Unpaired Anterior Cerebral Artery Associated with Double Origin of Vertebral Artery: Case Report and Genetic Consideration

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Abstract

The case demonstrates the co-development of two rare anatomical variations of the vascular pattern in 76-year-old man patient. By means of magnetic cerebral angiography the unusual shape of circle of Willis with fusion of the second segment of the anterior cerebral artery and absence of the anterior communicating artery was uncovered. Additionally, the duplicated cervical vertebral artery with one limb attached to the aortic arch distal to the origin of the left subclavian artery, and the other – from the left subclavian artery at the level of origin of the thyrocervical trunk was revealed during interpretation of angiographic images of the head and neck. While double origin of the vertebral artery does not influence the cerebral circulation directly, the unpaired anterior cerebral artery plays a predisposal role in the development of cerebral ischemic disorders and aneurysms.

The co-formation of these rare vascular patterns implies misbehavior of the primary epithelial cells due to dis-coordination of the genetic regulatory factors during the early vascular development. The aims of this paper are: 1) to trace the phylogenetic and embryologic formation of the anterior cerebral and vertebral arteries; 2) to summarize the known genetic pathways of regulation of angiogenesis; 3) to emphasize the importance of vascular plasticity of the cerebral circulation.

Keywords: Azygos Anterior Cerebral Artery, Duplicated Vertebral Artery, Phylogenesis, Embryogenesis, Angiogenesis.

Introduction

The association of two rare anatomical variants of vascular pattern is reported in this paper: an unpaired anterior cerebral artery (ACA) and a duplicated origin of the left vertebral artery (VA) with one limb rising distal to the origin of the left subclavian artery.

The unpaired ACA is an unfavorable and extremely rare variability of the circle of Willis (0.4-1%), characterized by absence of a typical anterior communicating artery and appearance of the ACA as an elongated fusion of its second segment (A2). It is sporadically described as an “Azygos ACA” by authors drawing the parallel between human and other mammal anterior circulation.2 High evidence of aneurysm formation and potential cause of ischemic vascular disorders in the basin of the sole ACA put this variant of norm close to the border of pathological development.2,4

There are several variants of duplicated origin of the vertebral artery described in literature. Those include: 1) the rising of both limbs from the subclavian artery, 2) the dominant limb originating from the thyrocervical trunk and the accessory one immediately from the aortic arch, and 3) the main limb ascending from the
subclavian artery and the second one from the aortic arch.\textsuperscript{5-7} However, the appearance of the aortic limb of the VA distal to the beginning of the left subclavian artery is an unusual pattern for the vertebral artery with double origin. To the best of our knowledge, no similar cases have been reported until now. Although the double origin of the vertebral artery does not influence the cerebral circulation directly, the majority of reported patients complained of vertigo, dizziness, weakness, headache and a number of other neurological symptoms.\textsuperscript{8}

A thorough understanding of anomalous vascular patterns is paramount when performing both diagnostic and interventional angiography. The development of these anatomical variabilities in one patient implies the possibility of altered gene expression with the following discoordination of the early angiogenesis. Additionally, such angiographic findings might be associated with structural deviations of the nervous system and may show a predisposition to malformations of the corpus callosum, hydranencephaly, and porencephalic cysts.\textsuperscript{4,9}

To evaluate the preconditions of the formation of unusual cerebral vascular patterns, the review of the phylogenetic and embryogenetic formation of the cerebral and vertebral arteries was performed in parallel with the analysis of known genetic factors involved in regulation of the vascular plasticity during early embryogenesis.

### Case report

A 76-year-old male patient with the loss of sensation in the right hand and suspected cerebrovascular pathology was referred to our department for angiographic evaluation of the carotid and vertebral arteries. Following the intravenous introduction of 20 ml of Di-Meglumine Gadopentate (Magnevist 469 mg/ml) MR angiography was employed for visualization of the head and neck vasculature (3-Tesla Verio Siemens AG, Germany). The obtained images with slice thickness 1.4 mm were analyzed in a RadiAnt DICOM viewer (version 3.4.2.) and 3D volume rendering (VR) was performed.

The magnetic resonance imaging (MRI) of the brain revealed a small acute infarction in the left centrum semiovale. Cranial magnetic resonance angiography (MRA) demonstrated a rare vascular pattern of the circle of Willis with no anterior communicating artery (ACOM) and unpaired ACA with the internal diameter 5.2 mm at its proximal part. The artery displayed the fused lumen along its second, third and fourth segments (A2-A4) (Figure 1,2).

