

*Harizi (Shemsi) E, Rroji A, Cekaj E, Gabrani S. Anatomical variations of the circle of Willis and cerebrovascular accidents in transitional Albania (Original research). SEEJPH 2014, posted: 20 December 2014. DOI 10.12908/SEEJPH-2014-35*

## **ORIGINAL RESEARCH**

### **Anatomical variations of the circle of Willis and cerebrovascular accidents in transitional Albania**

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### Abstract

**Aim:** The purpose of this study was twofold: i) in a case-control design, to determine the relationship between anatomical variations of the circle of Willis and cerebrovascular accidents; ii) to assess the association between anatomical variations of the circle of Willis and aneurisms among patients with subarachnoid hemorrhage.

**Methods:** A case-control study was conducted in Albania in 2013-2014, including 100 patients with subarachnoid hemorrhage and 100 controls (individuals without cerebrovascular accidents). Patients with subarachnoid hemorrhage underwent a CT angiography procedure, whereas individuals in the control group underwent a magnetic resonance angiography procedure. Binary logistic regression was used to assess the association between cerebrovascular accidents and the anatomical variations of the circle of Willis. Conversely, Fisher's exact test was used to compare the prevalence of aneurisms between subarachnoid hemorrhage patients with and without anatomical variations of the circle of Willis.

**Results:** Among patients, there were 22 (22%) cases with anatomical variations of the circle of Willis compared with 10 (10%) individuals in the control group ( $P=0.033$ ). There was no evidence of a statistically significant difference in the types of the anatomical variations of the circle of Willis between patients and controls ( $P=0.402$ ). In age- and-sex adjusted logistic regression models, there was evidence of a significant positive association between cerebrovascular accidents and the anatomical variations of the circle of Willis ( $OR=1.87$ ,  $95\%CI=1.03-4.68$ ,  $P=0.048$ ). Within the patients' group, of the 52 cases with aneurisms, there were 22 (42.3%) individuals with anatomical variations of the circle of Willis compared with no individuals with anatomical variations among the 48 patients without aneurisms ( $P<0.001$ ).

**Conclusion:** This study provides useful evidence on the association between anatomical variations of the circle of Willis and cerebrovascular accidents in transitional Albania. Furthermore, findings from this study confirm the role of the anatomical variations of the circle of Willis in the occurrence of cerebral aneurisms.

**Keywords:** Albania, aneurism, cerebrovascular accidents, circle of Willis, subarachnoid hemorrhage.

**Conflicts of interest:** none.

## Introduction

There is convincing evidence linking the anatomical variations of the circle of Willis with the development and harshness of cerebrovascular accidents including aneurysms, infarctions, or other vascular disorders which bear a significant negative health impact (1-3).

Normally, the circle of Willis consists of a symmetrical arterial circle, with a single anterior communicating artery and bilateral posterior communicating arteries (4-6). However, different types of anatomical variations of the circle of Willis have been described (1,4) including hypoplasia (of the posterior communicating artery, the circular part of the posterior cerebral artery, the circular part of the anterior cerebral artery, or the anterior communicating artery); accessory vessels (which are manifested as duplications or triplications of one of the components of the polygon); anomalous origin (persistence of the embryonic derivation of the posterior cerebral artery from the internal carotid); or absent vessels (of one or other posterior communicating arteries) (1,4).

Research has indicated that anatomical variations of the circle of Willis may be genetically determined and develop in early embryonic stage, persisting in postnatal life (1,7). In addition to development of cerebrovascular accidents, there has been suggested a possible link between the anomalies of the circle of Willis and mental illnesses and cerebrovascular catastrophe (1,8).

The available evidence about the prevalence and distribution of the anatomical variations of the circle of Willis in the adult population of Albania is scarce. After the collapse of the communist regime in early 1990s, Albania experienced a particularly rapid political and socioeconomic transition, which was associated with tremendous behavioral/lifestyle changes that have a significant health impact (9,10). Currently, almost twenty five years after the breakdown of its Stalinist regime, Albania remains one of the poorest countries in South Eastern Europe.

In this context, the aim of our study was twofold: i) in a case-control design, to determine the relationship between anatomical variations of the circle of Willis and cerebrovascular accidents; ii) to assess the association between anatomical variations of the circle of Willis and aneurisms among patients with subarachnoid hemorrhage.

## Methods

A case-control study was conducted in Albania in 2013-2014, including 100 patients with subarachnoid hemorrhage (hospitalized at the University Hospital Centre “Mother Teresa”) and 100 controls (individuals who showed up at the University Hospital Centre “Mother Teresa” without cerebrovascular accidents, but with signs of tension-type headache, or vertiginous syndrome).

