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Neurological and Neurosurgical Morbidity Risks due to Anatomical Variants of Circle of Willis Case Presentation and Literature Review

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Abstract

There are few articles in literature that report multiple anatomical variations of the constituent arteries of circle of Willis (COW) and fewer are dealing with the causes of death of patients presenting these vascular anomalies. The aim of the present paper is to demonstrate, based on the morphological aspects we have identified during the clinical autopsy, the role of multiple concomitant anatomical variants of the circle of Willis in the development of neurological and neurosurgical diseases, based on evidence of a case report.

We emphasize the fact that multiple anatomical variants of circle of Willis can be compatible with a long life, but patient and physician must pay attention to cardiovascular diseases in this category of patients as these are the leading cause of death anywhere in the world.

INTRODUCTION

The anatomical variations of the constituent arteries of the circle of Willis (COW) were identified even before it was described by Thomas Willis [1]. The first anatomist to mention the existence of anatomical variants in the arterial circle at the base of the brain was Andreas Vesalius (1514-1564), who, describing the anterior part of this unique anatomical structure stated: As these portions of the artery vary from dissector to dissector, we have drawn variants thereof". He attached the illustration that showed two such anatomical variants: lack of Anterior Communicating Artery (AComA) and duplication of the Internal Carotid Artery (ICA) [2]. A century later, De Humani Corporis Fabrica, Libri X, Tabulis XCIIX appeared posthumously, with Adriaan van den Spiegel (1578–1625) as its author, but edited by Daniel Bucretius (1562-1621). In Liber X, there is an illustration showing an asymmetrical arterial circle at the base of the brain because the Posterior Communicating Artery (PComA) appears to be formed by the union of two thinner vessels [2]. Later on, many anatomists described and illustrated different anatomical variants involving the constitutive arteries of the circle of Willis [3-5] as they identified them on autopsies they performed. In recent years, due to increasingly sophisticated angiographic techniques, but also the ability to highlight the arteries of COW using colored resins during

autopsies and the possibility of digital archiving of extensive series of cases, it has been possible to obtain very large series of COW and numerous articles regarding the presence and type of anatomical variants of COW have been published [6-9]. In 2021, we reported the results of our study realized on 96 COW, which were identified during clinical autopsies. There were 28 cases (29.17%) classified as "atypical" because they expressed anatomical variants of the constituent vessels. Of these, 19 cases (67.86%) presented multiple anatomical variants, and only 9 cases (32.14%) had a single anatomical variant [10]. The aim of the present paper is to demonstrate, based on the morphological aspects we have identified during the clinical autopsy, the role of multiple concomitant anatomical variants of the circle of Willis in the development of neurological and neurosurgical diseases, based on evidence of a case report.

CASE PRESENTATION

We present the case of a retired 72-year-old female patient, living in an urban environment, presenting multiple cardiovascular risk factors (age, arterial hypertension stage 3, with additional risk factors, obesity class 2, hypercholesterolemia), who was admitted to the Neurology Department of "Prof. Dr. N. Oblu " Clinical Hospital of Emergency, Iași, Romania, in November 2015, accusing dizziness, balance disorders, gait insecurity and right focal motor epilepsy seizures (2-3 seizures/month) and memory impairment related by her family. Among the medical family history, it should be mentioned that the patient's mother (who died at the age of 70) was also hypertensive and suffered a stroke. In the patient's past medical history it is worth to mention the following diseases, in chronological order: falcine meningioma partially removed in 1999 and surgical intervention for tumor recurrence in 2012, with a pathological diagnosis of a meningothelial meningioma grade I **(Figure 1)** arterial hypertension stage 3 with additional risk (2008), but also mild cognitive impairment, cerebral atherosclerosis, cerebral lacunarism, epileptic seizures, and obesity, all diagnosed in 2012. The patient was not a smoker; she did not drink alcohol, but she was an occasional drinker of coffee.

