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Anatomical variations in the circle of Willis are associated with increased odds of intracranial aneurysms: The Tromsø study

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ABSTRACT

Purpose: Studies on patients suggest an association between anatomical variations in the Circle of Willis (CoW) and intracranial aneurysms (IA), but it is unclear whether this association is present in the general population. In this cross-sectional population study, we investigated the associations between CoW anatomical variations and IA.

Methods: We included 1667 participants from a population sample with 3 T MRI time-of-flight angiography (40–84 years, 46.5% men). Saccular IAs were defined as protrusions in the intracranial arteries ≥2 mm, while variants of the CoW were classified according to whether segments were missing or hypoplastic (< 1 mm). We used logistic regression, adjusting for age and IA risk factors, to assess whether participants with incomplete CoW variants had a greater prevalence of IA and whether participants with specific incomplete variants had a greater prevalence of IA.

Results: Participants with an incomplete CoW had an increased prevalence of IA (OR, 2.3 [95% CI 1.05–5.04]). This was mainly driven by the variant missing all three communicating arteries (OR, 4.2 [95% CI 1.7–1 0.3]) and the variant missing the P1 segment of the posterior cerebral artery (OR, 3.6 [95% CI 1.2–10.1]). The combined prevalence of the two variants was 15.4% but accounted for 28% of the IAs.

Conclusion: The findings suggest that an incomplete CoW is associated with an increased risk of IA for adults in the general population.

1. Introduction

The pathogenesis of saccular intracranial aneurysm (IA) is believed to be initiated by hemodynamic stress and a subsequent inflammatory response resulting in the weakening of the arterial wall [1–3]. Hemodynamic stress may be caused by hypertension [4] or geometric features of the arteries affecting how hemodynamic forces are transferred to the arterial walls [5,6]. The latter is evident from the anatomical predilection for IA locations, e.g., at bifurcations or the outer curvature of arteries [1,5,6]. Computational fluid dynamics similarly show that these locations are subjected to greater hemodynamic stress [7]. Intracranial aneurysms are usually found in or near the Circle of Willis (CoW), most commonly in the internal carotid artery (ICA) or the middle cerebral artery (MCA), followed by either the posterior communicating artery (PCoA) or the anterior communicating artery (ACoA) [8–13].

Arterial segments of the CoW are often missing or hypoplastic. Recent well-powered studies place the prevalence of the complete variant at around 12% [14,15]. Missing or hypoplastic segments can affect the velocity and direction of the blood flow in the CoW [16,17], which in turn may impact the risk of IA development. There are at least

Abbreviations: ACA, anterior cerebral artery; ACoA, anterior communicating artery; BA, basilar artery; CoW, Circle of Willis; IA, intracranial aneurysms; ICA, internal carotid artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; PCA, posterior cerebral artery; PCoA, posterior communicating artery.

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two ways variations in the CoW anatomy may contribute to the formation of IA. First, some incomplete CoW variants necessitate that a single feeding artery supply blood to a larger portion of the brain, increasing the flow velocity in that artery [16–18]. This may lead to greater hemodynamic stress on the arterial walls, which increases the risk of IA. Second, some CoW variants may have suboptimal bifurcation angles that increase hemodynamic stress and IA risk [5,19–21].

Although it is well known that the anatomy of the Circle of Willis varies considerably, the potential association between IA and anatomical variations in the CoW has been little studied. A dissection study of 44 brains showed that a hypoplastic A1 segment of the anterior cerebral artery (ACA) was associated with IA in the anterior communicating artery (ACoA) [22]. While a more recent magnetic resonance (MR) angiography study of 131 patients with unruptured IA and 440 controls found a similar association between a missing A1 segment and IA in the ACoA and also that a missing P1 segment of the posterior cerebral artery (PCA) was related to IA in the ICA [23]. The two studies suggest that the CoW anatomy may be related to aneurysm risk, but the findings are difficult to generalize as they stem from relatively small and sparsely characterized patient cohorts.

The purpose of this study was to determine whether there is an association between incomplete CoW variants and increased prevalence of IA in the general adult population. To this end, we used data from a population study to compare the prevalence of IAs in participants with an incomplete CoW to those with a complete CoW, and to compare participants with specific incomplete CoW variants to those with a complete CoW while correcting for age, gender, and IA risk factors in both analyses.

2. Methods

The study was approved by the Regional Committee of Medical and Health Research Ethics Northern Norway (2014/1665/REK-Nord) and carried out in accordance with guidelines at UiT The Arctic University of Norway. All participants gave written informed consent before participating in the study. The data used in the analysis can be obtained by contacting The Tromsø Study (tromsous@uit.no).

