Blood vessel tortuosity is a widely observed angiographic finding, which has been reported in terms of veins and arteries in many different locations.\textsuperscript{11,38,40,48} It can affect large vessels,\textsuperscript{42,43} but it has also been observed in arterioles and venules.\textsuperscript{3,33} Many researchers have proved that tortuosity may be associated with a wide range of vascular abnormalities, especially in terms of retinal and coronary vessels.\textsuperscript{8,27,36} It can also be associated with systemic diseases, such as arterial hypertension and diabetes.\textsuperscript{18,30} In addition, it increases with age.\textsuperscript{1,42} One of the explanations for those associations may be the fact that tortuosity results from the mechanical factors of blood flow. Besides its relationship to elevated blood pressure,\textsuperscript{18} tortuosity is also associated with reduced axial tension and artery elongation.\textsuperscript{15} Another explanation may be the weakening of arterial walls, which can result from either elastin degradation\textsuperscript{12} or abnormal deposits within vessel walls.\textsuperscript{22} Also, degradation of surrounding tissue can lead to tortuosity of a vessel.\textsuperscript{32}

Many methods of tortuosity analysis have been pro-
posed, in both two and three dimensions.\textsuperscript{3,28} Currently, especially in terms of retinal vessels, most analysis is being performed automatically\textsuperscript{26,39} based on angiography or MR angiography.\textsuperscript{7,14}

In terms of cerebral vessels, tortuosity has been reported in basilar, middle, posterior, anterior, posterior communicating, and internal carotid arteries.\textsuperscript{19} It can also affect white matter arterioles.\textsuperscript{44} It has been linked with age, hypertension, and moyamoya disease.\textsuperscript{35,41} Tortuosity has also been analyzed in brain tumor vasculature as a potential indicator of tumor malignancy.\textsuperscript{3} Increased tortuosity of the middle cerebral artery (MCA) has been suggested to be associated with MCA atherosclerosis.\textsuperscript{20} To the best of our knowledge, however, there are no studies analyzing the impact of brain blood vessel tortuosity on the risk of aneurysm formation. Therefore, we performed a computer-aided analysis of MCA tortuosity, especially among patients diagnosed with MCA aneurysms, to elucidate whether MCA tortuosity may play an important role in aneurysm formation.

**Methods**

**Patients**

We retrospectively analyzed the data of patients with unruptured intracranial aneurysms, confirmed by digital subtraction angiography (DSA), who were hospitalized between January 2013 and March 2017. Patients who underwent aneurysm clipping or coiling were excluded from our study. We selected 54 patients with MCA aneurysms. The control group consisted of 54 patients without MCA aneurysm who were matched for sex, age (± 2 years), and side of MCA. From the medical records, we obtained each patient’s medical history including previous and current diseases and medications. The control group consisted of patients undergoing DSA due to suspicion of an intracranial aneurysm based on CT angiography. The study protocol was approved by the local bioethics committee, and all patients gave informed consent.

**Software**

To perform all image transformations and factor calculations, we used original software written in C# 7.0 by the first author of this study utilizing Microsoft Visual Studio Community 2017, licensed for noncommercial use, together with the Emgu CV image processing library.

**Image Processing**

To detect the course of the MCA, we performed a series of image transformations on the frontal projection of each patient’s DSA study. First, the bone structures were subtracted and image colors were reversed. Then we equalized the histogram to increase image contrast. Finally, images were binarized using an adaptive threshold to extract the image of the internal carotid artery, MCA, and anterior cerebral artery courses. Image binarization allowed us to apply a pathfinding algorithm. From the processed image, we automatically extracted the aforementioned segments by selecting the start and end points. To track the vessel course, we used the A* algorithm, which is one of the most efficient pathfinding algorithms and guarantees that the shortest path between two points will be found.\textsuperscript{49} The extracted path was transformed to a curve, which was used for further analysis (Fig. 1).

**Relative Length**

The first tortuosity descriptor that we used was relative length (RL), which is defined by the following formula: $\frac{l_{cc}}{l}$, where $l_{cc}$ is the curve length and $l$ is the length of the straight line between the start and end points of the curve (Fig. 2A). The more the curve deviates from straightness, the lower the RL.

**Sum of Angle Metrics**

To calculate the sum of angle metrics (SOAM), the curve is divided into subcurves of equal length. Then for each subcurve, we calculate the supplementary of the angles between lines connecting its center and ends. Angles from every subcurve are summed, and the result is normalized by the length of the entire curve, the SOAM:

$$\sum_{i=1}^{n} \frac{180^\circ - \alpha}{l_{c}}$$

where $\alpha$ indicates measured angles and $n$ is the number of measured angles (Fig. 2B). For a curve that is straighter, angles are smaller and thus the entire SOAM is smaller. This descriptor is also sensitive to local deviations from a straight line.

**Product of Angle Distance**

The product of angle distance (PAD) is calculated using the following formula: $\text{RL} \times \text{SOAM}$. This descriptor defines both global tortuosity, which is given by RL, and local tortuosity, which is given by the SOAM.

**Triangular Index**

To calculate triangular index (TI), the curve must again be divided into equal subcurves. Then a triangle is built with vertices on each end of the subcurve and in its middle point. The TI is calculated using the following formula:

$$\sum_{i=1}^{n} \frac{a_i + b_i}{c_i}$$

where $n$ is the number of subcurves, $a$ and $b$ are triangle sides, and $c$ is the triangle base (Fig. 2C). The TI is smaller for straighter curves.

