1. STUDY IDENTIFICATION

Unique Protocol Identification Number: NCT03493035

Brief Title: Risk Factors of Middle Cerebral Artery Aneurysm (MCAA)

Official Title: A Case-Control Study of Independent Predictors of Middle Cerebral Artery Aneurysm

Study Type: Observational

2. STUDY STATUS

Entered Document Date: July 12, 2017

Record Verification Date: February 14, 2019

Overall Recruitment Status: Completed

Study Start Date: June 2015

Study Completion Date: June 2017

3. SPONSORS/COLLABORATORS

Responsible Party, by Official Title: Principal Investigator

Investigator Information:

Investigator Name: Department of Neurosurgery, Regional Hospital in Sosnowiec, Medical University of Silesia in Katowice, Poland

4. OVERSIGHT

Human Subjects Review: The protocol of the study was approved by the Institutional Review Board, and written informed consent will be sought from all the study participants.

Human Subjects Protection Review Board Status: Submitted, approved

5. STUDY DESCRIPTION

Brief Summary:

Current evidence suggests that a principal factor involved in formation, enlargement and rupture of cerebral aneurysms are hemodynamic forces acting at arterial bifurcation [1]. Both experimental studies in dogs and computational fluid dynamics (CFD) studies demonstrated that high levels of wall shear stress (WSS) at arterial bifurcation and high positive WSS gradient (WSSG) may lead to remodelling of vascular epithelium and destruction of internal elastic membrane, and thus, may play a role in aneurysm formation [2]. While the contribution of WSS to aneurysm development raises no controversies, the question whether arterial bifurcation morphology might influence the shear stress level is still a matter of discussion. The results of glass model studies conducted in the 1970s and more recent CFD simulations imply that the magnitude of hemodynamic stress and its distribution at arterial bifurcation depend on blood flow characteristics and the bifurcation's geometry [3-7].

MCA is one of three sites predisposed to aneurysm formation [8]. Unlike other two predilected locations, anterior communicating artery complex (ACoA) and internal carotid artery (ICA), MCA is not strictly a part of the arterial circle of Willis. The use of the MCA model will enable to minimize the influence of collateral blood flow through communicating arteries in asymmetrical forms of the circle of Willis on hemodynamic parameters, and the effect of circle geometry on the size of bifurcation angles.

Objectives of Study:

i) to determine morphometric and hemodynamic parameters of aneurysmal and non-aneurysmal MCA bifurcations and ii) to analyse their relationship with aneurysm formation.

6. CONDITIONS AND KEYWORDS

Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study:

1. Patients (further referred to as cases) diagnosed with unruptured MCA aneurysm.
2. Patients (further referred to as controls) with no evidence of intracranial pathologies on 3D CTA, directed at CT examination due to minor symptoms, such as headache or vertigo.

7. STUDY DESIGN (OBSERVATIONAL)

Observational Study Model: Case-Control

Time Perspective: Prospective

Enrollment Type: Actual

Number of Groups/Cohorts: 2; Case/Control

Patient Registry Information: All patients were admitted to the unit based on their signed consent form

Target Follow-Up Duration: NA

Study Design:

3D CTA Protocol:

All studies will be performed with a 64-row 128-slice CT system (GE Optima CT 660, GE Healthcare, USA) using the following parameters: collimation 39.38 x 0.625 mm, spiral pitch

0.516:1, anode voltage 120 kV, anode amperage 40-500 mA, rotation time 0.6 seconds, slice thickness 0.625 mm. Patients will receive intravenous non-ionic contrast agent (Iomeron 350, Bracco Imaging Deutschland GmbH, Konstanz, Germany) at volume adjusted to their body weight, up to 50 mL, followed by a 30 mL NaCl flush. Iomeron 350 will be given to the basilic vein at a rate of 4-4.5 mL/second with the aid of an automatic syringe (OptiVantage DH, Mallincrodt, St Louis, MO, USA). The scanning will begin 15-20 seconds after administration of the contrast agent, after reaching attenuation of 100-HU above the baseline attenuation, and will last for 6 seconds. The images will be recorded as digital imaging and communications in medicine (DICOM) files on a HP Z800 workstation.

