Anatomical variants of the circle of Willis as imaging marker for intracranial aneurysm development in individuals with a familial predisposition for intracranial aneurysms.

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Abbreviations

ACA	anterior cerebral artery
Acom	anterior communicating artery
aSAH	aneurysmal subarachnoid hemorrhage
CoW	circle of Willis
IA	intracranial aneurysm
ICA	internal carotid artery
MCA	middle cerebral artery
MRA	magnetic resonance angiography
PCA	posterior cerebral artery
PCKD	polycystic kidney disease
Pcom	posterior communicating artery
UMCU	University Medical Center Utrecht
95% CI	95% confidence interval

Abstract

Objective: Hemodynamic stresses play an important role in the development of intracranial aneurysms (IA). Anatomical variants of the circle of Willis (CoW) affect the hemodynamics along the CoW and may therefore correlate with IA development and act as imaging marker. We investigated the relationship between anatomical variants of the CoW and IA development in a large cohort of individuals with a familial predisposition for IA development and aneurysmal subarachnoid hemorrhage (aSAH).

Methods: Variants in the anterior and posterior part of the CoW were compared in familial predisposed individuals with and without IAs. The anatomical variants of the CoW were categorized into six distinct variants in both the anterior and posterior part of the CoW, related to presence, proportional size or absence of different vessels in the CoW. Statistical analysis involved chi-square test for independence and z-test for independent proportions.

Results: Of the 1291 individuals included, 94 (7.3%) had IA(s). Individuals with IAs were older (mean age 55,2 years ± 10,5, vs 45,6 years ± 13,8) and more often women (73% (95% CI, 64-82) vs 55% (95% CI, 52-58)) compared to individuals without IAs. Within the anterior part of the CoW, the normal variant 1 was less prevalent among individuals with IAs compared to those without IA (35% (95% CI, 25 – 45) vs 50% (95% CI, 47 – 52), p = 0,008), whereas variant 4, characterized by Acom hypoplasia or absence, was more prevalent in individuals with IAs compared to those without IAs (42% (95% CI, 32 – 52) vs 29% (95% CI, 27 – 32), p =0,01). No differences were observed among other variants of the CoW.

Conclusion: In individuals with familial predisposition for IA and aSAH, individuals with IA showed less often a normal variant and more often a Acom hypoplasia or absence compared to individuals without IA.

Introduction

The socioeconomic impact of intracranial aneurysms (IA) remains high, with an estimated 3% of the general population having an IA[1]. Advances in non-invasive diagnostics have increased the detection of IAs[2]. While most IAs remain stable throughout life, their rupture leads to aneurysmal subarachnoid hemorrhage (aSAH) with severe consequences, including a 35% case fatality rate and 35% dependency among survivors[3,4].

Several factors contribute to aneurysm development and the subsequent risk of aSAH, such as hypertension, smoking, and a positive family history of aSAH[5,6]. First-degree relatives of aSAH patients face a significantly elevated risk for both IA development and aSAH, making repeated screening in this population to be a proven cost-effective preventive measure[7,8].

Despite population studies and systematic reviews, the pathogenesis of aneurysm development remains largely unknown. However, hemodynamic stress within the arteries of the circle of Willis (CoW) is consistently considered to play a significant role[9-11]. Variations in the CoW may affect hemodynamic stress, contributing to the development of IAs. This was supported by a recent systematic review on imaging markers for IAs, showing a large heterogeneity of imaging marker definitions amongst all studies and finding asymmetry in the A1 segments of the anterior cerebral arteries (ACA) as the only consistent CoW variation related to IA development of the anterior communicating artery (Acom)[12]. A large cross-sectional population study carried out in Norway showed a correlation between an incomplete CoW and IA development[13].

Previous studies on anatomical variations of the CoW predisposing to IA development have been conducted in the general population. It is uncertain whether these findings apply to individuals with a familial predisposition for IAs and aSAH. Given the increased screening tendency of this high-risk population, identifying anatomical variations of the CoW as imaging marker for IA development on initial screening is helpful to determine further clinical management and follow-up strategies in these individuals and its family members.

