THE SIGNIFICANCE OF LIFESTYLE, ASSOCIATED DISEASES, AND ANATOMICAL VARIANTS OF THE CIRCLE OF WILLIS IN THE FORMATION OF ANTERIOR COMMUNICATING ARTERY ANEURYSMS

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THE SIGNIFICANCES OF LYFESTYLE, ASSOCIATED DISEASES AND ANATOMICAL VARIANTS OF CIRCLE OF WILLIS IN THE FORMATION OF ANTERIOR COMMUNICATING ARTERY ANEURYSMS (Abstract): Intracranial aneurysm represent a cerebrovascular disease with a relatively low incidence, but among these the most common are aneurysms developed in the anterior part of the circle of Willis (CoW). **Material and methods:** We collected the demographic and morphological data of the patients admitted in "Prof. Dr. N. Oblu" Emergency Clinical Hospital, Iași, Romania, with ruptured AcomA aneurysms, who later deceased and were autopsied in the Pathology Department of the same hospital, over a period of 6 years (January 2014 to December 2019), and analyzed data related to: age, gender, lifestyle (heavy smoking and alcoholism), type of anatomical variant of circle of Willis, and presence of any associated diseases. **Results:** We identified 7 patients with ruptured AComA aneurysm. 57.14% were male patients. The average age was 60.85 (range 34 to 69). Left posterior communicating artery (PcomA) was hypoplastic in 100% of all deceased patients. Right PComA presented hypoplasia (71.42%) or fetal type variant (28.57%). 71.42% of all cases showed anatomical variants both in the anterior and the posterior part of CoW. 66% of the female patients with AComA aneurysm presented obesity, type 2 diabetes, atherosclerotic disease and hypertension. 100% of male patients presented hypertension and atherosclerotic disease, 75% of them were chronic alcohol consumers and 50% were heavy smokers. **Conclusions:** The lifestyle, associated diseases, and anatomical variants of the component arteries of the circle of Willis, both from its anterior and posterior parts, could be risk factors for the formation of anterior communicating artery aneurysm. **Keywords:** CIRCLE OF WILLIS, ANTERIOR COMMUNICATING ARTERY ANEURYSM, ANATOMICAL VARIANTS, LIFESTYLE.

Intracranial aneurysm represents a cerebrovascular disease with a relatively low incidence, as it ranges between 3.6 - 9% in the general population (1, 2).

Aneurysms located at the circle of Willis (CoW) level are defined as a localized dilatation of a component artery, being situated at weak points along this anatomical structure. Approximately 85% of aneurysms develop in the anterior part of CoW, predominately at its bifurcations (3). Aneurysms of anterior communicating artery (AComA) are the most common, representing 23% - 43.5% of all intracranial aneurysms (4-6).

Over time, numerous theories have emerged about the development of an intracranial aneurysm. At first it was considered that the embolic and inflammatory reactions were the significant factors in this process, but later it was found that the presence of some defects in the development of the vascular media at the bifurcation of an artery are necessary. In addition, some degenerative changes of muscle of the vascular media, as well as of internal elastic membrane were associated (7).

More recently, Stojanović *et al.* (2) concluded that the asymmetric configuration of the circle of Willis causes increased perfusion requirements in certain areas and thus initiates the process of blood vessel remodeling in the area of permanently increased perfusion flow. Some of the risk factors that contribute to the occurrence of an intracranial aneurysm have been identified so far: familial history of intracranial aneurysm, high blood pressure, cigarette smoking, alcohol consumption, and female gender (8). However, these factors do not seem to explain the entire way of aneurysm formation, especially in the case of AComA, because in 1991 some Japanese researchers published an article about an AComA aneurysm diagnosed in a 13-month-old child (9).

During its evolution, the AComA aneurysm ruptures and leads to the occurrence of subarachnoid hemorrhage, often with ventricular involvement, leading in 30-40% of cases to death or severe neurologic dysfunction and disability in survivors (8).