2.1. Study participants

We used data from the 7th Tromsø study, a population-based study of citizens 40 years or older in the Tromsø municipality, conducted between 2015 and 2016 [24]. The main part of the Tromsø 7 study collected demographic and health data, including blood pressure, body mass index (BMI), smoking status, serum cholesterol, and high-density lipoprotein used in the present study. A subsample of participants underwent an ultrasound examination of the carotid arteries ($N = 3027$), and these were also invited to a brain MRI. Of these, 975 did not respond, 169 had MRI contraindications, and five had moved or died, giving 1878 that underwent MRI in 2016–2017. We combined data from two previous studies on the participants' anatomical variation in the CoW [14] and the prevalence of IA [13], giving 1858 participants with information on the CoW anatomy and intracranial aneurysms (20 examinations were lost due to missing data, poor image quality and

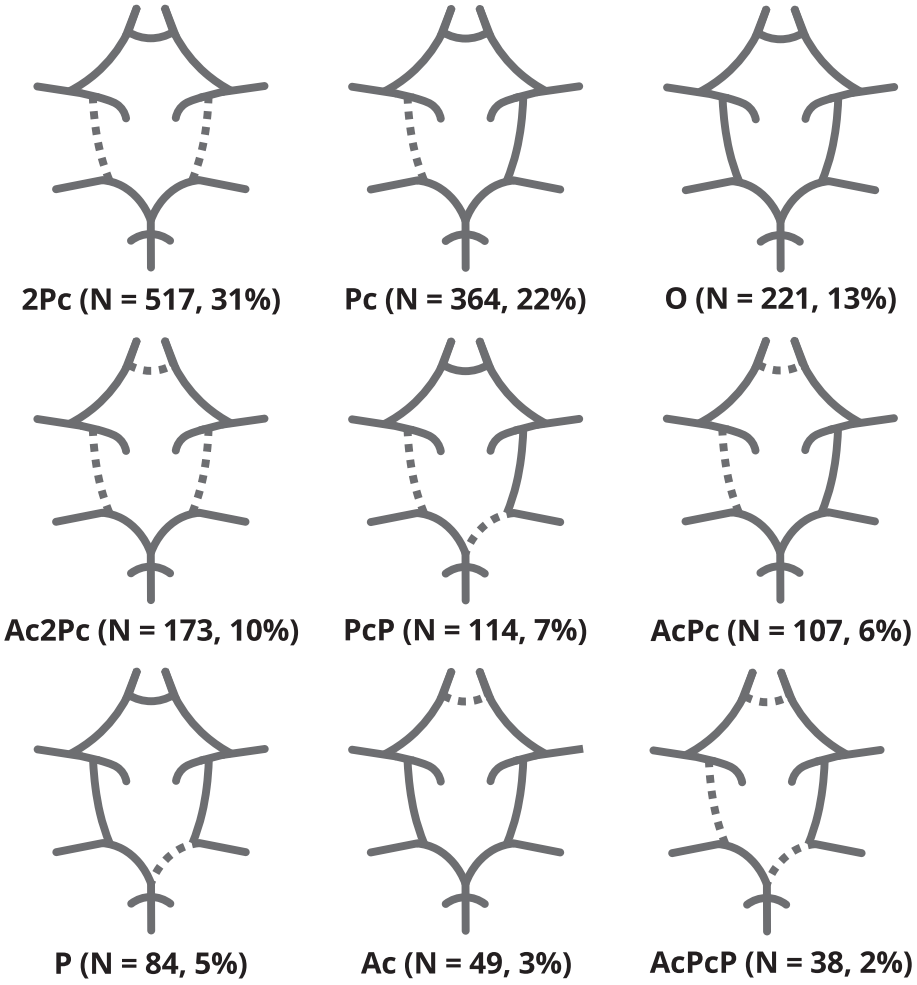

Fig. 1. The anatomical variants of the Circle of Willis used in the study arranged by prevalence. Note that left-right symmetric variants were merged, such that, for example, the P-variant, with a missing or hypoplastic P1 segment, included cases where either the left or right P1 segment is missing/hypoplastic.

participant's withdrawal from the study).