Therefore, the primary objective of this study was to investigate the relationship between anatomical variants of the CoW and IA development in individuals with a familial predisposition for IAs and aSAH.

Methods

Study Participants

Two different cohorts of individuals who underwent Magnetic Resonance Angiography (MRA) at the University Medical Center Utrecht (UMCU) were included. Cohort A was collected within the scope of clinical practice and consisted of a consecutive series of individuals who were screened for IAs due to a positive family history of aSAH. A positive family history was characterized as the presence of at least one-first degree relative with aSAH. Cohort B was assembled within the context of research and consisted of participants recruited from the ERASE (Early Recognition of persons at high risk of Aneurysmal Subarachnoid hemorrhage) study[14]; a screening study designed to identify IAs in first-degree relatives of patients afflicted with IAs. These two cohorts collectively constitute the cohort of individuals at increased risk of aneurysm development and a subsequent aSAH, which is the central focus group of the PRYSM (PRevent aneurYSMal subarachnoid hemorrhage) project[14,15]; a project with a primary focus on the early detection of aneurysms. Additional information about each of the two groups will be given in the subsequent two paragraphs.

Cohort A

All individuals who underwent screening for IA due to a positive family history of aSAH at the UMCU were systematically documented in a prospectively collected database. All available information from the period August 1996 until August 2023 was retrieved for analysis. Individuals admitted to the UMCU with aSAH and those referred for screening due to IAs are routinely interviewed regarding their familial medical history. First-degree relatives of individuals diagnosed with aSAH are strongly encouraged to share information with their relatives about the availability of screening for IAs at the outpatient clinic. Furthermore, individuals are also recommended for screening through referrals by general practitioners or by neurologists and neurosurgeons affiliated with other medical institutions. For this study, we incorporated individuals who underwent a 3D T1-weighted gradient echo TOF-MRA acquisition on a 1.5T or 3T MRI (Philips Healthcare, Best, The Netherlands). Exclusions encompassed individuals who had undergone prior treatments for IA, as such treatments may result in artefacts on the MRA, and individuals diagnosed with polycystic kidney disease (PCKD). As it is recommended to conduct periodic screening for IA due to their potential development over time[16], multiple MRA scans may exist for each individual. The data utilized in this study were derived from the most recent MRA scan available. In cases where individuals underwent endovascular or surgical treatment for IAs identified during screening, the most recent MRA conducted prior to the treatment was utilized for analysis.

Cohort B

A prospective observational cohort study involving 527 first-degree relatives of index patients with incidental IAs was conducted. These individuals were related to a consecutive series of index patients diagnosed with IAs at Neurology outpatient clinics of UMCU, Leiden University Medical Center, or Amsterdam University Medical Center in the Netherlands in the period spanning form April 2017 to October 2021[13]. Index patients were adults with incidental saccular IAs detected through MRA, computed tomography angiography, or conventional angiography, having no familial history of aSAH, no medical history of aSAH or PCKD, or other conditions known to predispose them to aneurysm development. Written informed consent was obtained from eligible index patients to contact their first-degree relatives. Exclusion criteria for relatives included age <20 or >70 years at time of screening, medical history of IAs, PCKD, Ehlers-Danlos syndrome, or fibromuscular dysplasia, prior IA screening, severe comorbidities affecting life expectancy, relative contraindications for MRA (such as pregnancy, presence of a pacemaker, claustrophobia), cognitive deficits, or language barriers. Participants underwent a 3D T1-weighted TOF-MRA on a 3.0 Tesla MRI system (Philips Healthcare, Best, The Netherlands). Poor image quality led to the exclusion of 3 individuals, resulting in a total of 524 participants in the study.

Standard protocol approvals, registrations, and patient consents

For the analysis of the data pertaining to cohort A, a 'non-WMO-declaration' was obtained from the local ethics review committee. The study protocol of cohort B was approved by the Medical Ethical Review Committee of the UMCU (approval number 16-777).