![Figure 1](image_url)

**Figure 1.** MRA of head and neck showing the appearance of the medial limb of the left vertebral artery (mVA) as a continuation of the vertebral artery over the first part of the left subclavian artery (LS); presented cerebral vessels are the middle cerebral arteries (MCA), the first segment of the anterior cerebral artery (A1), the unpaired second segment of the anterior cerebral artery (A2).
**Figure 2.** MRA of the head and neck, 3D volume rendering. Rare variant of the circle of Willis with the unpaired anterior cerebral artery is represented. Abbreviations: A1 – the first segment of the ACA; uA2 – unpaired second segment of the ACA; MCA – middle cerebral artery; PCA – posterior cerebral artery; PCom – posterior communicating artery; BA – basilar artery; ICA – common carotid artery.

**Figure 3.** Axial FLASH MRI at the level of the body of the lateral ventricle uncovering the unpaired second segment of the anterior cerebral artery (black arrow) and the right and left frontopolar branches (white arrows).
**Figure 4.** MRA of the aortic arch, lateral view (3D volume-rendered image) demonstrating the double origin of the left vertebral artery. Abbreviations: AA – aortic arch; LS – left subclavian artery; LCC – left common carotid artery; LVA – left vertebral artery; sL – subclavian (lateral) limb of the vertebral artery; aL – aortic (medial) limb of the vertebral artery; RS – right subclavian artery; rVA – right vertebral artery.

**Figure 5.** MRA of the aortic arch, superior view (3D volume-rendered image) showing the level of attachment of the subclavian limb of the left vertebral artery. Abbreviations: AA – aortic arch; LS – left subclavian artery; LCC – left common carotid artery; LVA – left vertebral artery; sL – subclavian (lateral) limb of the vertebral artery; aL – aortic (medial) limb of the vertebral artery; TCT – thyrocervical trunk.
Two frontopolar branches arose from the anterior side of the unpaired A2 with the 2 mm distance between their origins (Figure 3). The unpaired A3 continued backward as a pericalosal artery.

Assessment of the cervical MRA uncovered a double origin of the left VA with the dominant limb rising from the aortic arch distally of the origin of the left subclavian artery (5 mm in diameter at its origin), and the accessory limb (3.6 mm width) originating from the left subclavian artery at the same level as the beginning of the thyrocervical trunk (Figure 4, 5). Both limbs of the left VA fused at the level of C7 vertebra forming a single trunk just behind the subclavian artery. Symmetrically, the left and right VAs entered the C5 transverse foramen and ascended toward the cranial base.

**Discussion**

The anatomical variability of the arterial patterns encountered during routine angiographic scanning or anatomic dissection never ceases to amaze specialists. The wide diapason from duplication and triplication of separate vessels to their total fusion has been reported since the global implementation of radiographic technics. The arteries of the head and neck undergo peculiar attention by investigators as even inessential structural changes could affect cerebral circulation and lead to ischemia and stroke. The case which is presented in this paper is a bright example of a unique association of two rare vascular patterns such as an unpaired A2 of the anterior cerebral artery with no anterior communicating artery, and the duplicated origin of the left vertebral artery with one limb attached to the aortic arch distal to the origin of the left subclavian artery. The coexistence of these vascular exceptions in one patient suggests a mutual misbehavior of the primordial epithelial cells during early angiogenesis. Although the precise mechanisms of genetic control over growth and spatial orientation of primordial vessels is still unclear, it is evident that only minute shifts in gene expression might lead to the formation of such patterns. To understand the mechanism of the development of the vascular pattern reported in this case, the related phylogenetic and embryological data were matched with the results of recent genetic studies on regulation of the vascular plasticity.

### 3.1. Phylogenetical aspect

Trying to explain the appearance of the unpaired or “azygous” anterior cerebral artery in humans, previous reporters often referred to the animal world as a genetic pool of evolution. To illuminate the phylogenetic aspect of this issue, the revision of basic evolutionary steps of the cerebral vessels was executed.

The anterior cerebral artery is a unique vessel from the phylogenetic point of view. This evolutionary terminal cranial branch of the carotid artery supplies the primitive olfactory lobes of fish and amphibians, the primitive forebrain of reptiles and birds, and finally, it supplies the frontal lobes of mammals. In most of these animals, the trunk of the primitive ACA is paired with the exception for some species of lower primates. The first functional anastomosis between the right and left ACA forms in reptiles as a short midline fusion of the middle olfactory arteries - the evolutionary forerunners of the ACAs. The new-formed anastomosis is actually a primitive anterior communicating artery (ACom) which inaugurates the phylogenetic establishment of the circle of Willis. However, the middle olfactory arteries are still paired, even after this evolutionary development (Diagram 1). Consequently, the formation of an unpaired ACA in humans is more likely the variant of extensive fusion rather than incidental appearance of some primitive forms.