Variations in the CoW anatomy were classified according to whether one or more of the seven segments constituting the CoW (the A1 segments of the ACA, the ACoA, the PCoA, and the P1 segments of the PCA) were missing or hypoplastic using a 1 mm diameter threshold. The original classification of the CoW anatomy distinguished between left-right symmetric anatomical variants. These were merged into a single, non-lateralized variant. Uncommon variants with <2% frequency were excluded ($N = 191$) to avoid unreliable statistical estimates. The total sample thus consisted of 1667 participants with nine CoW variants (Fig. 1).

2.2. MRI protocol

Participants were scanned at the University Hospital North Norway with a 3 T Siemens Skyra MR scanner (Siemens Healthcare, Erlangen, Germany). We used a 64-channel head coil for most examinations except for 31, where a slightly larger 20-channel head coil was used to accommodate the participant's head. The MRI protocol consisted of T1-weighted, T2-weighted fluid-attenuated inversion recovery, TOF angiography, and susceptibility-weighted scans, but only TOF images were used in this study. TOF images were acquired with a 3D transversal fast low angle shot (FLASH) sequence with flow compensation and time to repeat/time to echo = 21/3.43 ms, generalized autocalibrating partially parallel acquisition (GRAPPA) parallel imaging acceleration factor 3, field of view 200 × 181 mm, with 7 slabs with 40 slices each and slice thickness 0.5 mm. The reconstructed image resolution was 0.3 × 0.3 × 0.5 mm.

2.3. Assessment of aneurysms

The participants were examined for IA by two neuroradiologists, each with more than ten years of experience (authors L.H.J. and M.H.), as detailed in full by Johnsen and coworkers [13]. Briefly, the presence of IA was read twice by one neuroradiologist (L.H.J.), and IA size measurements were done by both neuroradiologists (L.H.J. and M.H.). Interrater reliability was assessed by (M.H.) on 100 examinations drawn from a random sample of 160 participants without and 30 participants with IA. IAs were defined as focal protrusions in an intracranial artery with a size ≥2 mm. The intraobserver intraclass correlation coefficient (ICC) for detecting IA was 0.98, Cohen's Kappa for the interrater agreement was 0.79, and the interobserver ICC for the measurement of aneurysms size was 0.93.

Intracranial aneurysm location was classified according to the classification in Fig. 2. The ICA was defined as a single segment from the paraopthalmic region up to the PCoA branch. The terminus segment was defined as the segment between the PCoA branch and the ACA - MCA bifurcation. The MCA was defined as a single region, while the ACA was divided into the A1 and A2 segments. The anterior and posterior communicating arteries, ACoA and PCoA, respectively, were defined as separate locations. The PCA was separated into P1 and P2 segments. The vertebrobasilar arteries encompassing the basilar artery, superior cerebellar artery, posterior inferior cerebellar artery, and anterior inferior cerebellar artery were combined in the BA location.

2.4. Covariates and IA risk factors

In addition to age, the statistical models were adjusted for three known risk factors of IA in the general population: female sex, hypertension, and current smoking [25,26]. Hypertension was defined as systolic blood pressure equal to or larger than 140 mmHg or diastolic blood pressure equal to or larger than 90 mmHg. Smoking status was based on questionnaire data classifying smoking into "never," "previously," and "currently". The "never" and "previously" categories were merged to give a dichotomous "current smoking" variable. For the previous smoker category (48% of participants), the majority had quit smoking for more than ten years, median (IQR) 18 (10−32) years. Missing values among these risk factors were imputed with median values.

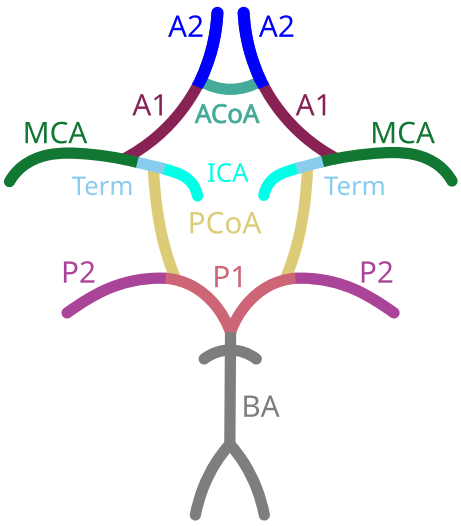

Fig. 2. Definition of the locations of the intracranial aneurysms. A1 = A1 segment of the anterior cerebral artery, A2 = A2 segment of the anterior cerebral artery, ACoA = anterior communicating artery, MCA = middle cerebral artery, ICA = intracranial part of the internal carotid artery, PCoA = posterior communicating artery with the anterior choroidal artery, P1 = P1 segment of the posterior cerebral artery, P2 = P2 segment of the posterior cerebral artery, BA = basilar artery, and upstream branching arteries.