Classification of Circle of Willis variants

To evaluate the anatomical variants of the CoW, a modification of the classification system introduced by Lippert and Pabst was used[17]. In the Lippert and Pabst classification system, anatomical variants within the anterior and posterior part of the CoW are described separately. This classification system yields a total of 10 distinct anatomical variations in the anterior part and an additional 10 distinct anatomical variations in the posterior part of the CoW. Because of the limited

occurrence of certain anatomical variants, we clustered hemodynamic correlated variants for the purpose of this study. The anterior circulation existed of the following variants: 1. Normal variant (type A Pabst), 2. Variants in Acom - A2 complex (type B, C, D and E Pabst), 3. Two separate trunks of middle cerebral artery (MCA), left or right (type F and J Pabst), 4. Hypoplasia or absence of the Acom (type G Pabst), 5. Hypoplasia or absence of one precommunicating segment (A1) of the ACA (type H Pabst) and 6. Hypoplasia or absence of one internal carotid artery (ICA) (type I Pabst). The posterior circulation contained the following variants: 1. Bilateral posterior communicating arteries (Pcoms), with or without unilateral or bilateral fetal type posterior cerebral artery (PCA) (type A, B, and C Pabst), 2. Unilateral Pcom, with or without fetal type PCA (type D and G Pabst), 3. Hypoplasia or absence of both Pcoms (type E Pabst), 4. Hypoplasia or absence of one precommunicating segment (P1) of the PCA, with uni- or bilateral fetal type PCA (type F and J Pabst), 5. Unilateral fetal type PCA and hypoplasia or absence of both a precommunicating segment (P1) of the PCA and the Pcom (type H Pabst), and 6. Bilateral fetal type PCA with hypoplasia or absence of both precommunicating segments (P1) of the PCAs (type I Pabst) (figure 1a and 1b).

Measurements of the Circle of Willis

To enable classification of the CoW, the arterial diameters of the CoW were measured by one observer (MV) on the following arteries (both left and right, at 50% of total segment length): A1 segments of ACA, M1 segments of MCA, P1 segments of PCA and Pcom. Additionally, the Acom was measured and the A2 segments of ACA at 5 mm after the Acom.

Statistical Analysis

Descriptive analyses of demographics and clinical characteristics of patients with and without aneurysms were performed. Categorical data were presented as numbers and percentages, while continuous data were presented through means and standard deviations. The anatomical variants of the anterior and posterior part of the CoW were compared between individuals with and without IAs through an assessment of differences in proportions, utilizing a chi-square test for independence followed by a z-test for independent proportions. To ensure adequate statistical power in examining group differences in anatomical variations, our analysis focused solely on anatomical variants that exhibited a minimum of 5 occurrences within each group. All reported p-values are considered two-tailed, and significance was determined at a threshold of <0,05. The entirety of statistical analyses was performed utilizing the IBM Statistics Package of Social Sciences (SPSS) (Version 29, IBM, Armonk, NY, USA).

