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Article

Influence of Circle of Willis Configuration on the Rupture of Cerebral Aneurysms

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Abstract: ***Background:*** Formation and rupture of cerebral aneurysms may be related to certain types of configuration of the circle of Willis. Analysis of their interdependence can be of great importance. *Methods:* A group of 114 patients treated operatively for the cerebral aneurysm rupture and a group of 56 autopsied subjects were involved in the study. Four basic types of the circle of Willis configurations were formed–two symmetric types A and C, and two asymmetric types B and D. *Results:* A statistically significantly higher presence of asymmetry of the circle of Willis in the group of surgically treated subjects ($p=0.006$) with a significant presence of asymmetric Type B in this group ($p=0.017$) were determined. The presence of changes in the A1 segment in the group of subjects with solitary aneurysms on the anterior communicating artery showed a statistically significant presence in the group of autopsied subjects ($p=0.0004$). Analyzing the presence of symmetry of the circle of Willis between the two groups, that is, the total presence of symmetric types A and C indicated their statistically significant presence in the group of autopsied patients ($p=0.043$). *Conclusion:* Changes such as hypoplasia or aplasia of A1 and the resulting asymmetry of the circle of Willis directly affect the possibility of the rupture of cerebral aneurysms. Detection of the corresponding types of the circle of Willis after diagnostic examination can be the basis for the development of a protocol for monitoring such patients.

Keywords: Cerebral aneurysms; circle of Willis

1. Introduction

Intracranial aneurysms are on average asymptomatic until the moment of rupture. Intracranial hemorrhage caused by aneurysm rupture occurs in almost 10% [1,2]. However, the presence of cerebral aneurysms is much more common and ranges between 3.6-9% depending on the series [3-7].From these data it is clear that there is a big difference between the incidence of cerebral aneurysms and frequency of their rupture. All this leads us to think about the causes of cerebral aneurysm rupture.

Locations of cerebral aneurysms are typically the sites of arterial junctions on the blood vessels of the base of the brain. The interconnected blood vessels at the base of the brain form a specific ring-like configuration, named after Willis who first described them. There are various forms of interconnected blood vessels within the circle of Willis itself [8]. The perfusion characteristics of each configuration of the circle of Willis directly depend on its anatomical characteristics i.e. the presence of normoplastic, hypoplastic or aplastic parts [9,10]. Basically, all configurations of the circle of Willis can be divided into symmetric and asymmetric. Connecting the appropriate circle of Willis configurations with its perfusion characteristics can indicate which configuration has an

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increased perfusion load in certain parts [11,12]. This plays a key role in understanding the hemodynamic mechanism for the creation and rupture of cerebral aneurysms.

Linking the presence of aneurysmal changes with the corresponding configuration of the circulation ring at the base of the brain can indicate the predisposition of some types of configurations for the formation and rupture of cerebral aneurysms. An analysis of their association can be very important for making the right decisions on therapeutic approaches and monitoring of unruptured cerebral aneurysms.

2. Material and methods

The presence of morphological variations in the blood vessels of the base of the brain was monitoredin two groups of subjects. The first group was made up of 114 patients who underwent surgical treatment for ruptured aneurysmal changes in the cerebral blood vessels. The second group was formed from 56 subjects who were subjected to autopsy after a fatal outcome that was not caused by hemorrhagic intracranial disease.

The subjects in the first group were subjected to MSCT and angiographic imaging of the cerebral blood vessels. A preoperative analysis of angiographic images was made and the existence of corresponding configurations of the circle of Willis was established. A dominant flow was determined in relation to the position of aneurysm. The corresponding blood vessel diameters were compared to the symmetric blood vessel diameters on the opposite side. Reduction of the blood vessel diameter by 1/3 to 2/3 in relation to the diameter of the blood vessel on the opposite side was marked as hypoplasia, and a decrease in the blood vessel diameter below 1/3 of the thickness of the opposite vessel was marked as pronounced hypoplasia. The presence of hypoplasia determined the symmetry or asymmetry of the circle of Willis. Intraoperatively, the relationship between visualized parts of the circle of Willis and aneurysm was analyzed, and then compared with the angiographic finding.