The hypothesis that anatomical variants of the component arteries of CoW can influence the formation of intracranial aneurysms was first reported by Padget *et al.* in 1944 (10). Considering AComA aneurysms, hypoplasia of one or both Anterior Cerebral Arteries (ACAs) play a defining role in its development by disturbing local hemodynamics (11-14). There are only few studies identifying the presence of a fetal-type of Posterior Communicating Artery (PComA) in patients with AComA aneurysms (15-17).

The first aim of our study was to analyze the anatomical variants of the anterior and posterior parts of CoW in a series of autopsy specimens in order to identify the relationship between any of its component arteries and AcomA aneurysm formation and rupture. Our second aim was to identify the risk factors that intervene in the formation and rupture of an AComA aneurysm by analyzing associated diseases and lifestyle of the patients included in our series.

MATERIAL AND METHODS

We collected the demographic and morphological data of the patients admitted in the main neurological and neurosurgical regional centre in North-Eastern Romania ("Prof. Dr. N. Oblu" Emergency Clinical Hospital of Iasi) with ruptured AComA aneurysms, who later deceased and were autopsied in the Pathology Department of the same hospital, over a period of 6 years (January 2014 to December 2019), analyzing both medical records and protocols of the autopsies.

Based on the resulting list, we created a database with the following data:

1. Demographic data: age, sex, lifestyle (heavy smoking and alcoholism)

2. Morphological data: the presence of any type of anatomical variant for each component artery of CoW, taking into account the literature definitions, as well as the presence of any associated diseases (obesity, hypertension, type 2 diabetes).

According to literature, we considered that:

- "hypoplasia" of a component artery of CoW is defined by an external diameter of less than 1 mm, except for communicating arteries, which are considered hypoplastic at an external diameter of less than 0.5 mm (18).
- the posterior communicating artery (PComA) is defined as complete fetal (fPComP) when it originates entirely from the internal carotid artery (ICA), with no connection to the Basilar Artery (BA). We defined the posterior communicating artery as partially fetal (pfPComA) when it originates from ICA and retains a small atresic connection with BA (19).

The obtained results were collected in a database using the *Microsoft Excel* 2007 program and were used to calculate the mean, number and percentage, as well as to make the corresponding graphs. At the end, we compared our results with the data from the specialized literature.

RESULTS

We identified 7 deceased patients with ruptured AComA aneurysm and fatal outcome. Among them, 57.14% were male patients (fig. 1), with a M:F ratio of 1.33. The average age of the patients from our series was 60.85 (range 34 to 69). Mean age of female patient was 66 (range 60 to 69), while for male patients was 57 (range 34 to 71).

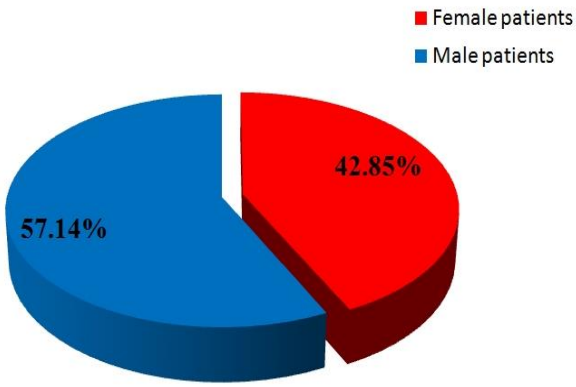


Fig. 1. Chart showing the gender ratio

Macroscopic examination showed that none of our patients presented a symmetrical circle of Willis. AComA presented a normal conformation in 100% of all cases but left PComA was hypoplastic in 100% of all deceased patients. Right PComA presented hypoplasia in 71.42% of cases and partial fetal type in 28.57% of cases.