Figure 1a: anatomical variants in the anterior part of the CoW

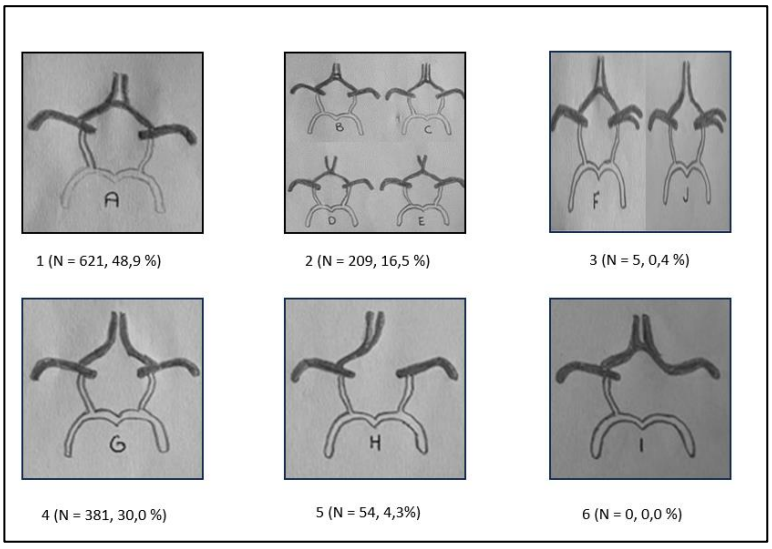

Fig 1a. Schematic representation and prevalence in the total study population of the anatomical variants in the anterior part of the circle of Willis used in the study (modified from Ophelders et al[18]). 1. Normal variant (type A Pabst), 2. Variants in Acom- A2 complex (type B, C, D and E Pabst), 3. Two separate trunks of MCA, left or right (type F and J Pabst), 4. Hypoplasia or absence of the Acom (type G Pabst), 5. Hypoplasia or absence of one precommunicating segment (A1) of the ACA (type H Pabst) and 6. Hypoplasia or absence of one ICA (type I Pabst).

Figure 1b: anatomical variants in the posterior part of the CoW

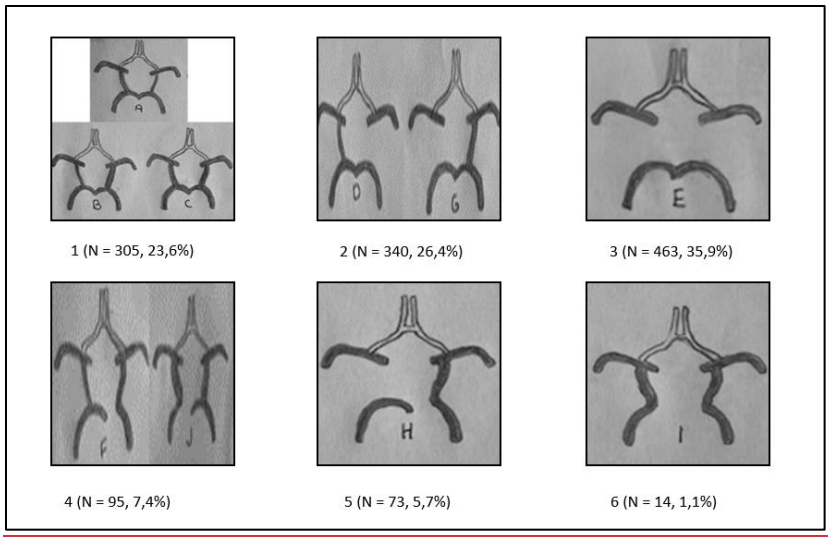

Fig 1b. Schematic representation and prevalence in the total study population of the anatomical variants in the posterior part of the circle of Willis used in the study (modified from Ophelders et al[18]). 1. Bilateral Pcoms, with or without unilateral or bilateral fetal type PCA (type A, B, and C Pabst), 2. Unilateral Pcom, with or without fetal type PCA (type D and G Pabst), 3. Hypoplasia or absence of both Pcoms (type E Pabst), 4. Hypoplasia or absence of one precommunicating segment (P1) of the PCA, with uni- or bilateral fetal type PCA (type F and J Pabst), 5. Unilateral fetal type PCA and hypoplasia or absence of both a precommunicating segment (P1) of the PCA and the Pcom (type H Pabst), and 6. Bilateral fetal type PCA with hypoplasia or absence of both precommunicating segments (P1) of the PCAs (type I Pabst).

Results

Baseline Characteristics

A total of 746 individuals fulfilled the inclusion criteria in cohort A, and 524 in cohort B. The baseline characteristics of individuals with and without IAs are shown in table 1. The mean age of all included patients was 46,3 ± 13,8 years and 56% was female. The baseline characteristics between individuals with and without IA did differ significantly for age and sex. In total 125 UIAs were detected in 94 individuals (7,3% prevalence), of which 18 individuals had multiple UIAs. The individuals with IA had a higher proportion of women in comparison to the individuals without IA (73% (95% CI, 64-82) vs 55% (95% CI, 52-58)). Furthermore, individuals with IA had a higher average age compared to individuals without IA (55,2 years ± 10,5 (95% CI, 53,1-57,3) vs 45,6 years ± 13,8 (95% CI, 44,8-46,4)). The majority of IAs were detected in the ICA (33%) and the MCA (31%).