2.5. Statistical analysis

Three binary logistic regression models were used to examine the association between anatomical variations in the CoW and IA: A simple crude model for examining the odds of IA for any incomplete CoW variant relative to the complete CoW without any adjustment. A simple model for examining the odds of IA for any incomplete CoW variant relative to the complete CoW, and a full model for examining the odds of IA for the eight incomplete CoW variants relative to the complete CoW variant by treating each variant in Fig. 1 as a separate factor. The latter two models were adjusted for age, sex, hypertension, and current smoking. The full model had 12 parameters, excluding intercept, and 1667 observations, of which 110 had IA, giving an acceptable events-per-variable (EPV) ratio in a logistic model with binary predictors [27]. Statistical analyses were done with R (v3.5.2). We considered p-values <0.05 as significant.

3. Results

Table 1 shows the key characteristics of the participants. The same characteristics stratified by CoW variant are given in Supplementary Table 1. Participants with incomplete CoW variants had elevated systolic blood pressure (SBP) and more hypertension compared to those with a complete CoW (Supplementary Table 1). The 191 participants with uncommon CoW anatomical variants excluded from the analysis were, on average, older and had greater systolic blood pressure and a higher rate of hypertension compared with those included in the analysis (Supplementary Table 2).

One hundred and seventeen IAs were found in 110 participants (6.6% prevalence), of which six had multiple IAs (Table 2). Intracranial aneurysms were most prevalent in the ICA and MCA. Seven (6.4%) of the 110 participants with IA had a complete CoW. The median size of the 117 IAs was 3.1 mm (range 2.0–11.6 mm), and the IA size per CoW variant is shown in Supplementary Fig. 1. Of the 191 excluded participants, 10 had one or more IAs (5.2% prevalence).

Table 1
Demographic and clinical characteristics of the 1667 participants.

Variable	All participants*	Missing	Min	Max
Age (years)	63.5 (10.6)	0	40	84
Sex				
Female	892 (53.5)	0		
Male	775 (46.5)			
BMI (kg/m^2)	27.1 (4.2)	1	13.9	45.9
Chol./HDL	3.7 (1.4)	6	1.3	23.0
SBP (mm Hg)	133.4 (20.6)	6	78	220
DBP (mm Hg)	75.1 (9.9)	6	44	112
Hypertension				
No	1038 (62.5)	6		
Yes	623 (37.5)			
Current smoker				
No	1437 (87.2)	19		
Yes	211 (12.8)			

* Mean (SD) reported for continuous variables and count (percentage) for categorical variables. SD = standard deviation, BMI = body mass index, Chol. = total cholesterol, HDL = high density lipoprotein, SBP = systolic blood pressure, and DBP = diastolic blood pressure.

The simple crude logistic regression model showed that having any of the incomplete CoW variants included in this study was associated with higher odds of IA compared to the complete CoW variant (OR, 2.3 [95% CI, 1.08–5.11]). Adjusting for age, sex, hypertension, and smoking had minimal effect on the odds ratio (OR, 2.3 [95% CI, 1.05–5.04]). In the full model, two specific variants had significantly higher odds of IA compared to the complete CoW variant, the Ac2Pc (OR, 4.2 [95% CI, 1.7–10.3]) and the P variant (OR, 3.6 [95% CI 1.2–10.1]). (See Table 3).

4. Discussion

To our knowledge, this is the first study that has examined whether there is an association between IA prevalence and the anatomy of the CoW in a well-characterized population sample. The main finding was that having an incomplete CoW was associated with increased odds of IAs. Furthermore, two specific incomplete CoW variants were significantly associated with increased odds of IA. One variant had a missing or hypoplastic proximal P1 segment, while all communicating arteries were missing or hypoplastic in the other. The findings suggest that incomplete CoW variants may be associated with an elevated risk of IAs.

Although incomplete CoW variants, in general, had a higher prevalence of IA, it is unclear why participants with the Ac2Pc and P variants had the highest risk of IA. If certain anatomical variants lead to unfavorable flow conditions that increase the risk of IAs, one should expect an association between these variants and IA location. Our data suggest such an association: Most IAs were in the MCA (13 out of 22) for the Ac2Pc variant, while most IAs were in the ICA (4 out of 9) for the P variant (Table 2). Conversely, there was only one IA in the ICA for the Ac2Pc variant and none in the MCA for the P variant. These differences

Table 2
Location of saccular intracranial aneurysms (IA) in participants for each Circle of Willis variant. The six last rows are the six participants with multiple aneurysms.