All other vessels presented only hypoplasia. Right ACA presented hypoplasia in 57.14% of all cases, but left ACA showed hypoplasia only in 14.28% of the analyzed specimens. Right Posterior Cerebral Artery (PCA) was hypoplastic în 28.57% of the deceased patients and left PCA in 14.28% of cases (fig. 2).

57.14% of all circles of Willis presented three anatomical variants, 28.57% had four variants, and 14.28% exhibited only two variants (fig. 3).

In our series, 71.42% of all cases presented anatomical variants both in the anterior and the posterior part of CoW. 28.57% presented variants only in the anterior part. None of the analyzed cases had only the anterior part affected (0%) (fig. 4).

The analyzed AComA aneurysms varied in diameter from 4 mm to 13 mm, with a mean diameter of 8.42 mm (figs. 5-7).

66% of the female patients who died with AComA aneurysm were previously diagnosed with obesity, type 2 diabetes, atherosclerotic disease and arterial hypertension, but none were heavy smoker or alcohol drinker. 100% of male patients with AComA aneurysm were previously diagnosed with arterial hypertension and atherosclerotic disease, and 75% of them were chronic alcohol consumers and 50% were heavy smokers (fig. 8).

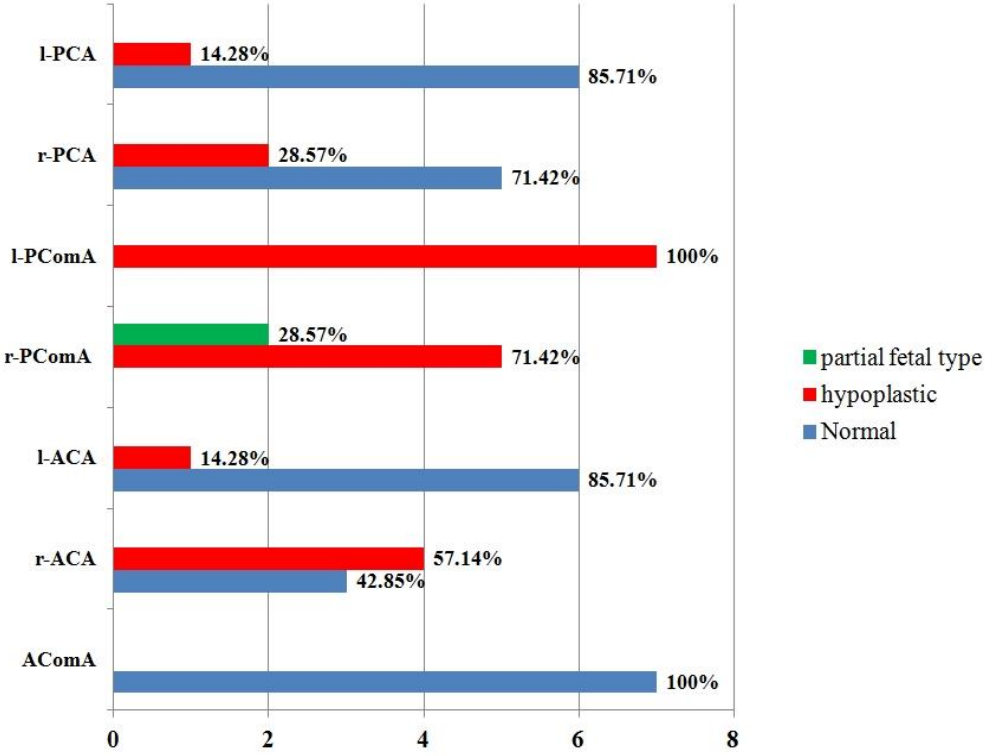


Fig. 2. Chart showing the relation between each artery of the circle of Willis and the anatomical variant it expressed in our case series. Abbreviations: r =right; l =left