All patients with subarachnoid hemorrhage underwent a CT angiography procedure. On the other hand, all individuals in the control group underwent a magnetic resonance angiography procedure either in Tirana, or at the Regional Hospital in Durres (second largest city in Albania). Based on these respective examinations, the presence of cerebrovascular accidents was determined, in addition to the presence and type of anatomical variation of the circle of Willis. Among patients with subarachnoid hemorrhage, the presence of aneurisms was additionally determined. Data on age and sex of participants were also collected.

Fisher’s exact test was used to compare the prevalence and types of anatomical variations between cases and controls, and the prevalence of aneurisms between subarachnoid hemorrhage patients with and without anatomical variations of the circle of Willis. Conversely, Mann-Whitney U-test was used to compare the age distribution between patients

and controls. Binary logistic regression was used to assess the association between cerebrovascular accidents and the anatomical variations of the circle of Willis. Odds ratios (ORs), their respective 95% confidence intervals (CIs) and p-values were calculated. Initially, crude (unadjusted) ORs were calculated. Subsequently, age- and-sex adjusted ORs were calculated in a simultaneous multivariable-adjusted logistic regression model. The overall goodness-of-fit of the multivariate model was formally assessed through the Hosmer-Lemeshow test. For all the statistical tests, a p-value of  $\leq 0.05$  was considered as statistically significant. Statistical Package for Social Sciences (SPSS, version 17.0) was used for all the data analyses.

## Results

Table 1 describes the demographic characteristics of the patients and controls included in this case-control study. Mean age was significantly higher among patients ( $53.4 \pm 9.8$  years) compared with the control group ( $36.8 \pm 12.6$  years) (Mann-Whitney U-test:  $P < 0.001$ ). There were 18 (18%) controls aged 50 years or older, compared with 47 (47%) individuals in the sample of patients. As for the sex distribution, 41 (41%) individuals in the control group were males and 59 (59%) were females, whereas in the sample of the patients there were 46 (46%) males and 54 (54%) females.

**Table 1. Demographic characteristics of the patients with subarachnoid hemorrhage and the control group**

Characteristic	Cases (N=100)	Controls (N=100)	P-value
<b>Age (years):</b>			
Mean (SD)	53.4±9.8	36.8±12.6	<0.001*
Median (interquartile range)	55.0 (8.0)	35.5 (20.0)	
Range	24-74	16-63	
<b>Age-group:</b>			
<50 years	53 (53.0) <sup>†</sup>	82 (82.0)	<0.001‡
≥50 years	47 (47.0)	18 (18.0)	
<b>Sex:</b>			
Male	46 (46.0)	41 (41.0)	0.568‡
Female	54 (54.0)	59 (59.0)	

\* Mann-Whitney U-test.

<sup>†</sup> Absolute numbers and column percentages (in parentheses).

<sup>‡</sup> Fisher's exact test.

Table 2 presents the anatomical variations of the circle of Willis in the sample of patients and in the control group. In the sample of the patients, there were 22 (22%) cases with anatomical variations of the circle of Willis compared with 10 (10%) individuals in the control group, with a statistically significant difference between the two groups (Fisher's exact test:  $P = 0.033$ ). In the sample of patients with any type of anatomical variation (N=22), there were 10 (45.5%) cases with ACA (A1 segment) anomaly, 7 (31.8%) cases with A.Com.A. variation (anterior communicant artery), 3 (13.6%) case with P.Com.A. anomaly (posterior communicant artery) and 2 (9.1%) cases with PCA (P1 segment) variation. The distribution of these anomalies among individuals in the control group who presented any type of

anatomical variations of the circle of Willis (N=10) was as follows: 3 (30.0%), 2 (20.0%), 4 (40.0%) and 1 (10.0%), respectively – with no evidence of a statistically significant difference with the sample of the patients (Fisher’s exact test: P=0.402) (Table 2).

**Table 2. Anatomical variations of the circle of Willis in patients with subarachnoid hemorrhage and the control group**

Characteristic	Cases	Controls	P-value <sup>†</sup>
<b>Circle of Willis:</b>			
Normal	78 (78.0)*	90 (90.0)	0.033
Variation	22 (22.0)	10 (10.0)	
<i>Total</i>	<i>100 (100.0)</i>	<i>100 (100.0)</i>	
<b>Variation type:</b>			
ACA (A1 segment)	10 (45.5)	3 (30.0)	0.402
A.Com.A.	7 (31.8)	2 (20.0)	
P.Com.A.	3 (13.6)	4 (40.0)	
PCA (P1 segment)	2 (9.1)	1 (10.0)	
<i>Total</i>	<i>22 (100.0)</i>	<i>10 (100.0)</i>	

\* Absolute numbers and column percentages (in parentheses).

† Fisher’s exact test.