The second group consisted of subjects who underwent clinical or postmortem autopsy and who did not die due to some intracranial haemorrhagic disease. The subjects were selected by random sample method. During the autopsy, the brain was taken out from the cranial fossa together with the blood vessels of the base of the skull using a precise technique, and those at the entrance to the cranial cavity were resected. By precise preparation all blood vessels were separated from the base of the brain and distributed on a homogeneous flat surface with the formation of the typical configuration of the circle of Willis. The thickness of the blood vessels, the presence of anomalities, their arrangement and the symmetry of the present changes were observed. After suchpreparation, the circles of Willis were photographed by a digital camera, and then analyzed on a computer for a possible update of the original finding (Figure1).

For the purpose of comparing and analyzing the presence of the corresponding configurationsof the circle of Willis, 4 basic types of configuration and one sub-type were formed.

Type A represents a symmetric circle of Willis with different variations at the level of the anterior communicating artery (ACoA).

Type B is an asymmetric circle of Willis with hypoplasia/aplasia of the A1 segment of the anterior cerebral artery (ACA).

Type C represents a symmetric circle of Willis with varying degrees of the hypoplasia/aplasia of the posterior communicating artery (PCoA) bilaterally, or the presence of a bilateral fetal PCoA type.

Type D is an asymmetric circle of Willis with single-sided PCoA hypoplasia or a single-sided fetal PCoA type

Subtype B/D represents an asymmetric circle of Willis with hypoplasia/aplasia of the A1 segment of the anterior cerebral artery, in combination with changes in the posterior segment (due to hypoplasia of PCoA or PCA)(Figure 2).

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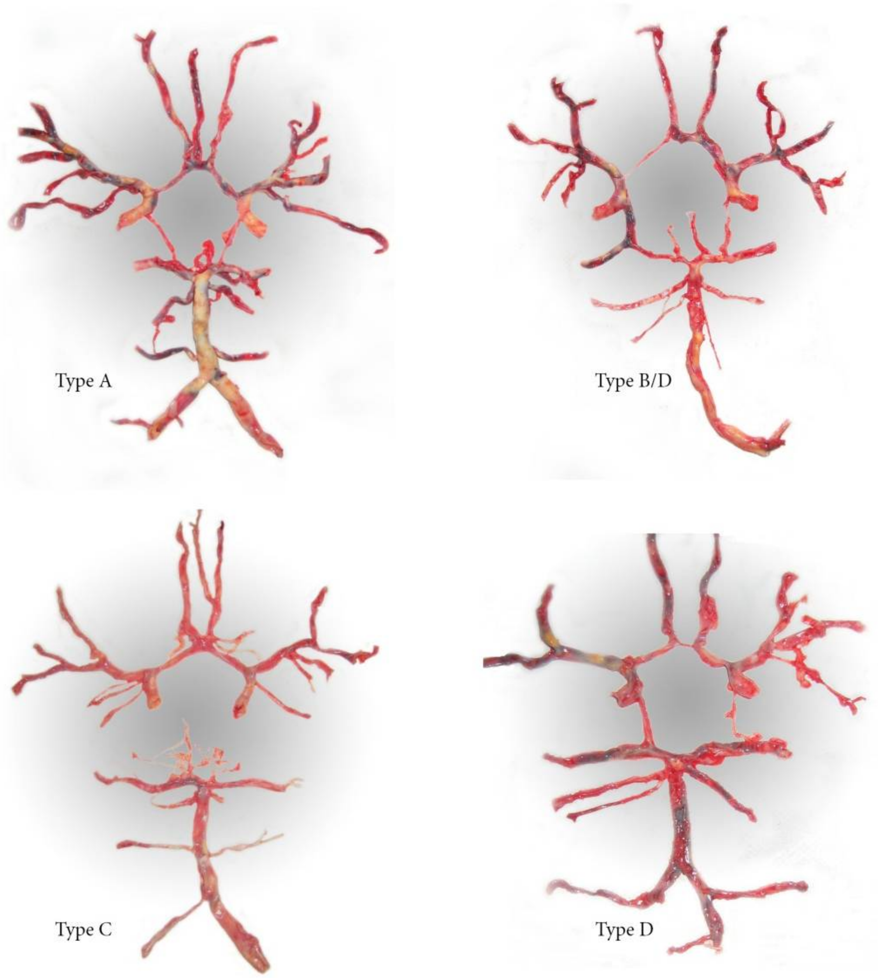