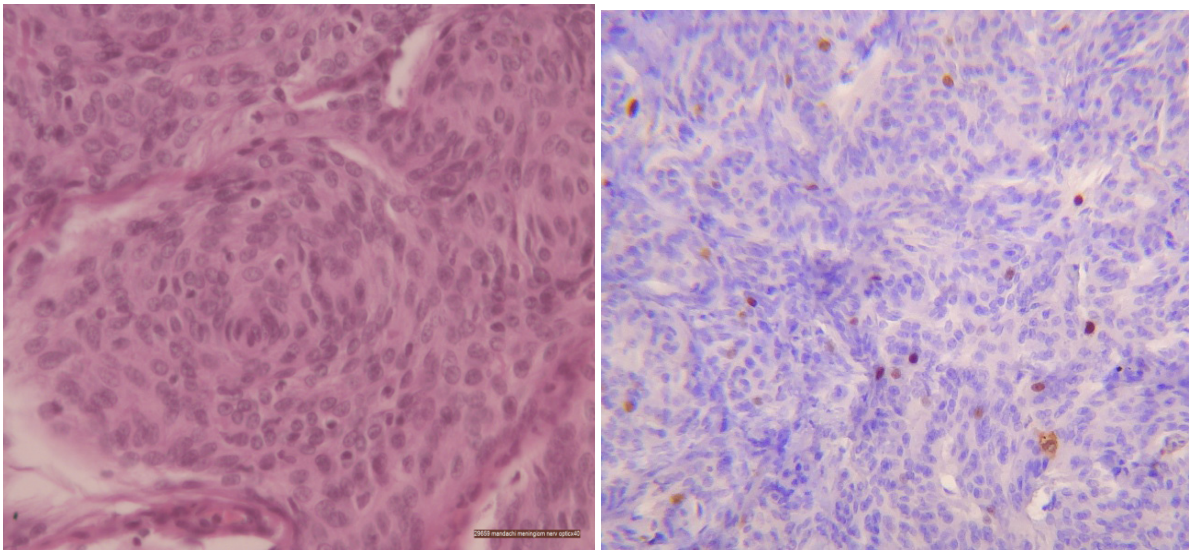

Figure 1. Microphotograph of the meningothelial meningioma grade I. A). Spindly-looking cells with ample cytoplasm and indistinct borders (syncytia) that were arranged in lobules separated by fibrovascular septa. In the center of the lobules, tumor cell formed characteristic whorls (HE stain, X 400) and B). Low expression of Ki67 labeling index in tumor cells (5% nuclear staining) (immunohistochemical staining using MIB-1 clone, X 100).

The physical examination revealed: high blood pressure (150/90 mm Hg), heart rate=90b/min, systolic murmur in the right internal carotid artery (ICA) territory, peripheral pulse identified at dorsalis pedis arteries, and moderate lower limbs edema. The neurological examination showed insecure gait, with diminished length of the steps, slow execution of movements, decreased muscle strength in the upper and lower limbs, Muscle Power Assessment (MRC Scale) Grade 4/5 bilateral, increased bilateral deep tendon reflexes, left palm mental reflex, discrete facial asymmetry with flat right nasolabial fold and right drooping of the mouth, speech comprehension and expression disorders. It should be mentioned that the patient presented 2-3 focal motor seizures per month without lateralization. The electrocardiogram (EKG) identified sinus rhythm of 90 beats/min, left axis deviation, left ventricular hypertrophy, secondary repolarization disorders, pathological Q wave in DIII. Electroencephalographic (EEG) pattern showed an alpha rhythm, migrated on the anterior part of the right hemisphere, where rare isolated synchronous peaks are recorded, and the laboratory analyzes revealed a non-specific inflammatory syndrome (ESR=38 mm/h) and hypercholesterolemia (cholesterol = 225 mg/dl), which was also present during the previous hospitalizations (in 2008 and 2012). Magnetic Resonance Imaging (MRI) examination establishes the diagnosis of cerebral lacunarism, and no residual meningeal tumor. Psychological evaluation certified on Mini-Mental State Examination (MMSE) with a score of 23 points was compatible with moderate cognitive impairment. The patient is discharged with the following positive diagnoses: Cerebral Atherosclerosis; Epilepsy with Tonic-Clonic Seizures with Focal Motor Onset without Bilateralization (Vascular Epilepsy); Leukoaraiosis; Multiple Lacunar Infarcts; Right Internal Carotid Artery Stenosis; Arterial Hypertension Stage 3 with high additional risk factors; Mild Aortic Stenosis; Stable Angina; NYHA class II Congestive Heart Failure; Hypercholesterolemia; Obesity Class II; Moderate Cognitive Impairment. The patient received hygienic-dietary recommendations and the following medication was prescribed: antihypertensive drugs (angiotensin