Classification of CoW

The prevalence of the different anatomical variants in the CoW is shown in table 2. Within the anterior part of the CoW, the presence of a complete and normal variant of the CoW (variant 1) was significantly less prevalent among individuals with an IA compared to those without an IA (respectively 35% (95% CI, 25 – 45) vs 50% (95% CI, 47 – 52), p = 0,008). Conversely, the anterior CoW variant characterized by hypoplasia or absence of the Acom (variant 4) was significantly more prevalent in individuals with an IA (respectively 42% (95% CI, 32 – 52) vs 29% (95% CI, 27 – 32), p =0,01). No significant differences were observed among the remaining variants in the anterior part of the CoW. For the variants in the posterior part of the CoW, there were no significant differences between individuals with and without an IA.

The classification of the anterior part of the CoW was not available for six individuals with IA and for 15 individuals without IA. Similarly, the classification of the posterior part was not available for one individual without IA. Lacking information of the CoW variants was mainly due to suboptimal image quality.

Table 1. Baseline characteristic

Characteristic	Total	UIA	No UIA
No. of individuals	1291	94	1197
Women (%) (95% CI)	728 (56) (53-59)	69 (73) (64-82)	659 (55) (52-58)
Mean age in years (95% CI) ± SD	46,3 (45,5-47,1) ± 13,8	55,2 (53,1-57,3) ± 10,5	45,6 (44,8-46,4) ± 13,8
No. individuals with multiple UIAs (%)	18 (1,4)	18 (19,1)	-
Intracranial aneurysms			
No. Identified IAs (%)	125 (10)		
Women (%)	98 (78)		
Location in anterior part of COW			
Middle cerebral artery (%)	41 (33)		
Internal carotid artery (%)*	39 (31)		
Posterior communicating artery (%)	16 (13)		
Anterior communicating artery (%)	17 (14)		
Pericallosal artery (%)	4 (3)		
Anterior cerebral artery (%)**	2 (2)		
Location in posterior part of CoW			
Basilar artery (%)	2 (2)		
Superior cerebellar artery (%)	2 (2)		
Posterior inferior cerebellar artery (%)	1 (1)		
Posterior cerebral artery (%)	1 (1)		

95% CI = 95% confidence interval

* Include both proximal (para- ophthalmic) and distal (ICA top) IA's

** Include one proximal A1 segment IA and one IA at the A1-A2 junction.

Table 2. Anatomical variants of the CoW for individuals with and without intracranial aneurysms

	NO UIA (N=1197)		UIA (N=94)			
ANTERIOR CIRCULATION VARIANT	N	Proportions (95% CI)	N	Proportions (95% CI)	Difference in proportions (95% CI)	P-value
1	590	**0,50 (0.47 – 0.52)**	31	**0,35 (0.25 – 0.45)**	**0,15 (0,04 – 0,25)**	**0,008**
2	195	0,17 (0.14 – 0.19)	14	0,16 (0.08 – 0.24)	0,01 (-0,08 – 0,08)	0,89
3	4	0,00 (0,00 – 0.01)	1	0,01 (-0.01 – 0.03)	-0,01 (-0,05 – 0,01)	NA
4	344	**0,29 (0.27 – 0.32)**	37	**0,42 (0.32 – 0.52)**	**-0,13 (-0,24 – -0,03)**	**0,01**
5	49	0,04 (0.03 – 0.05)	5	0,06 (0.01 – 0.11)	-0,02 (-0,08 – 0,03)	0,49
6	0	-	0	-	-	NA
TOTAL:	*1182*		*88*			
POSTERIOR CIRCULATION VARIANT						
1	283	0,24 (0.21 – 0.26)	22	0,23 (0.15 – 0.32)	0,00 (-0,09 – 0,09)	0,96
2	320	0,27 (0.24 – 0.29)	20	0,21 (0.13 – 0.30)	0,06 (-0,04 – 0,14)	0,25
3	432	0,36 (0.33 – 0.39)	31	0,33 (0.24 – 0.43)	0,03 (-0,07 – 0,13)	0,54
4	86	0,07 (0.06 – 0.09)	9	0,10 (0.04 – 0.16)	-0,02 (-0,09 – 0,03)	0,39
5	65	0,05 (0.04 – 0.07)	8	0,09 (0.03 – 0.14)	-0,03 (-0,10 – 0,02)	0,21
6	10	0,01 (0.00 – 0.01)	4	0,04 (0.00 – 0.08)	-0,03 (-0,09 – 0,00)	NA
TOTAL:	*1196*		*94*			

NA = not applicable

Discussion

In a large sample of individuals with a familial predisposition for aSAH and unruptured IAs, the normal variant with a complete anterior part of the CoW was less prevalent in individuals with IA compared to those without IA, whilst the incomplete variant, characterized by Acom hypoplasia or absence, was more prevalent in individuals with IA compared to those without IA. No differences were observed among other variants of the CoW.