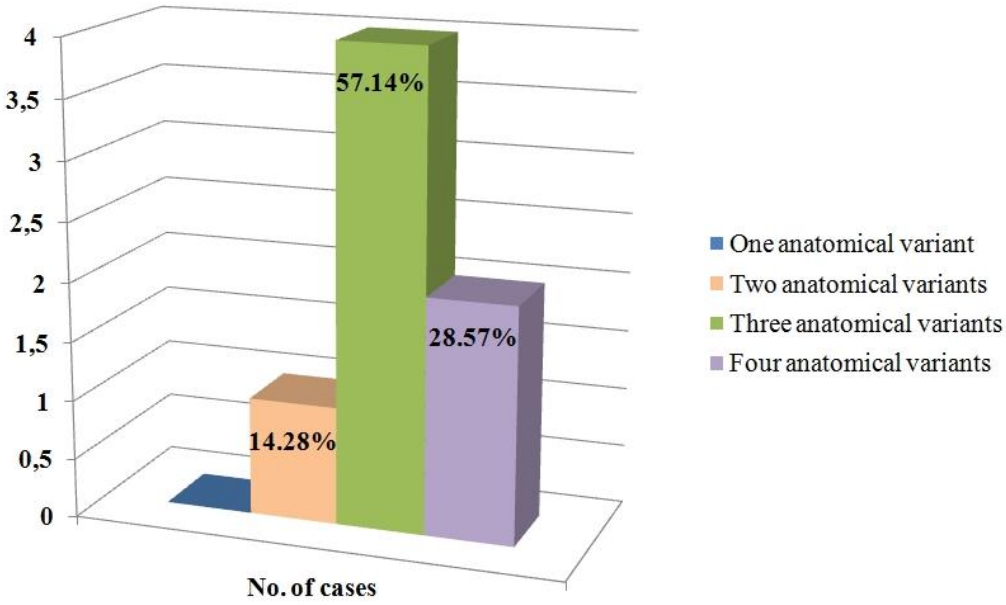


Fig. 3. Chart showing the number of anatomical variants expressed by the component arteries of the circles of Willis in our case series.

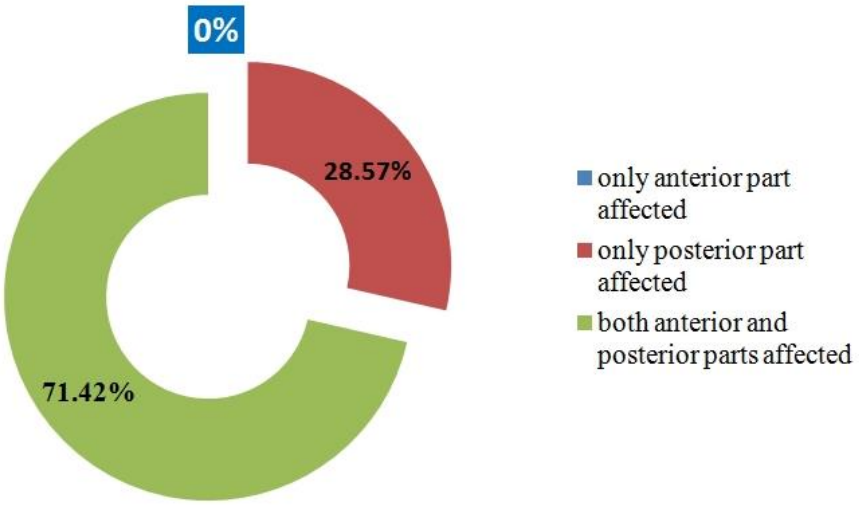
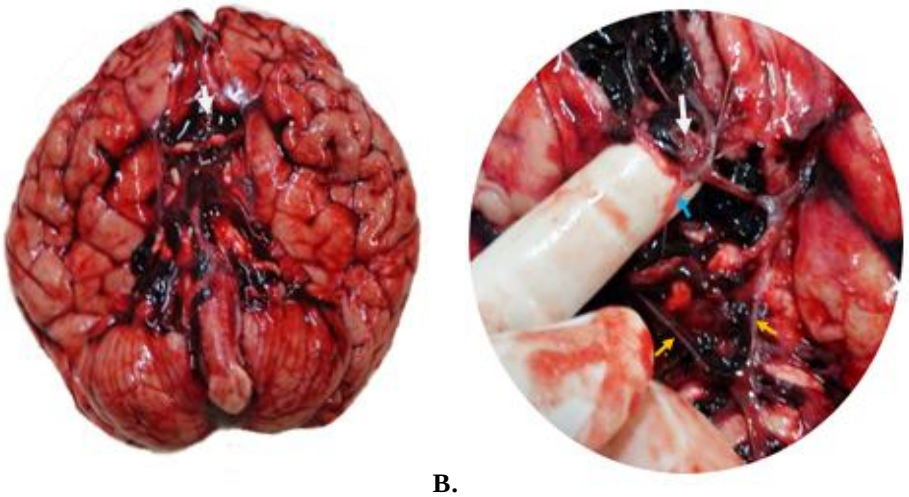