inhibitor), statins, antiplatelet, antiepileptic treatment, and meantime. From the information obtained from her family, the patient was not compliant with drug therapy. One month after patient's discharge, she was taken from her home by ambulance due to dizziness and chest pain she have had less than an hour ago. During the transport with the ambulance, the patient installed cardio-respiratory arrests, for which resuscitation maneuvers were initiated and also continued in the emergency unit of the same hospital. Resuscitation maneuvers were performed according to the hospital protocol, but the patient was not responsive and was declared dead. An autopsy was performed to establish the diagnosis of death. Cardiac pathology was established as the direct cause of death: i.e. acute pulmonary enema, acute interventricular septal myocardial infarction, atherosclerotic plaque with marked stenosis of coronary arteries, extensive calcifications of the aortic sigmoid valves, and cardiac failure. Also, the autopsy revealed brain atrophy and left parietal tumour bed showing brown discoloration, but no residual dural tumour **(Figure 2)** along with atherosclerotic plaques and marked stenosis of both internal carotid arteries (ICAs), disseminated atherosclerotic plaques along all constitutive arteries of circle of Willis (COW), multiple anatomical variants of the circle of Willis [Anterior Communicating Artery (AComA) duplication, left Posterior Communicating Artery (PComA) hypoplasia, and right Posterior Communicating Artery (PComA) hypoplasia] **(Figure 3),** and cerebral lacunarism.

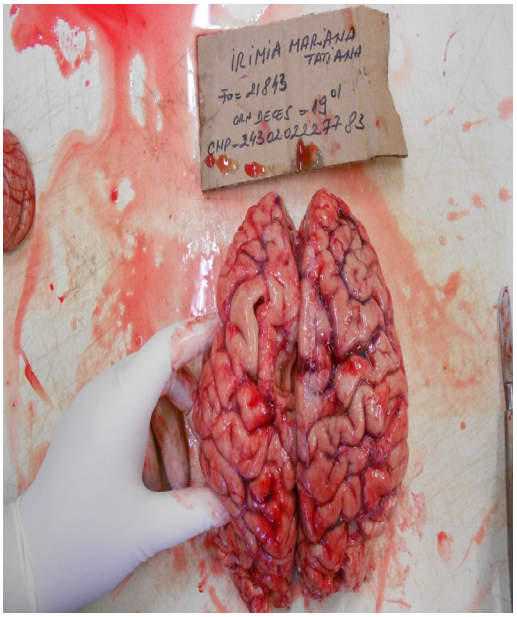

Figure 2. Brain atrophy and tumour bed with brown discoloration, marker of a previous haemorrhage (*orange arrow*), but no residual tumour, on brain convexity.

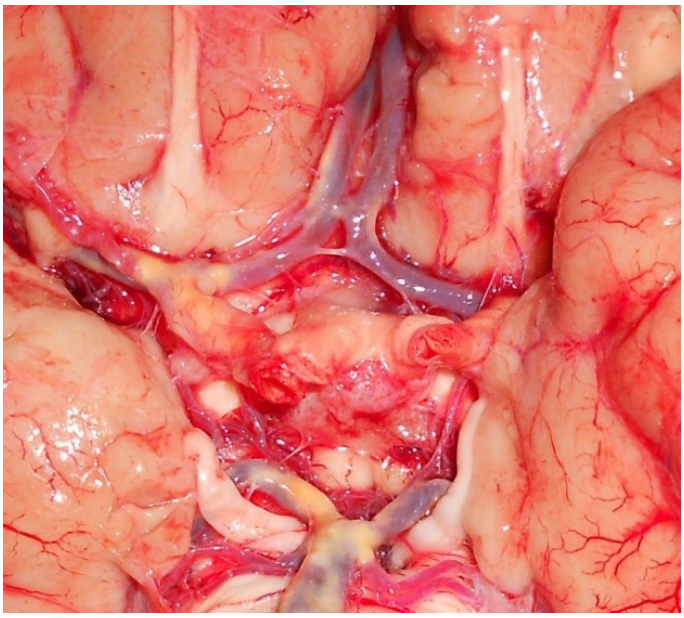

Figure 3. The base of the brain with the constitutive arteries of the circle of Willis revealed the atherosclerotic plaques distributed along all the vessels, and the following anatomical variants: Anterior Communication Artery (AComA) duplication (black arrow), left Posterior Communicating Artery (PComA) hypolasia, and right Posterior Communicating Artery (PComA) hypoplasia (blue arrows).