**Inflection Count Metrics**

Inflection point is a point on a curve where it changes from being concave to being convex, or vice versa.\textsuperscript{20} The inflection count metrics (ICM) is defined with the following formula: $(n_i \times l_i)/l$, where $n_i$ is the number of the curve’s inflection points, $l_i$ is the curve length, and $l$ is the distance between the start and end points of the curve (Fig. 2D). This factor is more sensitive to global curvature than RL and is lower for more straight curves.
**Statistical Analysis**

We used the Shapiro-Wilk test to assess normality. As appropriate for continuous variables, we used the t-test for normally distributed variables and the Mann-Whitney U-test for nonnormally distributed variables. We used the $\chi^2$ test for proportional variables. We expressed continuous variables as the mean ± standard deviation. To find factors independently associated with the presence of an MCA aneurysm, we used multivariate and univariate logistic regression analyses. A $p$ value < 0.05 was considered to be statistically significant. To perform all statistical analyses, we used Statistica version 10 for Windows (StatSoft Poland).

**Results**

We studied 108 patients, and 82 (75.93%) of them were females. Fifty-eight (53.70%) analyzed MCAs were located on the right side. Mean age for all patients was 57.64 ± 11.45 years. The mean RL was 0.78 ± 0.09, mean SOAM was 0.52 ± 0.15, mean PAD was 0.41 ± 0.15, mean TI was 0.84 ± 0.06, and mean ICM was 2.66 ± 1.42. The aneurysm and control groups were fully comparable—the only variables that differed are presented below.

Patients with an MCA aneurysm significantly more often were smokers (29.63% vs. 9.26%, $p = 0.01$), had a history of ischemic heart disease (7.41% vs. 0%, $p = 0.04$), and were treated with $\beta$-blockers (16.67% vs. 1.85%, $p = 0.01$; Table 1).

Patients with an MCA aneurysm had significantly lower RLs (0.75 ± 0.09 vs. 0.83 ± 0.08, $p < 0.01$), SOAMs (0.45 ± 0.10 vs. 0.60 ± 0.17, $p < 0.01$), and PADs (0.34 ± 0.09 vs. 0.50 ± 0.17, $p < 0.01$). They also had significantly higher TIs (0.87 ± 0.04 vs. 0.81 ± 0.07, $p < 0.01$) and ICMs (3.07 ± 1.58 vs. 2.26 ± 1.12, $p < 0.01$; Table 1). Female patients had significantly higher RLs (0.76 ± 0.11 vs. 0.80 ± 0.09, $p = 0.03$) than male patients (Table 2).

On multivariate logistic regression analysis, after adjustment for possible confounders, smoking (OR 4.12, 95% CI 1.41–13.96, $p < 0.01$) and higher ICM (OR 1.54, 95% CI 1.15–2.12, $p < 0.01$) remained independently associated with MCA aneurysm occurrence.

**Discussion**

Our study showed statistically significant differences in tortuosity descriptors between patients with MCA aneurysms and those without. We found that RLs for patients with an aneurysm were lower and that TIs along with ICMs were higher. On the other hand, SOAMs and PADs were higher for patients without MCA aneurysms. As a lower RL is associated with higher global tortuosity and a higher SOAM is associated with higher local tortuosity, our study results suggest that increased global tortuosity plays a role in MCA aneurysm formation instead of local inflection points. This theory is further confirmed by the fact that a higher ICM was independently associated with a higher risk for MCA aneurysm occurrence, as ICM is higher for curves with more inflection points.

Our findings are consistent with those of Labeyrie et
al., who showed that internal carotid artery tortuosity is linked with intracranial aneurysm formation. However, Labeyrie et al. defined arterial tortuosity as simple elongation in the course of the artery. It can also be defined as two markedly tortuous turns, kinking, or acute angulation of the artery with an angle between the two segments of more than 60°, or coil elongation of the artery resulting in 360° degrees of rotation. An association between tortuosity and aneurysms was also shown in terms of vertebral arteries in the Virgilio et al. study; however, the association was not further confirmed by the Nasr et al. study. Tortuosity also plays a role in aortic aneurysm analysis. It was proven to be associated with a higher risk of rupture, as well as with higher maximum wall stress. An explanation for the association between higher tortuosity and MCA aneurysm occurrence may be the fact that higher tortuosity is associated with arterial wall weakening. There are a few rare genetic syndromes that are linked to...
the formation of aneurysms. 

Another explanation that female patients are at higher risk for atherosclerosis.9,10 This fact may be correlated with a higher prevalence of intracranial aneurysms in female patients.46 It is also known that female patients are at higher risk for atherosclerosis.2

The present study has certain limitations, including the limited size of the study sample. As patients with unruptured MCA aneurysms do not routinely undergo DSA, we were able to obtain only 54 examinations over a period of 4 years. We were able to perform analysis on age-, sex-, and side-matched patients. On the other hand, we were not able to recruit and match patients according to all risk factors. Further analysis should be performed on larger and more varied patient groups. Despite this limitation, this is the first study to analyze MCA tortuosity in terms of aneurysm formation.

Conclusions

We found that an increased deviation of the MCA from a straight axis (described by RL), a decreased sum of all MCA angles (described by SOAM), a local increase of the MCA angle heterogeneity, and an increase in changes in an artery’s course (described by ICM) are associated with MCA aneurysm formation. Smoking and ICM are independently associated with MCA aneurysm formation.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Krzyżewski, Kliś. Acquisition of data: Krzyżewski, Kliś. Analysis and interpretation of data: Krzyżewski, Kliś, Tomaszewski. Critical revision of the article: Kliś, Kwinta, Stachura, Moskała, Tomaszewski. Reviewed submitted version of manuscript: Krzyżewski, Kliś, Tomaszewski. Approved the final version of the manuscript on behalf of all authors: Krzyżewski. Statistical analysis: Kliś.

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