94
95 **Figure 1.**Preparations of the circle of Willis
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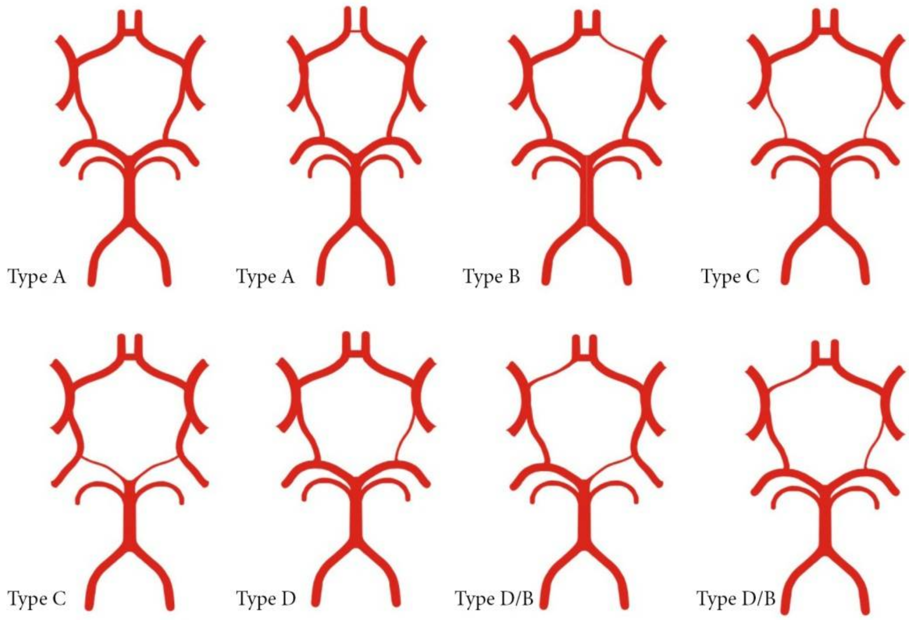

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99 Figure 2.Basic types of configurationof the circle of Willis.

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The study complies with the Declaration of Helsinki. The study protocol (No CLI-1000) form was approved by the Ethics Committee of the Clinical Center Niš, Serbia (01-2016-03). The autopsies were done in accordance with the health care law and the bylaws of the Ministry of Health. The patients undergoing surgery gave verbal consent that the results of their angiographic recording and surgery findings can be used in the study.

Statistical Analysis

All the findings were numerically processed, tabulated and subjected to statistical analysis of the existing differences between the groups. Student's t-test was used (if there was a normal distribution of frequencies within the group) or non-parametric Mann-Whitney Rank Sum Test, if the frequency distribution was unequal. A p-value of <0.05 was selected as statistically significant.

3. Results

In the group of autopsied patients, there was a total of 15 (26.8%) asymmetries of the circle of Willis, while 73 (64%) of asymmetric configurations were found in the group of surgically treated patients. Of these, 9(16%) findings were with asymmetry due to changes in the anterior segment of the autopsied patients, while in surgically treated subjects the asymmetry of the anterior segment was found in 50 (43.9%) cases. The incidence of asymmetry in the group with multiple aneurysms is somewhat higher than in the group with solitary aneurysms (Table 1,2).

Table 1. Configuration of the circle of Willis – the group of autopsied patients.