DISCUSSION

There are few articles in the literature that report multiple anatomical variations of the constituent arteries of COW. In India, of the 1000 brains obtained during forensic autopsies, Kapoor (2008) reported a percentage of only 7.4% of circles of Willis as having multiple anatomical variants [11]. In Italy, of the 100 healthy subjects investigated by angio-MRI, Macchi(1996) found in 16% of cases multiple anatomical variants of COW. In 3% of cases, they identified the association between the absence of AComA and hypoplasia of left AComP [12]. Iqbal (2013), in India, analyzed 50 COW and found multiple abnormalities in 28% of the cases they have investigated, of which 20% had two anatomical variants and 8% had more than two variants [13]. Among the multiple abnormalities, the association of hypoplastic PComA with fetal contralateral PCA, or the association of hypo plastic PComA with duplicated AComA was recorded. The case presented by us demonstrates this last morphological entity, an event quite rarely recorded. Analysing 1000 COW obtained by autopsy, Kapoor [11] found that only 0.8% of them had more than two anatomical abnormalities, consisting mainly of hypoplasia of two vessels, for example ACA and PComA on the same side or hypoplasia of PCA on one side and PComA on the opposite side, or hypoplasia of the PComA and duplication of AComA, which is the same multiple anomaly we encountered in our patient. The mechanism of anatomical variants development was discussed extensively in literature [13-17]. Some authors stated that these anomalies appear due to neck movements in the later years of life [14] but others took into consideration some changes in the prenatal life, like the genetic factors, or biochemical and physical factors [15]. Some others emphasize the role of hemodynamic tuning of all arterial segments during neck movements [16]. Stehbens affirms the role of topographical modifications of the arterial circle occurring due to morphological changes of collateral vessels in pathological occlusive disease [17]. However, even if the circle of Willis (COW) did not show any anatomical variant, in case of atherosclerotic vascular obstruction, a suboptimal blood supply to the brain could be identified and this condition is associated with cognitive impairment and dementia, either vascular or Alzheimer's, as it causes cerebral hypo perfusion. Dearborn et al. have observed that atherosclerosis of the arteries of the circle of Willis is associated with dementia when: ACA is affected by plaque, >2 territories present plaques and the presence of stenosis >50% could be identified [18]. These authors emphasize the fact that the presence of ACA plaque could be strongly associated with the prevalence of dementia even after adjustment for vascular risk factors, but PCA plaque is associated with mild cognitive impairment (MCI) and did not reach statistical significance for dementia. Another group of authors analysed high-resolution 3T magnetic resonance angiography, a neuropsychology battery and neurologic examination to detect mild cognitive impairment (MCI) and dementia in 1701 participants without a history of stroke. After adjustment for demographic and vascular risk factors, intracranial atherosclerosis (ICAS) ≥ 50% (versus no ICAS) was strongly associated with dementia and with cognitive impairment [19]. In the case presented here, it was also shown that atherosclerosis of the arteries of COW contributed to progressive cognitive impairment of our patient because atherosclerotic plaques were identified both in the two ACAs, in the internal carotid arteries (ICAs), but also in the two PCAs. Some clinical studies [19] have suggested that intracranial atherosclerosis causes cerebral hypoxia, but also atherothrombotic embolization and spontaneous cerebral micro embolism, which, all together, may play a role in the genesis of vascular dementia through the occurrence of cortical micro-infarcts. We consider that our patient had vascular dementia, according to the NINDS-AIRENS Criteria for the diagnosis of probable vascular dementia, which were established in 1993 by a working group [20]. Our affirmation is supported by multiple lacunar cerebral infarctions, leukoaraiosis and cerebral atrophy, identified at autopsy and on imaging examination, with clinical presentation of unsafe walking, small steps, and slowness in the execution of movements, and certified by psychological evaluation. There are very few studies that analysed the causes of death in patients with anatomical variations of COW. Nordon and Rodrigues Júnior (2012) reported as being in the first place the respiratory failure caused by pneumonia, bronchopneumonia, pulmonary collapse and pulmonary enema. In their study, heart failure ranked second and included: acute myocardial infarction, dilated cardiomyopathy, chronic pulmonary heart disease caused by pulmonary embolism. The septic or ischemic shock ranked third [21-22]. Recently, we investigated the causes of death in 28 patients with PAW with "anatomical variants", and we identified that 60.71% of them died of cerebrovascular diseases, such as stroke and ruptured aneurysm, and 39.29% died due to other medical conditions, the acute myocardial infarction being in the first place (17.85%) Hookana autopsied 3737 cases of sudden cardiac death and 3081 control cases, which were treated with antiepileptics. They affirmed that the use of antiepileptic treatment by patients with coronary heart disease could lead to sudden cardiac death (SCD), although in a small number of cases On the other hand, Bandai et al., analysing 926 patients with epilepsy and sudden cardiac death and 9832 control patients, concluded that both epilepsy and the use of antiepileptic's are both associated with an increased risk of SCD in the general population. The mechanisms by which SCD occurs may be either poor seizure control or sodium channel blockage in antiepileptic's users our patient had focal motor epilepsy for which she was receiving antiepileptic treatment. In addition, she also presented atherosclerosis of the coronary arteries, heart failure, and arterial hypertension stage 3, so there is the possibility of associating several mechanisms in the occurrence of her SCD due to acute myocardial infarction, which was macroscopically counted at autopsy. Reporting of anatomical variants of COW associated with a meningioma is very rare in the literature. We have identified two articles published so far. Meguins et al, in 2017, stated that the presence of long-term arterial hypertension associated with irregular use of antihypertensive drugs are risk factors for the development of meningioma especially in females in the age group of 60–69 years Also, Elnahry and Elnahry (2019) published the case of a 61-year-old male patient with complete paralysis of the coulometer nerve, sinuously duplicated left middle cerebral artery with fenestration of his proximal part, an aneurysm of the anterior communicating artery and a meningioma of left parietal convexity, accidentally identified Our case featured a falcine meningioma, middle type, with tumour recurrence following incomplete resection of the tumour, but no hemodynamic complications were observed after the operation. The tumour was irrigated by the calloso-marginal artery, a branch of the pericallosal artery, a terminal branch of ACA. It is possible that the growth of the tumour is correlated with the duplication of Acoma, which probably altered the hemodynamic of the anterior part of COW.