The caudal branches of the primitive carotids are already fused along the midline in fishes forming the primordium of the future BA. Thus, the proximal half of the circle of Willis develops much earlier in evolution. However, the development of the longitudinal neural arterial system and the establishment of functional anastomoses with the vertebral circulatory system is significantly delayed in the phylogenetic chain. Actually, only in higher primates does the verteobasilar system exert the craniofugal flow and start to supply the brainstem and cerebellum independently from the carotid system. That particularly explains the high variability rate of the verteobasilar vessels; the young evolutionary development undergoes testing.

The direct precursor of the VA appears in lower vertebrates as a longitudinal vessel supplying the costal plates and territory of the spinal cord. In ophidian reptiles, a single median subvertebral artery arises as a proximal branch of the right aortic arch, which extends forward and supplies spinal and intercostal arteries to each side of the body. In chelonian reptiles, paired vertebral arteries branch off from the axillary artery and pass upward along the vertebral column. In the class of birds, the right-sided arch of the aorta gives off two branches called “arteria innominata” which serve as a common trunk for the carotid, subclavian, vertebral, and thoracic branches. In birds with heavy bodies, the vertebral artery becomes a branch of the common carotid artery. On the same phylogenetic stage, the cervical vertebrae gain the transverse foramen, and the vertebral artery enters the cranial cavity predisposing it to the formation of anastomosis with the primitive basilar artery. In quadrupeds, progressive development of cerebral hemispheres appears to become connected with the magnitude of their vertebral arteries, which are the constant branches of subclavian arteries here.
3.2. Embryological aspect

The early development of human vasculature reflects the phylogenetic process to a certain extent. The paired cranial and caudal carotid branches feed the developing cerebral vesicles through the whole prechoroidal and choroidal stages (3-5 weeks), and the primitive anterior circulation remains dominant over the forming vertebrobasilar system until the beginning of the 8-9-week embryological stage\textsuperscript{15}. The phylogenetically oldest cranial branch becomes the supply for the primary forebrain in the human embryo, representing the future ACA. The caudal branches feeding the midbrain and hindbrain give origin to the posterior communicating artery, the first segment of the posterior cerebral arteries, and the cranial part of the BA. The chaotic vascular network around the spinal cord displays the first signs of longitudinal arrangement only at the 6th week of development, then the paired longitudinal spinal and longitudinal vertebral systems begin to form. During the 7th week, the paired longitudinal spinal artery fuses into one vessel that is the future anterior spinal artery and the caudal part of BA; only two weeks later the blood flow in the vertebrobasilar system reverses from the craniocaudal to the craniofugal direction indicating formation of the posterior cerebral circulation, as is normally seen in adults\textsuperscript{12}. Coincidently or not, the same timing is assumed for the formation of the ACom as a result of the medial sprout of the proximal parts of ACAs with following fusion\textsuperscript{15}. According to the results of Takakuwa et al (2016), examining the development of the circle of Willis in the human embryo at 7-9 weeks, the transverse connection between the ACAs is already present on these stages, and the failure of the development of the ACom is the most common variant of an incomplete circle of Willis encountered in 50% of embryos\textsuperscript{16}. The high rate of variability and respectively late embryogenetic formation allow us to suggest that the ACom represents recent evolutionary development, and the length of this segment may vary to a certain extent.

3.3. Mechanisms of genetic regulation of angiogenesis

The early development of the vascular system is a highly coordinated process of proliferation, differentiation, and migration of endothelial stem cells. During the seventh and eighth embryonic days, they combine into angioblasts at the locus of the future dorsal aorta to begin the formation of paired tubular structures via the process referred to us as vasculogenesis\textsuperscript{15}. Then, the primary vessels undergo the process of angiogenesis characterized by sprouting, growth, and pruning of the primordial arterial branches. Although the remodeling of the vascular tree is especially intensive during embryogenesis, it continues into the fetal and postnatal periods of human development\textsuperscript{15}. Tight and specific interaction of hierarchical genetic and environmental factors coordinates this complex process, incidentally ending up in creation of unusual vascular patterns. Although the factors that influence angiogenesis are still largely unknown, recent research has greatly improved our understanding of the origin and growth of the vascular system.
Thus, by analysis of gene transcripts of mice and zebrafish, Herpers R.L. has distinguished 61 genes with the expression pattern closely linked to the process of vascular development. The realization of encoded information of these genes is mediated by secretion of ligands capable to stimulate homologous receptors embedded into a basal membrane of epithelial cells (EC), the primary builders of the vascular wall.

A number of major interactors have been already identified

1. A vascular endothelial growth factor (VEGF) is the most important heparin-binding glycoprotein that is secreted by most types of cells, except the endothelial cells themselves. It is able to induce angiogenesis and plays a central role in regulation of proliferation and differentiation of endothelial cells. Fife isoforms of VEGF are secreted by growing cells – VEGF-A, VEGF-B, VEGF-C, VEGF-D, PLGE, and three specific receptors on the endothelial basal membrane facilitate their function: a) FLK-1 shows binding affinity to VEGF-B, b) FLT-1 binds with VEGF-A, c) FLT-4 is distinguished by binding with VEGF-C and D (Diagram 2). The VEGF-A and VEGF-B are directly involved into formation of arterial vessels, while VEGF C and D facilitate the establishment of the venous and lymphatic channels.