Configuration of the circle of Willis			**Σ**
Symmetric Willis			**41(73.2%)**
Asymmetric Willis	Changes in the A1 segment	**9**(16%)	15(26.8%)
Asymmetric Willis -	Changes in the posterior segment	6(10.8%)	
Σ			56(100%)

Table 2. Configuration of the circle of Willis – the group of surgically treated patients.

	Asymmetric Willis		**Symmetric Willis**	**Σ**
	Changes in the A1 segment	Other changes		
Solitary aneurysms	**33**	15	33	81
Multiple aneurysms	**17**	8	8	33
	50 (43.9%)	23(20.1%)		
Σ	73 (64%)		**41(36%)**	114(100%)

By comparing the presence of asymmetry of the circle of Willis among the groups, the significantly higher presence of asymmetry was determined in the group of surgically treated subjects (p=0.006). The presence of changes in the A1 segment in the group of subjects with solitary aneurysms on the anterior communicating artery showed a statistically significant presence in the group of autopsied patients (p=0.0004).

In the group of surgically treated patients there were 23 (20.2%) changes in the posterior segment in terms of unilateral hypoplasia or fetal type PCoA, and 6 (10.8%) changes in the posterior segment were present in the group of autopsied subjects. By comparing the relationship between the representation of changes in the posterior segment and PCoA and its impact on the occurrence of asymmetry of the circle of Willis, no statistically difference was found between thegroup of subjects undergoing surgery and the group of autopsied subjects.

The presence of the corresponding configurations of the circle of Willis in the group of autopsied patients is shown in Table 3.

Table 3. Types of configuration the circle of Willis – the group of autopsied subjects.

Type Circle of Willis		
Type A	27	(48.2%)
Type B	4	(16%)
sub type B/D	5	
Type C	14	(25%)
Type D	6	(10.8%)
Σ	56	(100%)

The presence of the corresponding types of the circle of Willis configuration was examined in the group of surgically treated patients with solitary aneurysms separately from patients with multiple aneurysms (Table 4,5).

Table 4. Types circle of Willis configuration – group of patients with solitary aneurysms.

Type Willis	Locations of ruptured solitary aneurysms						**Σ**
	ACoA	MCA	ICA	PCoA	perA	VBA	
Type A	9	5	2	2	1	1	20(24.7%)
Type B	24	3	2	/	3	/	34(42%)
subtype B/D	/	/	/	2	/	/	
Type C	/	8	2	2	/	1	13(16%)
Type D	/	/4	24	6	/	/	14(17.3%)
Σ	33	20	10	12	4	2	81(100%)

ACoA-anterior communicative artery, MCA-medial cerebral artery, ICA-internal carotid artery
PCoA- posterior communicative artery, perA-pericalosis artery, VB-vertbrobasilar artery

Comparison of the presence of symmetric Type A in the group of autopsied patients and in the group of patients with solitary aneurysms shows that there is a statistically significant presence of symmetric Type A in the group of autopsied subjects (p=0.048). Statistical differences in the presence of symmetric Type C between the groups of surgically treated and autopsied subjects were not found. Analyzing the presence of symmetry of the circle of Willis between the groups, i.e., total presence of symmetric types A and C, indicated their statistically significant presence in the group of autopsied patients (p=0.043).

The presence of asymmetric Type B is significantly higher in the group of surgically treated patients with solitary aneurysms (p=0.017). A statistically significant presence of asymmetric Type B compared to the group of autopsied subjects was seen by observing the entire group of patients undergoing surgery. (p=0.009)

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The presence of asymmetric Type D did not show any statistical differences between the groups.

Table 5. Circle of Willis configuration types – group of patients with multiple aneurysms.