At the same time, it is possible that the relatively rapid growth of the residual tumour is due to this anatomical variant. However, it is possible that the two entities could coexist without any causal link. Recently, we presented the case of an 82-year-old male patient with multiple co-morbidities and an asymmetric COW due to the presence of a left fetal PCA and a right hypo plastic PComA, with paradoxically cerebral infarction located in the right ACP territory. We concluded that the fetal left PCA provides good irrigation on the left side, but probably performs a kind of "theft" of blood from the internal carotid system, and therefore only some blood remains for the opposite side. Also in 2020, we reported the case of an adult patient with a ruptured aneurysm located on AComA and associated with an asymmetric COW due to the numerous anatomical variants of its constitutive arteries: i.e. a thin (less 1mm) right ACA, a thin (less than 1mm) right PComA, and a thin (less than 0,5 mm) left PComA. Moreover, left PComA runs posterolaterally and ended into an unnamed extra loop originating in the left Posterior Cerebral Artery (PCA) and thus forming an extra segment in the posterior boundary of COW.

Although numerous studies have reported that an asymmetric or incomplete COW is associated with stroke severity and patient prognosis, in this case, the role of anatomical variants of COW in patient's death cannot be stated. Sonne et al. recently reported a case with an absent ICA, but with intact COW. The patient did not died due to this anatomical variant, but because of a ventricular tachycardia, even if such a rare case of agenesis of ICA can be associated with a wide range of neurological conditions such as stroke, migraine, tinnitus, and Horner's syndrome Also, Vasović et al. reported that among their series of 110 circles, only one cadaver had cerebral infarction, while the other patients have died because of cardiac, respiratory, incidental and other causes of no cerebral pathology The present case, in which three anatomical variants of COW were identified, did not die due to their actual consequences on cerebral irrigation, although there were such effects, quantified by the presence of cerebral lacunae and vascular dementia, but the autopsy did not show the presence of a brainstem infarction. The cardiovascular pathology that led to the sudden death of the patient was systemic atherosclerosis, including coronary arteries, which caused acute myocardial infarction, which was probably associated with the administration of antiepileptic treatment because there are publications in the literature that signal this association. Therefore, our case can be included among the cases that, although they have anatomical variants of the circle of Willis, can survive to an advanced age, without severe stroke or aneurysm development.

CONCLUSION

All studies our data offers the possibility to compare the neurological and neurosurgical pathology associated/caused by anatomical variants of the circle of Willis. We emphasize the fact that multiple anatomical variants of circle of Willis can be compatible with a long life, but patient and physician must pay attention to cardiovascular diseases in this category of patients as these are the leading cause of death anywhere in the world.

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