Fig. 4. Chart showing the percentage of the affected part of the analyzed CoW by anatomical variants.



A. **B.**

Fig. 5. M, 34 years-old. A) AComA ruptured aneurysm (white arrow), having a diameter of 9 mm, with subarachnoid hemorrhage and massive intraventricular hemorrhage. B). Aneurysm is associated with right ACA hypoplasia (blue arrow), and bilateral PComAs hypoplasia (orange arrows).

Fig. 6. M, 50 years old. AComA ruptured aneurysm (white arrow), with a diameter of 4mm) with subarachnoid hemorrhage associated with left ACA hypoplasia (blue arrow), right PComA hypoplasia (yellow arrow), partial fetal type left PcomA (green arrow), and left PCA hypoplasia (purple arrow).

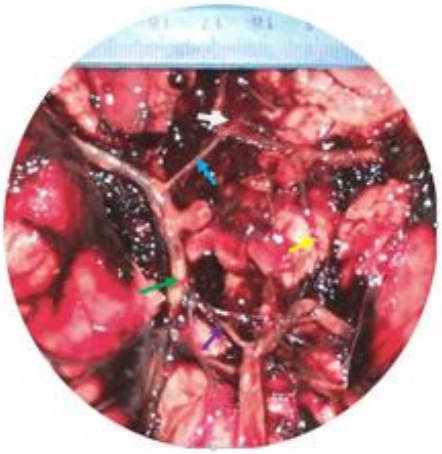


Fig. 7. F, 60 years old. AComA ruptured aneurysm (white arrow), with a diameter of 8mm, with subarachnoid hemorrhage and massive intraventricular hemorrhage associated with right ACA hypoplasia (blue arrow), partial fetal-type right PcomA (green arrow), right PCA hypoplasia (purple arrow), and left PComA hypoplasia (yellow arrow).

DISCUSSION

Regarding the circle of Willis, aneurysms developed mostly in the anterior part (20, 21). Literature unequivocally states that ruptured intracranial aneurysms are associated with the female sex (8), but, in the case of AComA aneurysms, male patients outnumbered female patients (22, 23). Ghods *et al.* also found that male patients with ruptured AComA aneurysm were diagnosed at a significantly younger age than female patients (23). Even though our series included a small number of cases, we identified the same gender differences and found out that male patients were diagnosed with ruptured AComA aneurysms 9 years earlier than female patients.

Previous angiographic studies demonstrated that abnormalities of the AComA complex, most frequently hypoplasia of A1 segment of ACA, are associated with AComA aneurysm in more than two thirds of cases (11, 12, 24, 25). Our study demonstrated on an autopsy series the same association in almost three quarters of the cases.