Table 3 presents the relationship between cerebrovascular disorders with the anatomical variations of the circle of Willis. In unadjusted logistic regression models, there was evidence of a strong positive association between cerebrovascular accidents and the anatomical variations of the circle of Willis, which was statistically significant: OR=2.54, 95%CI=1.13-5.69, P=0.024) (Table 3, model 1). Findings were attenuated upon simultaneous adjustment for age and sex, but the significant positive association between cerebrovascular disorders and the anatomical variations of the circle of Willis was still evident (OR=1.87, 95%CI=1.03-4.68, P=0.048; Table 3, model 2).

**Table 3. Association of cerebrovascular accidents with the anatomical variations of the circle of Willis; odds ratios (ORs) from binary logistic regression**

Model	OR	95%CI	P-value
<b>Model 1*</b>			
Anatomical variations	2.54	1.13-5.69	0.024
Normal circle	1.00	reference	
<b>Model 2<sup>†</sup></b>			
Anatomical variations	1.87	1.03-4.68	0.048
Normal circle	1.00	reference	

\* Crude (unadjusted) models (OR: cases vs. controls).

† Age- and-sex adjusted models.

Within the patients’ group, the prevalence of aneurisms was 52% (N=52). Of these, there were 22 (42.3%) cases with anatomical variations of the circle of Willis compared with no

cases with anatomical variations among the 48 patients without aneurisms – a finding which was highly statistically significant ( $P < 0.001$ ) (Table 4).

**Table 4. Anatomical variations of the circle of Willis by presence of aneurisms among patients with subarachnoid hemorrhage**

Characteristic	Without aneurisms	With aneurisms	P-value <sup>†</sup>
<b>Circle of Willis:</b>			
Normal	48 (100.0)*	30 (57.7)	<0.001
Variation	-	22 (42.3)	
<i>Total</i>	<i>48 (100.0)</i>	<i>52 (100.0)</i>	

\* Absolute numbers and column percentages (in parentheses).

<sup>†</sup> Fisher's exact test.

## Discussion

This study informs about the link between anatomical variations of the circle of Willis and cerebrovascular accidents consisting of subarachnoid hemorrhage in Albanian adults. In addition, this study provides important evidence on the association between anatomical variations of the circle of Willis and presence of aneurisms among patients with subarachnoid hemorrhage.

The main finding of this study relates to a positive association between the anatomical variations of the circle of Willis and subarachnoid hemorrhage. Furthermore, among individuals who experienced subarachnoid hemorrhage, there was a positive association between anatomical variations of the circle of Willis and the presence of aneurisms.

Our findings are compatible with previous international studies which have linked the anomalies of the circle of Willis with the development and severity of symptoms of different cerebrovascular accidents including infarctions, aneurysms, and several other vascular disorders (1,3). Based on the available scientific evidence, it is recommended to assess comprehensively the form of the circle of Willis in order to determine the capacity of the brain circulation in operations for cerebral aneurysms, as well as in interventions involving the internal carotid artery (1). In this regard, magnetic resonance angiography displays the functional morphology of the arterial circle (2,4,11-13) and additionally provides a useful means for hemodynamic assessment of blood flow and direction through different techniques and procedures (3,4,14). In particular, detailed information about the anatomical variations of the circle of Willis is rather valuable to surgeons for a suitable and rational planning of their operations, which involve complex situations associated with other serious co-morbid conditions (1).

In our study, all patients with anatomical variations of the circle of Willis had also aneurisms, a finding which confirms the evidence about the role of arterial variations of the circle of Willis as a leading factor for cerebral hemodynamic disorders which cause aneurisms (1-3). These, in turn, are a risk factor for cerebrovascular accidents. Indeed, in this sample of Albanian patients, aneurisms were involved in the occurrence of subarachnoid hemorrhage.

This study may have some limitations due to the relatively small sample size and the selection of the control group. During a two-year period, we included all consecutive patients

with subarachnoid hemorrhage hospitalized at the University Hospital Center “Mother Teresa”, which is the only tertiary health care facility in Albania. However, the relatively small sample size may have influenced the stability of the estimates. On the other hand, we cannot entirely exclude the possibility of selection bias in the control group. Nonetheless, we included in the control group only individuals who did not had evidence of cerebrovascular disorders. In any case, if there is a positive link between cerebrovascular accidents and the anatomical variations of the circle of Willis and if there were a few cases of unnoticed negligible cerebrovascular disorders in the control group, these possibilities would tend to diminish the strength of the association observed instead of producing a spurious finding.

In conclusion, our study provides useful evidence on the association between anatomical variations of the circle of Willis and cerebrovascular accidents in transitional Albania. Furthermore, findings from this study confirm the role of the anatomical variations of the circle of Willis in the occurrence of cerebral aneurisms. As reported from previous studies on this topic, the anomalies of the circle of Willis play an important role in the occurrence, manifestation of symptoms, treatment options and recovery process of several cerebrovascular disorders (1).

Larger studies should be carried out in the future in Albania and other countries in order to confirm and extend the findings of the current case-control study.

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