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Risk Factors and Associated Diseases in the Case of Aneurysm Formation in Patients with Variants of the Circle of Willis

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Introduction

The circle of Willis (CoW) distributes and balances the cerebral blood flow, but only within normal conditions, in the case of a complete CoW, because of pressure equality between the main two elements composing it: the vertebro-basilar and internal carotid systems.

In the specialized literature, there are several articles reporting various variations of the PAW, defined as those changes that lead to the impossibility of this anastomotic structure to maintain an adequate flow at the cerebral level, namely: the lack of some of the vessels that compose this structure; the anomalous origin of some of the branches, found to be obviously different to the right and to the left of this structure [1]. Anatomical variations are generally represented by additional arteries and the presence of a smaller diameter of an artery compared to the contralateral artery [2].

In pathological cases (obstructions, ligatures, etc.), CoW demonstrates its ability to replace the deficient main vessel. The ideal circle, with all sides present and well-calibrated, has a remarkable capacity for filling, allowing normal survival even in the case of obstruction of three of the four arterial mains [3]. The numerous anatomical variants give its performance of filling a random character; therefore, its functional value is unpredictable, depending on its deformation mode (normal or damaged) as well as the caliber of the vessels that supply it.

The branches of the CoW that supply the diencephalon, the striatum, and the internal capsule are four as follows:

- antero-medial branches, which derive from the Anterior Communicating Artery (AcoA) and Anterior Cerebral Artery (ACA) and enter the anterior perforated substance. It is distributed to the preoptic and supraoptic regions of the anterior hypothalamus;
- paired antero-lateral branches: distributed to the striated body and internal capsule;
- postero-medial branches: derived from Posterior Communicating Artery (PcoA) and Posterior Cerebral Artery (PCA);
- paired postero-lateral branches, which are distributed to the caudal part of the thalamus, geniculate bodies, and lateral thalamic nuclei and derive from the PCA [4].

In the presence of cerebrovascular risk factors such as grade 3 hypertension with very high additional risk, systemic atherosclerosis, insulin-requiring type 2 diabetes, associated with at least one anatomical variant of the posterior part of CoW or hypoplasia of the vertebral artery, regional cerebral hypoperfusion can occur, resulting in stroke in either the anterior or posterior circulation [5].

Material and Methods

There was made a research of medical data from articles written in the last 20 years from several international medical libraries and databases, such as Google Scholar and PubMed. There were used the following keyword combinations: "intracranial aneurysm, circle of Willis, variants" and " risk factors, circle of Willis, aneurysm." Out of a total of 50 abstracts related to our topic, there were selected only 19 most relevant full articles published between 2003 and 2023. Thus, there was realized a descriptive review on the topic of risk factors and associated diseases related to the formation of aneurysms in patients with anatomical variants of the circle of Willis.

Results

The interrelation between variants of the CoW and the formation of intracranial aneurysms

In a study conducted in Brazil on 221 brains preserved in alcohol, Suemoto et al. (2008) also found more anatomical variations in the posterior part of the CoW compared to its anterior part [6]. Nordon and Rodrigues Júnior (2012) identified, on a number of 50 brains, CoW variations in the anterior part of the CoW in percentage of 11.5% and in the posterior part 8 times more (88.5%).

Raghavendra et al. (2014), in an Indian study, found more variation in CoW on the right side than on the left side [7]. Likewise, Nordon and Rodrigues Júnior (2012), in Brazil, in an autopsy study on 50 fresh brains, found only 40.3% abnormalities on the left side of CoW and 59.7% on its right side.

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The anterior communicating artery (ACoA) and two anterior cerebral arteries (ACA) form the anterior communicating artery complex (ACAC), which consists of an A1 segment (from the internal carotid artery to the ACoA), an A2 segment (which extends from the ACoA), and an A3 segment.