Types Willis	Multiple aneurysms Locations of ruptured aneurysms						**Σ**
	ACoA	MCA	ICA	PCoA	perA	VBA	
Type A	/	3	1	1	/	/	5(15.2%)
Type B	12	/	3	/	/	/	17(51.5%)
Sub type B/D	/	/	/	2	/	/	
Type C	/	1	2	/	/	/	3(9%)
Type D	/	6	/	2	/	/	8(24.3%)
Σ	12	10	6	5			33(100%)

ACoA-anterior communicative artery, MCA-medial cerebral artery, ICA-internal carotid artery
PCoA- posterior communicative artery, perA-pericalosis artery, VBA-vertbrobasilar artery

In the group of patients with multiple aneurysms there was a greater presence of asymmetric Type B than in the group with solitary aneurysms, but without statistical significance (Table4,5).

The presence of asymmetric type B in the group of patients operated on was observed in 50 (43.9%) patients. Of these, 31 (62%) patients were with right-sided hypoplasia of the A1 segment, and 19 (38%) with left-sided A1 hypoplasia. Thirty-six (72%) ruptured aneurysms which were associated with hypoplasia of the A1 segment were localized on the ACoA. If we consider only the correlation between A1 hypoplasia and rupture of the aneurysm on AcoA, it can be seen that 70% of cases show the presence of right-sided hypoplasia (Table 6). Fourteen (28%) ruptured aneurysms associated with A1 hypoplasia were at other locations (MCA, ICA, PCoA, perA), with 12 of them being positioned on the side of the hypoplastic segment.

Table 6. Correlation between hypoplasia of A1 and location of the ruptured aneurysm.

Locations rupturedaneurysms	**Hypoplysia A1 right**	**Hypoplysia A1 left**	**Σ**
ACoA	25	11	36(72%)
MCA	1	2	3(6%)
ICA	1	4	5(10%)
PCoA	2	1	3(6%)
perA	2	1	3(6%)
Σ	31(62%)	19(38%)	50(100%)

ACoA-anterior communicative artery, MCA-medial cerebral artery, ICA-internal carotid artery
PCoA- posterior communicative artery, perA-pericalosis artery

In the group of 114 surgically treated patients, the presence of right-sided A1 hypoplasia was recorded in 27.2% (31) of patients, and of left-sided hypoplasia in 16.7% (19), while in the group of 56 autopsied subjects 4 (7.1%) were with left-sided hypoplasia of the A1 segment and 5 (8.9%) with

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right-sided hypoplasia. By comparing these findings, we obtained statistically significant representation of A1 segment hypoplasia in the group of patients undergoing surgery compared to the group of autopsied patients (p = 0.027).

4. Discussion

Our results suggest that asymmetric configuration of the circle of Willis was much more frequent in the patients operated on after the rupture of an aneurysm than in subjects from autopsy. In addition, it has been established that there is a statistically significant presence of hypoplasticchanges on the A1 segment in the group of patients undergoing surgery, which correlates with other studies [13-15]. The obtained results on the high prevalence of type B configuration with A1 segment hypoplasia in the ruptured aneurysm group indicate its high haemodynamic instability. In addition, the type B configuration is in the greatest correlation with the rupture of aneurysm on AcoA.

This finding clearly indicates that the morphological characteristics of the type of hypoplasia or aplasia in the anterior segment lead to an increase in blood flow from the opposite side, and a compensatory increase in flow through ACoA [9,16]. Increasing intramural pressure on the connective parts of the ACoA complex can initiate the process of remodeling the blood vessel resulting in the formation of an aneurysmal sac and then to its rupture[17].

Unlike the anterior segment, changes in the posterior segment of the circle of Willis have not shown significant association with the formation of cerebral aneurysms. During embryogenesis and with the development and differentiation of the carotid and basilar basin, the posterior communicating artery has a tendency for regression and decrease of blood flow[18]. Its functioning at the level of zero flow [19] indicates that stress at its exit from the carotid artery is not caused by blood redistribution, but by other haemodynamic disorders. This is also suggested by the fact that despite identical characteristics of the PCoA junction with ICA and PCA, aneurysms occur primarily on the carotid portion of PCoA. The dependence of the formation of aneurysms on PCoA from hemodynamic relationships in the ICA itself is clearly noticed in cases of the fetal type of the PCoA, the existence of which has not shown significant association with the formation of aneurysms. If we observe the point of separation of PCoA in relation to ICA, as a point of bifurcation angle, then we can apply the principle of optimal distribution of flow for the given angle [10]. Any increase in this angle leads to a direct increase in stress on the site of separation of PcoA, so that the formation of aneurysm on PcoA is due to the geometry itself and the course the ICA takes in that part of PcoA [20,21].