Morphometric Analysis of MCA Bifurcations:

3D CTA scans data in DICOM format will be transferred to Mimics Innovation Suite (MIS) platform (Materialise, Leuven, Belgium). Image segmentation and creation of 3D models will be carried out with Mimics v.17.0 MIS software (Materialise, Leuven, Belgium). The process of segmentation will include main trunks of the MCA and the post-bifurcation branches. Trifurcations of the main MCA trunk will be excluded from the morphometric analysis. MCA bifurcations from the aneurysm patients will be divided into two groups: the An group with aneurysmal MCA bifurcations and the non-An group with contralateral non-aneurysmal MCA bifurcations. Also, MCA bifurcations from the controls will be divided into two groups: R-MCA group with bifurcations of the right MCA and the L-MCA group with bifurcations of the left MCA. Before the morphometric calculations, the MCA aneurysms in the An group will be digitally erased using the Mimics software. After completing the 3D model, the vessel centreline will be fitted automatically with a computer-aided design (CAD) tool. The other parameters: tortuosity, the largest curvature of MCA main trunk and the largest curvatures of the two post-bifurcations branches will be calculated automatically according to the centreline. The points of the largest curvature will be set as close to the bifurcation as possible, but in a distance longer than 5 mm. Based on these points, the cross-sectional area and the best fit diameter of the MCA trunk (p_0 and d_0, respectively) and its two post-bifurcation branches (p_1, d_1 and p_2, d_2 for the larger and smaller branch, respectively) will be estimated. The best fit diameters will be then used to calculate the radii of the main MCA trunk (r_0) and its branches (r_1 and r_2 for the larger and smaller branch, respectively) using the following formula:

$$r=d/2 \qquad (1)$$

where r – radius and d – the best fit diameter. The radii will be used to calculate two ratios describing the bifurcation asymmetry:

$$\text{asymmetry ratio}=r_2^2r_1^{-2} \quad (2)$$

and

$$\text{area ratio}=(r_1^2+r_2^2)r_0^{-2} \quad (3)$$

The centrelines and the largest curvature points will be exported to 3-matic v.9.0 MIS software to determine angles between the bifurcation components. The apices of the angles will be defined as the largest curvature points for the MCA trunk and its both branches, and the intersection of both centrelines. The angle between the post-bifurcation branches (α angle) will be calculated, along with the angles between the MCA trunk and the larger and the smaller branch (β and γ angle, respectively). Finally, the angles between each post-bifurcation branch and the direction of the MCA trunk will be calculated as:

$$\Phi_1=180-\beta \quad (4)$$

$$\Phi_2=180-\gamma \quad (5)$$

Transcranial Color-Coded Sonography (TCCS) Protocol:

All TCCS examinations will be performed by the same researcher using a Vivid 3 Pro (GE Healthcare, Chicago, Illinois, USA) equipped with a multi-frequency transcranial probe (1.5-3.6 MHz), according to the previously described standards [9]. Anterior cerebral circulation will be imaged through the temporal acoustic window with the subject in a supine position. Angle-corrected mean blood flow velocity (V_m), peak systolic velocity (V_{ps}) and end-diastolic velocity (V_{ed}) will be measured for both MCAs. Pulsatility index (PI) and volume flow rate (VFR) in each vessel will be calculated as:

$$PI=(V_{ps}-V_{ed})V_m^{-1} \quad (6)$$

$$VFR=V_mp_0 \quad (7)$$

where p_0 – a cross-sectional area of the main MCA trunk.