Other authors performed univariate and multivariate analyzes of ACoA aneurysms and identified that the risk of ACoA aneurysm formation is determined by several independent clinical, morphological, and hemodynamic factors. Kaspera et al. (2014) showed that smoking, hypertension, asymmetry of A1 segments, angle between A1 and A2 segments, diameter of A1 segment, Mv (mean velocity), PI (Pulsatility Index) and VFR (volume flow rate) in the A1 segment were found to be significantly associated with the presence of ACoA aneurysms on univariate analysis, but the strongest independent risk factors include smoking, asymmetry of A1 segments >40%, low blood flow pulsatility, and angle between A1 and A2 segments ≤100°.

Hashimoto showed that increased blood flow due to experimentally induced hypertension results in the formation of aneurysms in the collateral circulation pathways.

Hemodynamic stress results in degeneration of the internal elastic lamina, followed by thinning of the muscle media due to a decrease in medial smooth muscle cells. Cigarette smoke induces an endothelial inflammatory response and proinflammatory phenotypic modulation of vascular smooth muscle cells, and subsequent aneurysm formation. Hemodynamic forces, particularly wall shearing, play a crucial role in initiating cerebral aneurysm formation [8-10].

Stojanović et al. (2019) investigated a group of 114 patients treated surgically for unruptured cerebral aneurysms and a group of 56 autopsied subjects. Asymmetry of the polygon of Willis was identified in the group of subjects treated surgically. Changes such as A1 hypoplasia or aplasia leading to asymmetry of the circle of Willis directly affect the possibility of cerebral aneurysm rupture [11].

The ACA is a terminal branch of the internal carotid artery and forms the anterior component of the PAW together with the ACoA. It supplies blood to the orbital-frontal and medial hemispheric portions of the brain, including the paracentral lobe and the outer superior band of the frontal lobe. The A1 segment hypoplasia is an uncommon fetal variant of PAW. The frequency of this congenital variation is 1-13%, as derived from angiograms and autopsy reports in various experimental studies [12]. Among all ischemic strokes, strokes in the territory of the ACA constitute only 0.6-3% and are correlated with anatomical variations of the A1 segment of the ACA. The most common abnormalities of the ACA are agenesis, hypoplasia, and duplication, also as we identified, to which we added the fenestration, longer length, and tortuous course of the ACA.

The A1 segment of the ACA is a major supplier of anterior collateral blood flow. This segment is also a source for numerous penetrating striatal arteries that supply the anterior hypothalamus, the septum pellucidum, and the anterior and inferior portions of the striatum.

In general, most hypoplastic or aplastic A1 segments of ACAs are asymptomatic and not directly related to any particular neurological disease, but may cause insufficiency of inter-or intra-hemispheric collateral circulation, which may represent an increased risk of cerebral stroke in the area irrigated by the normal ACA.

It appears that A1 segment hypoplasia in the pediatric population is predominantly associated with headaches and dizziness, which may play a role in the incidence of neurological disease later in life. The mechanism of these symptoms may be represented by progressive cerebral ischemia [13].

In general, arterial "fenestration" is described if the cerebral artery is doubled in one part of its trunk into two independent channels, which have their own tunica intima and tunica media, and sometimes even a tunica adventitia, and after the appropriate course, these channels reform the original artery. Fenestration of the A1 segment may occur due to the absence of fusion of the primitive plexiform anastomosis between the ACA and the primitive olfactory artery, normally present at the 18-43 mm embryonic stage.

Consequently, insufficient ACA development may increase blood flow in one of the A1 segments due to possible A1 hypoplasia or A1 aplasia on the opposite side and result in increased hemodynamic stress and tunica media defects at the ipsilateral A1 bifurcation or fenestration, and finally in the formation of an aneurysm.

Some findings on ACA fenestrations in the specialty literature have indicated controversy regarding their pathophysiological and clinical significance. Some have shown that ACA fenestration causes ACA aneurysms; others have not found fenestration of the A1segment to be associated with ischemic stroke, nor are they "weak points" for aneurysm development, especially if the caliber of the ACA does not vary in its different parts [14].