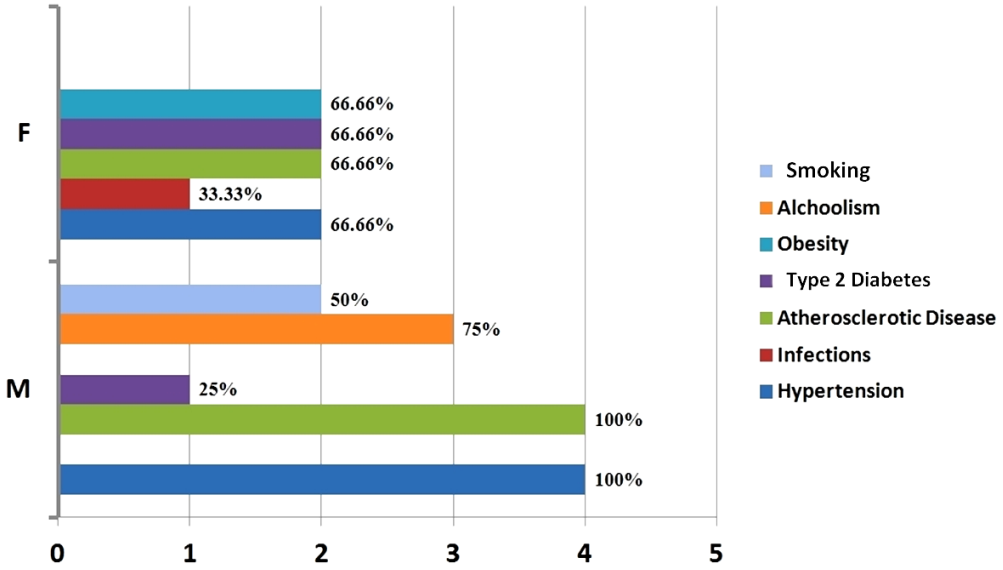


Fig. 8. Chart showing the relation between gender and associated diseases to the AComA aneurysm. Abbreviations: M=male patients; F=female patients

Tarulli and Fox, in 2010, showed that the presence of an asymmetric configuration of the A1 segment of ACA facilitates the development of AComA aneurysms by flow stresses (13). More recently, in 2017, Rinaldo *et al.* analyzed digital subtraction angiography images of 204 patients with AComA aneurysm. Of their patients, only 1/6 were found to have a hypoplastic A1 segment, even if they had no history of smoking (14), but they also took into consideration the unruptured aneurysms.

The relative lack of traditional risk factors for aneurysm formation (such as smoking) in patients with A1 segment hypoplasia should direct researchers' attention to investigating some other hemodynamic factors with a role in AComA aneurysm

formation. Therefore, it may be of interest to search for associations between AComA aneurysm and some other types of anatomical variants along with A1 segment hypoplasia. We already found in our series that patients with AComA aneurysm presented an association between hypoplasia of A1 segment and hypoplasia or partial fetal type of at least one of the two PComAs.

Rinaldo *et al.* reported that AComA aneurysms associated with hypoplastic A1 segment have a mean diameter of 7.7 mm (14), a value similar to that identified in our study.

A group of Turkish researchers analyzed the intraoperative anatomic vascular variations associated with AComA aneurysms in 120 patients. They found that more than half of them had anatomical variants in the vicinity of the AComA aneurysm, such as: marked hypoplasia of the A1 segment in more than a quarter of cases, but less often the median artery of the corpus callosum, duplication of AComA, duplication of A1 segment and azygos artery (26). Another intraoperative study conducted on 130 cases with AComA aneurysms by Bazowski *et al.* identified anatomical variants in more than one third of them. The most common abnormality reported was hypoplasia of the A1 segment of ACA (27). More than one third of Polish patients and one-third of Egyptian patients with AComA aneurysms were reported to present hypoplasia/aplasia of A1 segment of ACA (28-30). Thus, aneurysms of AComA were most often associated with an asymmetry of A1 segment of ACAs.