Analysis Plan:

The following variables will be evaluated as potential risk factors for MCA aneurysm formation: radii and cross-sectional area of the main MCA trunk (r_0, p_0) and its branches (r_1, p_1 and r_2, p_2 for the larger and smaller branch, respectively), tortuosity of MCA trunk, asymmetry ratio, $r_2^2r_1^{-2}$, area ratio, $(r_1^2+r_2^2)r_0^{-2}$, Φ_1 (°), Φ_2 (°), α (°), V_m, (cm/s), VFR (cm^3/s) and PI. Normal distribution of the study variables will be verified with Shapiro-Wilk test. The significance of intergroup and intragroup differences will be verified with Mann-Whitney Utest and Wilcoxon signed-rank test, respectively. All morphological and hemodynamic parameters shown to differ significantly between the study groups will be subjected to logistic regression analysis with stepwise addition mode. The potential predictors of MCA aneurysm will be identified on univariate analysis, and the relationship between pairs of the significant predictors will be determined based on Pearson's linear correlation coefficients. The variables with P-values <0.1 on univariate analysis, except those being correlated with one another, will be included in multivariate logistic regression model, to identify independent predictors of MCA aneurysm. The results will be presented as odds ratios (ORs) and their 95% confidence intervals (CIs). The independent predictors of MCA aneurysm will be subjected to receiver operating characteristic (ROC) analysis to identify their cut-off values with optimal sensitivity and specificity. The results will be considered statistically significant for p-values < 0.05. Statistical analyses will be performed with Statistica v.13.3 package (StatSoft, Tulsa, Oklahoma, USA).

Limitations:

First, we will examine patients who had already been diagnosed with the MCA aneurysms. Thus, it cannot be excluded that at early stages of the aneurysm formation, morphometric and hemodynamic parameters of the MCA bifurcation might have been slightly different than they will be at the time of the study. Second, although the MCA aneurysms will be erased from the vascular images before the morphometric analysis, their presence might interfere with the bifurcation geometry. Third, the study might also suffer from a selection bias. Although the participants will be enrolled prospectively, some might be inadvertently excluded due to small size of aneurysms missed on CT scans.

8. OUTCOME MEASURES

Primary Outcome Measure:

1. Computed tomography angiography (CTA) analysis of the cross-sectional area of the MCA bifurcations.

CTA scans in DICOM format will be used to create three-dimensional (3D) models of MCA bifurcation using Mimics Innovation Suite platform (Materialise, Leuven, Belgium). The points including the largest curvature of MCA main trunk and two post-bifurcations branches will be automatically calculated according to the centreline fitted with a computer-aided design (CAD) tool. In these points the cross-sectional area (mm2) of the MCA trunk and its two post-bifurcation branches will be calculated automatically.

2. Computed tomography angiography (CTA) analysis of the best fit diameter of the MCA bifurcations.

CTA scans in DICOM format will be used to create three-dimensional (3D) models of MCA bifurcation using Mimics Innovation Suite platform (Materialise, Leuven, Belgium). The points including the largest curvature of MCA main trunk and two post-bifurcations branches will be automatically calculated according to the centreline fitted with a computer-aided design (CAD) tool. In these points the best fit diameter (mm) of the MCA trunk and its two post-bifurcation branches will be calculated automatically.

3. Computed tomography angiography (CTA) analysis of the angles between the MCA bifurcations components.

CTA scans in DICOM format will be used to create three-dimensional (3D) models of MCA bifurcation using Mimics Innovation Suite platform (Materialise, Leuven, Belgium). The points of the largest curvature of MCA main trunk and two post-bifurcations branches will be calculated according to the centreline fitted automatically with a computer-aided design (CAD) tool. The centrelines and the largest curvature points will be exported to 3-matic v.9.0 MIS software. Three points of the largest curvatures (the main MCA trunk and two post-bifurcations branches) together with the point of the intersection of both centrelines passing through the main trunk MCA and both branches will determine the arms and the apex of the three angles. The following angle values will be calculated automatically: the angle between the post-bifurcation branches (α angle) and the angles between the MCA trunk and the larger and the smaller branches (β and γ angle).