On the other hand, the ACoA, as an unpaired artery on the midline of the base of the brain, is characterized by the appearance of multiple fenestrations or duplications, but these variants have not been associated with cerebrovascular diseases.

The association of aneurysms with CoW showing variations at the level of the component arteries is well documented. Kapoor et al. (2008) found intracranial saccular aneurysms in 10% of the 100 CoW analyzed [15].

However, there are also reports of higher percentages of the presence of an aneurysm at the CoW level, especially when analyzing patients with subarachnoid hemorrhage. Siddiqi, Ansar, and Fasih (2013) found an incidence of aneurysms at the CoW level in a high percentage (20.3%). The respective authors suggested that variants of the CoW are statistically more frequently associated with aneurysm formation. The configuration of this primary collateral pathway is a major risk factor for circulatory impairment during acute hemodynamic change. There is a well-defined correlation between asymmetric proximal segments of the anterior cerebral arteries and aneurysms of the anterior communicating artery. A statistically significant relationship is found between asymmetric posterior communicating arteries and the development of aneurysms at the junction of the internal carotid arteries with the posterior communicating arteries due to the hemodynamic stress determined by these variations of CoW [16].

Classification of anatomical variants of the CoW

In recent years, with the help of angiographic investigations, it has been found that the most common variation found in the CoW would be the AcoA duplication (10% of subjects), but it could also be ACoA hypoplasia, fenestration, or an artery with an oblique trajectory. The rarest are the plexiform pattern (3%) and triplication of ACoA (1%). The plexiform variant is considered as incomplete regression of embryonic ACoA, and hypoplasia or aplasia is considered as abnormal regression of ACoA (Niederberger et al., 2010). As an anomaly, the absence of ACoA is described [17].

Other cerebrovascular or medical pathologies associated with variants of the circle of Willis

There are very few studies that have analyzed the causes of death in patients with variations in the CoW. Nordon and Rodrigues Júnior (2012) first reported respiratory failure caused by pneumonia, bronchopneumonia, pulmonary collapse, and pulmonary edema. In the studies, heart failure was located at the second site and included: acute myocardial infarction, dilated cardiomyopathy, chronic pulmonary heart caused by pulmonary embolism. In the third place, in their study, the above authors identified septic or ischemic shock.

The hemorrhagic vascular accident has as a possible mechanism on the pathological changes in the arterial walls at the CoW level determined by both hypertension and atherosclerosis and diabetes, which led to the rupture of the walls in the presence of anatomical variants that no longer allowed the functioning of the PAW as an arterial system of anastomosis type.

In acute pancreatitis, pancreatic enzymes are released (trypsin, pancreatic elastase) that pass into the blood due to pancreatic injury. Trypsin causes direct organ damage, such as cardiac necrosis and electrical disturbances, and elastase leads to a temporary hypercoagulable state inducing platelet dysfunction and increased clotting factors such as fibrinogen and factor VIII. Thus, pancreatitis is associated with arterial and venous thrombosis, including at the level of cerebral vessels [18], which represents an important risk factor in the presence of one or more anatomical variants at the PAW level. Acute pancreatitis can also cause a pancreatic metabolic encephalopathy, but also a fatal intracerebral haematoma [19].

There is also a great heterogeneity of clinical manifestations of anatomical variants at CoW level because they are correlated not only with the type of variants, but also with the risk factors that each patient has. The most significant risk factors are atherosclerosis (ATS) and hypertension, to which is added insulin-requiring type II diabetes, which extends the effect of the first two risk factors. To these, there are added liver cirrhosis and drug coagulopathy, which contribute also in the occurrence of hemorrhagic stroke, as well as acute hemorrhagic pancreatitis, which, by inducing hypercoagulability status, causes ischemic stroke even in patients with a single anatomical variant, regardless of their age.