A previous review study[19] on anatomical variations in the CoW and formation and rupture of IAs, including 21 articles, found that the presence of a hypoplastic or absent A1-segment of ACA was significantly correlated with the formation of IAs as well as rupture of Acom aneurysms. Also, a fetal type PCA was associated with both formation and rupture of Pcom aneurysms. Another systematic review[12] on imaging markers of IA development, including 36 articles, described converging evidence for A1-segment asymmetry as anatomical imaging marker of Acom aneurysm development, and moderate evidence for several other imaging markers. Furthermore, a recent cross-sectional population study[13] with 1667 participants identified an association between an incomplete CoW, including hypoplasia or absence of the Acom, and the development of IA in the general population. The results from the review studies and the general population study are in line with the findings of our study, in which we found that individuals with IA have higher prevalence of the incomplete variant of the anterior part of the CoW characterized by Acom hypoplasia or absence. However, the findings of our study did not confirm the correlation between fetal type PCA and development of IAs. This observation might be impacted by the limited number of individuals exhibiting an aneurysm in the posterior part of the CoW.

The findings of anatomic variation in the A1-Acom complex suggest that these anatomical variants play a role in influencing the hemodynamic stress within the CoW. This may result in increased mechanical stress on the vascular wall, making the vessel wall more susceptible to the development of IAs. In addition, the higher prevalence of the normal variant in individuals lacking IA implies more optimal hemodynamic conditions within the CoW in these individuals. Therefore, the findings in this study confirm the hypothesis that hemodynamic changes are causally linked to anatomical variations, and that these conditions are generalizable from the general population to individuals with familial predisposition for IA and aSAH.

Strengths and limitations

A strength of our study is the use of a large sample size of individuals with a familial predisposition, allowing for a comparative analysis of the anatomical variants of the CoW between those with and without IAs. Next, the CoW variants were scored according to a commonly used and standardized method[15], and therefore our results are well comparable and applicable to other populations. However, a limitation of this study was that certain variants were limited to a small number of individuals only (respectively anterior circulation variant 3 and 6, and posterior circulation variant 6), making good comparisons between groups not feasible, and no conclusions can be drawn of the relation between these variants and the development of IAs.

Implications for future research and clinical practice

This study investigated a group of individuals with increased risk of IA development due to a familial predisposition for IA and aSAH. The CoW variants linked to the development of IAs within the general population exhibit resemblances to the variants identified in individuals with a familial predisposition for IA and aSAH. However, future studies should explore the association between the less prevalent variants, which were underrepresented within our study, and the formation of IAs in individuals with a familial predisposition for IA and aSAH. Comprehension of these imaging markers will contribute significantly to advancing our understanding of the pathogenesis underlying IA formation. Furthermore, within first-degree relatives of individuals affected by aSAH or IA, the utilization of these imaging markers may enhance the accuracy of predicting high-risk individuals susceptible to IA development during follow-up screening, utilizing data obtained from the first screening[20].

Conclusion

Among individuals with a familial predisposition for IA and aSAH, those with IA exhibit a higher prevalence of Acom hypoplasia or absence and a lower occurrence of the variant with a normal anterior circulation compared to individuals without IA. These findings correspond to previously reported correlations of CoW variants and IA development observed in general populations. Consequently, this implies a link between hemodynamic changes and anatomical variations, applying to both the general population and individuals with a familial predisposition for IA and aSAH. Knowledge on these imaging markers as risk factors for IA development could assist in directing the most effective preventive screening for first-degree relatives of individuals affected by IA and aSAH.

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