4. Pulsatility Index (PI) as calculated from transcranial color-coded sonography (TCCS) blood flow velocities (cm/s)

The assessment of blood flow velocities in both MCAs will be performed by transcranial color-coded sonography (TCCS) using a Vivid 3 Pro (GE Healthcare, Chicago, Illinois, USA) equipped with a multi-frequency transcranial probe (1.5-3.6 MHz). For both MCAs the following will be automatically measured:

1. mean blood flow velocity (V) [cm/s]
2. peak systolic velocity (Vps) [cm/s]
3. end-diastolic velocity (Ved) [cm/s] The velocity measurements will be used to calculate in each vessel the pulsatility index (PI), calculated using the following formula: PI=(Vps-Ved)/V

5. Volume Flow Rate (VFR) as calculated from transcranial color-coded sonography (TCCS) blood flow velocities (cm/s)

The assessment of blood flow velocities in both MCAs will be performed by transcranial color-coded sonography (TCCS) using a Vivid 3 Pro (GE Healthcare, Chicago, Illinois, USA) equipped with a multi-frequency transcranial probe (1.5-3.6 MHz). For both MCAs the following will be automatically measured:

1. mean blood flow velocity (V) [cm/s]
2. peak systolic velocity (Vps) [cm/s]
3. end-diastolic velocity (Ved) [cm/s] The velocity measurements will be used to calculate in each vessel the volume flow rate (VFR) using the following formula: VFR=V*p, where p - a cross-sectional area of the main MCA trunk, calculated from the morphometric analysis

9. ELIGIBILITY

Sex/Gender: male and female, a minimum of 75 cases and 75 age- and sex-matched controls

Age Limits: <75 years

Eligibility Criteria: The study will include patients (further referred to as cases) with unruptured MCA aneurysm diagnosed on three-dimensional computed tomography angiography (3D CTA).

Case inclusion criteria

- all patients with unruptured MCA aged between 18-75 years

Case exclusion criteria

- refusal to participate in the study
- inability to give informed consent
- presence of multiple cerebral aneurysms

- presence of pathologies, other than MCA aneurysm, in the central nervous system that could have a potential effect on cerebral blood flow (e.g. ischemic stroke, intracerebral or subarachnoid haemorrhage)
- severe systemic disorders (e.g. neoplastic disease)
- severe heart failure or multi-organ failure
- hemodynamically significant internal carotid artery stenosis
- pregnancy
- family history of cerebral aneurysms.

Definition and Recruitment of Controls:

The control group will include patients with no evidence of intracranial pathologies on 3D CTA, referred to establish the ethology of minor symptoms, such as headache or vertigo.

Inclusion criteria for the control group

- all patients aged between 18-75 years with no evidence of intracranial pathologies on 3D CTA

Exclusion criteria for the control group

- refusal to participate in the study
- inability to give informed consent
- presence of pathologies in the central nervous system that could have a potential effect on cerebral blood flow (e.g. ischemic stroke, intracerebral or subarachnoid haemorrhage)
- severe systemic disorders (e.g. neoplastic disease)
- severe heart failure or multi-organ failure
- hemodynamically significant internal carotid artery stenosis
- pregnancy
- family history of cerebral aneurysms.

10. CONTACTS, LOCATIONS, AND INVESTIGATOR INFORMATION

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11. REFERENCES

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Abbreviations: 3D, three-dimensional; ACoA, anterior communicating artery complex; AUC, area under curve; BA, basilar artery; CAD, computer-aided design; CFD, computational fluid dynamics; CI, confidence interval; CT, computed tomography; CTA, computed tomography angiography; DICOM, digital imaging and communications in medicine; ICA, internal carotid artery; MCA, middle cerebral artery; MIS, Mimics Innovation Suite; OR, odds ratio; PI, pulsatility index; ROC, receiver operating characteristic; SD, standard deviation; TCCS, transcranial color-coded sonography; VFR, volume flow rate; WSS, wall shear stress.