Disseminated intravascular coagulation (DIC) associated with ischemic stroke is a rare phenomenon and as a pathological syndrome belonging to the group of thrombo-hemorrhagic disorders, it causes a series of changes in the arterial and venous system of the entire body, including at the level of cerebral structures [20].

The causes of DIC are numerous, as are its clinical manifestations. The mechanism of occurrence of cerebral strokes, either ischemic or hemorrhagic, located in the cerebral hemispheres, in the situation where they have DIC as cause, unfolds along three stages. Hypercoagulation occurs first, then incomplete consumption coagulopathy, and later marked consumption coagulopathy [21].

There are studies that mention the presence of a coagulopathy of the DIC type that can occur in patients with advanced gastric cancer and metastatic disease, which in the conditions of an anatomical variant of CoW can lead to the occurrence of a stroke, especially if other risk factors such as ATS and/or hypertension are added [22,23].

Mukherjee et al. (2018) suggest that the presence of anatomical variants at the level of the CoW may impact the trajectory of microemboli and thereby lead to infarcts in more unusual, distal areas of the brain [24]. Hypoplastic arteries are the most common anatomical variants of PAW seen in adults. The significance of these variants has not yet been fully validated in population-based studies, but autopsy series have shown that hypoplastic arteries are more common in patients who have had cerebral infarctions. Hypoplastic arteries have a patent lumen so that in the absence of stenosis of the proximal large arteries, the communicating arteries do not appear to affect the final volume of blood flow to the brain unless there are risk factors such as hypertension, ATS, type II insulin-requiring type 2 diabetes, acute hemorrhagic pancreatitis, liver cirrhosis or disseminated intravascular coagulopathy.

However, in the context of large artery occlusion or severe stenosis, communicating arteries become crucial. In this context, the caliber of the communicating arteries is inversely proportional to the risk of stroke, because the smaller these communicating arteries are, the lower the ability to compensate for reduced or lost flow will be. Although hypoplastic arteries can be found at birth, there is an increasing prevalence of hypoplastic arteries with age and in association with ischemic heart disease, suggesting that some hypoplastic arteries in adults may undergo hypotrophic wall remodeling, possibly in the context of vascular disease [25]. The clinical significance of the anatomical variants of CoW is revealed especially in the case of an atypical stroke model.

Conclusion

The awareness given towards the correct knowledge of the variants in the CoW becomes important for specialists in surgery, internal medicine, paediatrics and general practitioners. For neurosurgeons managing aneurysms, understanding the variations in the CoW anatomy is essential. In addition, knowing their prevalence may also be of real importance. Considering, for example, that the prevalence of PCoA hypoplasia is high, either unilaterally or bilaterally, in the case of a treatment modality applied to an intracranial aneurysm that involves sacrificing one of the PCoAs or relies on one or both PCoAs to ensure collateral circulation throughout the procedure, it would be extremely useful to know the probability of existence of the anatomical variant. It would allow a surgeon to assess the risk of a particular approach and consider the need for an alternative approach once the patient is undergoing surgery. Based on the data obtained so far, which emphasize that PCoA hypoplasia is the most common anatomic variant at the level of the posterior part of the CoW, the neurosurgeons can plan the surgical procedures in order to find an alternative approach that would less disrupt blood supply to the brain. Patients with bilateral paramedian thalamic lesions without other lesions outside the thalamus are more likely to have hypoplastic P1 segments or unilateral or bilateral absences.

Understanding the anatomy of the most common variations and their prevalence can help us predict the likelihood of patients suffering a cerebral stroke and which regions are likely to be affected. In the absence of traditional risk factors for stroke, such as high blood pressure, type 2 Diabetes, dyslipidemia, sedentary lifestyle or smoking, it would be indicated to consider whether an anatomic variation of the CoW is the causative factor.

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