As far as we know, only recently were published three articles that angiographically confirmed the role of partial fetal type AComP associated with hypoplasia of A1 segment of ACA in the formation and rupture of the AComA aneurysm as a result of hemodynamic stress in susceptible patients (16-17). So, our article brings more knowledge to this matter.

The hypothesis that anomalies of the posterior part of CoW could play a role in the development of AComA aneurysm seems to be possible because in cases with hypoplasia of PCA, the blood from the ICA is no longer directed to the ipsilateral PCA and thus the blood pressure is directed to the ipsilateral ACA and implicitly to the AComA, favoring the development of aneurysms at this location by increasing the flow pressure, even in the absence of an anatomical variant of any of the two ACAs.

Considering the formation of aneurysms along CoW, Permiakov *et al.* emphasized the fact that the etiopathogenetic element underlying the appearance of such an aneurysm is the existence of congenital dysplasia of the arterial wall, which is also associated with certain risk factors such as essential or transient arterial hypertension and atherosclerosis (21). Other authors have considered the following as risk factors for the occurrence of intracranial aneurysms: smoking, hypertension, excessive alcohol consumption, one or more relatives affected with subarachnoid hemorrhage, autosomal dominant polycystic kidney disease, and a previous episode of subarachnoid hemorrhage (31).

Recent evidence shows that type 2 diabetes and atherosclerosis share common mechanisms for arterial wall alteration, such as lipid regulation, apoptosis, endothelial activation and inflammation, mitochondrial oxidative stress, changes in extracellular matrix components, and disruption of cellular defense systems (32).

On the other hand, in arterial hypertension all layers of the vascular wall are af-

fected due to aberrant vascular signaling, oxidative and inflammatory responses. Subsequently, hypertensive vasculopathy predisposes to atherosclerosis as a result of increased transmural pressure, blood flow and shear stress, as well as endothelial dysfunction and vascular stiffness (33). On the other hand, obesity directly contributes to cardiovascular risk factors, being itself associated with obvious atherosclerotic lesions (34). Therefore, it seems reasonable to state that the presence of hypertension, type 2 diabetes and obesity may be risk factors for the occurrence of AComA aneurysm as we found in our series.

Literature reveals that smoking plays a role both in aneurysm formation, its growth, its rupture, as well as in its recurrence after endovascular repair, probably due to the effects that the cigarette substances have on the artery walls during a multi-step process, i.e. initial vascular inflammation and hemodynamic stress, then endothelial dysfunction, and, finally, wall weakening and rupture (35, 36).

CONCLUSIONS

Our study brings new information regarding the association between patients' gender and certain risk factors for the formation, progression, and rupture of Anterior Communicating Artery aneurysm. We can conclude that the lifestyle (alcohol consumption, and heavy smoking) of our patients as well as their associated diseases (obesity, type 2 diabetes, atherosclerotic disease, arterial hypertension) could represent risk factors in the formation and rupture of Anterior Communicating Artery aneurysm. Also, the hemodynamic factor must also be taken into consideration because all our patients with Anterior Communicating Artery aneurysm presented at least two anatomical variants of the component arteries of the circle of Willis, both from its anterior and posterior parts. We emphasize the fact that neuroradiologists and neurosurgeons must keep in mind that, in cases with an unruptured Anterior Communicating Artery aneurysm, not only the anatomical variants of Anterior Cerebral Arteries should be searched on computed tomography angiographies or Magnetic Resonance Angiography, but also the anomalies of the posterior part of the circle of Willis in order to prevent the rupture of that aneurysm.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest regarding this scientific research. This article was co-funded from the European Social Fund - the Human Capital Operational Programme, Project/ Grant No: POCU/993/6/13/154722.

ETHICAL APPROVAL

The current study was approved by the Ethics Committee of "Prof. Dr. N. Oblu" Emergency Clinical Hospital Iasi, Romania.

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