The significant prevalence of symmetric Type A in the group of autopsied subjects (in correlation with other studies) [22,23] and the statistically significant presence of asymmetric Type B in the group of subjects operated on due to cerebral aneurysm rupture clearly points to the direct influence of the configuration of the circle of Willis on the formation and rupture of cerebral aneurysms.

The presence of C and D configurations in the tested groups did not show significant effect on the formation and rupture of cerebral aneurysms. All this indicates that the presence or absence of PCoA changes cannot be associated with the onset or rupture of cerebral aneurysms.

The significant presence of the right-sided hypoplastic A1 in the group of patients undergoing surgery is interesting. The tendency of the types B and D to right-sided positioning of the morphological variants of A1 segment can be considered as part of the embryologic development of the vascular network and perfusion needs of the corresponding brain hemispheres.

Rupture of an aneurysm on MCA, ICA, PCoA perA, with the presence of the B type configuration (hypopasia of A1), was in 90% on the side of the hypoplastic segment. This in turn indicates that the flow through the ICA and MCA on the side of hypoplasia has been significantly increased due to reduced flow through the hypoplastic A1.

In an experimental study with rabbits Ersin et al. demonstrated the hemodynamic effect of increased perfusion requirements in the formation of aneurysms [24], and Guangyu Zhu and al.

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pointed to the significance of collateral circulation within the various anatomical variations of the circle of Willis [16].Ren and al. mathematically proved the influence of different anatomical variations as well as their perfusion characteristics [25]. Just like in our study, in a study conducted by Rojj et al. the configuration of the circle of Willis was identified as a risk factor for the rupture of cerebral aneurysm, suggesting that ruptures are also influenced by the direction of blood flow and the shape of aneurysms[28].

All this demonstrates that the hemodynamic load of asymmetric configurations directly influences the development of the process of remodeling certain parts towards achieving the appropriate perfusion, which can also affect the formation of cerebral aneurysms. Basically, asymmetric configuration has increased perfusion requirements in certain parts, which in turn can lead to the process of blood vessel remodeling in the part of permanent increase of the perfusion flow. Remodeling can be directed towards achieving an appropriate expansion of collateral circulation and achieving appropriate perfusion while reducing existing stress in the area of the burdened parts. Any further increase in perfusion requirements can lead to the continuation of the cascade of remodeling the blood vessel wall towards dilatation at the site of the greatest stress and to the gradual formation of an aneurysmal sac.

5. Conlusion

Asymmetric configuration basically has increased perfusion requirements in certain parts, which in turn can initiate the process of blood vessel remodeling in the part of permanent increased perfusion flow. Remodeling can be directed towards achieving an appropriate expansion of collateral circulation and achieving the appropriate perfusion, while reducing the existing stress in the area of the loaded parts. Any further increase in perfusion requirements can lead to the continuation of the cascade of remodeling the blood vessel wall in the direction of dilatation at the site of the greatest stress and to the gradual formation of an aneurysmal sac, followed by its rupture

Hypoplasia of the A1 segment entails significantly disturbed perfusion relationships in the AcomA area and the stress burden of the junction angle between A1 and A2, which in turn prompts the formation of an aneurysmal sac. In addition, there is a high correlation of AcoA aneurysm rupture with the asymmetric circle of Willis configuration

Formation of the basic circle of Willis configuration types and association with their susceptibility to cerebral aneurysm rupture can be used to make a protocol for monitoring unruptured aneurysms that are detected after MSCT or NMR angiography.

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