2. Protein tyrosine kinase 7 (PTK7) is a pseudokinase expressed in several types of vascular EC. The research of Hyung Lee et al (2011) revealed that this substance plays the crucial role in activation of ECs by triggering the phosphorylation of FLT-1 and induces DNA synthesis and cell proliferation amplifying the angiogenic response (Diagram 2). However, the PTK7-FLT1 binding requires availability of the VEGF-A in the extracellular matrix.

3. Forkhead box C1 (Foxc1) is a protein encoded by the same named gene. The role of the Foxc1 gene in the early stage of vascular formation in the telencephalon was examined by Prasitsak et al, who found that mutation or knocking-down of Foxc1 gene leads to an increase in density of the EC basal membrane and widening of the area of IV collagen deposition around it. The Foxc1 was suggested to be involved into stabilization of the integrity of endothelial BM and control over sprout formation.

4. Netrin-1 is another protein (NTN1 gene) related to the maintenance of the stability of the vascular basal membrane. Cirulli V. et al have suggested that it might function as a guidance cue for endothelial cells during angiogenesis by limiting excessive lateral filopodia extensions from the endothelial tip cells. Additionally, netrin-1 inhibits the excessive branching of blood vessels by binding with the Unc-5 Netrin Receptor B (UNC5B) and facilitates magistralization of the developing vessels.

5. A peptid, Apelin (Apln), binds with G-protein coupled angiotensin receptor like 1b (AGTRL 1b) and triggers the emerging of tip cells, sprouting, and growth of filopodia. It takes a central role in the origin of segmental vessels from the dorsal aorta and their normal growth. The knock-down of the Apln gene in experiments led to the failure of the formation of dorsal longitudinal anastomotic vessels. Possibly, the localization of AGTRL 1b receptors in the EC basal membrane determines the locus of origin of the segmental vessels. That might illuminate the nature of variable origins and double-origins of the vessels with metamorphic roots such as in our case.

6. Delta-like 4 (Dll4) protein binding with the specific Notch receptor also participates in the provoking of a primary sprouting from the dorsal aorta. Knocking-down of the Dll4 induced an arterial hyper-branching phenotype. Additionally, Notch-to-Notch activation via end-to-end contact of growing sprouts had inhibitory influence and limited angiogenesis (Diagram 2). In his experiment, Herpers R. observed an increased filopodic...
Diagram 2. The possible pathways of regulation of angiogenesis are schematically summarized into 6 steps: 1) Foxc1 ligand binds with FLK-1 transmembrane receptor inducing reduction of collagen IV deposition around the epithelial cell and thinning of the basal membrane; 2) PTK 7 interacts with the FLT-1 receptor triggering cell proliferation (VEGF-mediated reaction); 3) Dll4 binds with Notch receptor provoking primary sprouting of EC; 4) Apln ligand activates the Agtrl 1b receptor and triggers emerging of tip cells, sprouting and growth of filopodia; 5) Netrin-1 peptide guides the growing sprout by limiting of excessive lateral filopodia extension and extensive branching, the UNC5B-mediated process; 6) the mutual firing of Notch receptors located on tip cells of growing sprouts inhibits their growth. Abbreviations: EC – endothelial cell; BM – basal membrane; VEGF-A, B – vascular endothelial growth factors A and B isoforms; FLK-1 - fetal liver kinase 1; FLT-1 - fms-like tyrosine kinase 1; Notch – transmembrane receptor; Agtr1 b - angiotensin receptor like 1b; Foxc1 – forkhead box C1 peptide; PTK7 – protein tyrosine kinase 7; Dll4 – delta-like 4; Apln – apelin peptide.

behavior of the endothelial cells at the ventral base of a sprout even after formation of end-to-end anastomosis. The prolonged angiogenetic potential of the ventral cells of the sprout might be a source of extensive fusions between arterial segments in the mature vascular tree, for instance, the extensive fusion of A2 in our case.

Detecting of anomalous vascular patterns is the mandatory diagnostic goal for the planning of surgical and endovascular interventions on the vessels of the aortic arch and components of the anterior and posterior cerebral circulations. Thorough interpretation of the MRA images requires related professionals to have detailed knowledge of both typical and theoretically possible variants of vascular patterns. Thorough understanding of the phylogenetic and embryologic development of the cardiovascular system in aggregate with the genetic mechanisms of regulation of angiogenesis opens our minds toward the wisdom of vascular plasticity and variability.

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