corpses used for anatomy teaching purposes, or during the autopsy, on angiograms obtained in imaging laboratories, or during the surgical interventions. Most frequent, anatomical variants have been identified in the renal artery [41] and in the arteries that supply blood to the digestive tract [42].

☒ Conclusions

The recognition and interpretation of anatomical variations that can be discovered at the level of the CoW during autopsy or angiographic investigations are strictly correlated with a very good knowledge of the embryological development of the constituent arteries.

Embryological development of the constituent arteries of the CoW is a complex process during which these vessels are constantly developing and changing. It was shown that certain vascular channels develop and persist, but some other channels disappear according to the blood irrigation needs of the areas at which they must be distributed. Thus, we can appreciate that in the intrauterine period

there is a high plasticity inside this arterial circle from the base of the brain.

Any intervention upon the factors that actively influence the processes of vasculogenesis, angiogenesis and development of the arteries of the CoW during the embryonic period may lead to the emergence of many anatomical variants with significant role in adulthood because all these anomalies can influence the development of cerebrovascular diseases, such as aneurysms, atherosclerosis, and stroke.

Conflict of interests

The authors declare that they have no conflict of interests.

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