IA location(s)		Circle of Willis variant								
	Sum:	O	Ac	AcPc	Ac2Pc	AcPcP	Pc	2Pc	PcP	P
Sum:	110	7	2	6	22	2	24	30	8	9
A1	1						1			
ACoA	9				1		2	2	2	2
PCoA	7				5				1	1
P1	1							1		
Terminus	6			2			1	3		
ICA	31	3	1	1	1		7	12	2	4
MCA	42	3	1	3	13	1	9	9	3	
BA	7				2	1	2	1		1
A1 + ACoA	1						1			
PCoA + ACoA	1							1		
PCoA + PCoA	1	1								
P2 + BA + MCA	1							1		
ICA + BA	1						1			
MCA + MCA	1									1

A1 = A1 segment of the anterior cerebral artery, ACoA = anterior communicating artery, PCoA = posterior communicating artery, P1 = P1 segment of the posterior cerebral artery, P2 = P2 segment of the posterior cerebral artery, ICA = internal carotid artery, MCA = middle cerebral artery, BA = basilar artery.

Table 3
Logistic regression models for the presence of at least one intracranial aneurysm. Coefficients in the table are unstandardized and exponentiated to show odds per unit and odds ratios for binary factors.

	Crude Simple Model		Adjusted Simple Model		Adjusted Full Model	
	Odds	95% CI	Odds	95% CI	Odds	95% CI
Intercept	0.03 ***	0.02–0.07	0.02 ***	0.0–0.09	0.03 ***	0.01–0.10
Incomplete (all)	2.34 *	1.08–5.11	2.31 *	1.05–5.04		
2Pc					1.86	0.80–4.33
Ac					1.26	0.25–6.27
Ac2Pc					4.28 **	1.77–10.32
AcPc					1.76	0.57–5.38
AcPcP					1.61	0.32–8.10
P					3.63 *	1.30–10.14
Pc					2.14	0.91–5.07
PcP					2.36	0.83–6.73
Age			1.01	0.99–1.03	1.00	0.98–1.02
Sex (male)			0.73	0.49–1.08	0.74	0.50–1.11
Hypertension			1.21	0.80–1.83	1.21	0.80–1.83
Current smoker			1.48	0.88–2.48	1.52	0.90–2.57

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

in IA locations for the two CoW variants support the idea of an association between CoW anatomy and IA.

For the P variant, flow measurements in healthy participants and patients with IA show that fetal-type posterior CoW anatomy (i.e., equivalent to the P variant if the PCA P1 diameter is <1 mm) is associated with increased flow in the ICA and decreased flow in the BA compared to those with the complete variant [16–18]. Therefore, the ICA carries a larger part of the total cerebral blood flow [17], which may explain the greater prevalence of IAs in the ICA for participants with the P variant. However, this interpretation should be considered with caution due to the low number of observations.

The flow pattern of the Ac2Pc variant is different from the other CoW variants we examined since all communication arteries are hypoplastic or missing, such that it is minimal or no collateral flow in this variant. This suggests that some other factor than a redistribution of the blood flow in the CoW is the underlying cause of the increased IA prevalence. The Ac2Pc variant also differed from the P variant in that most aneurysms were in the MCA. Aneurysms in the MCA have been associated with bifurcation angles deviating from the principle of minimum work in the MCA-1 and MCA-2 sections of the MCA [5,20,21]. We speculate that participants with the Ac2Pc variant could have a predisposition for unfavorable bifurcation angles when all communicating arteries are hypoplastic or missing. It has also been suggested that the communicating arteries in the CoW play a role in dampening pulsatile blood pressure [28,29]. MCA pulsatile pressure is associated with the size of MCA aneurysms [30], which could indicate that the diminished communicating capacity of the Ac2Pc variant leads to less dampening in the CoW, increasing the pulsatile pressure in the MCAs and increasing the risk of IA.

In a previous study on the same material, we found that participants with an incomplete CoW were generally older than those with a complete CoW [14]. This has also been reported by others [31–33], and the same trend is evident from Supplementary Table 1, where the average age for the participants with incomplete variants, except the Ac variant, is greater than those with the complete variant. Supplementary Table 1 also shows that SBP and the rate of hypertension are, on average higher for the participants with incomplete CoW variants, in agreement with previous studies [34,35]. Although we corrected for age and hypertension in the regression models, these risk factors for IA may contribute to the higher prevalence of IA in participants with incomplete CoW variants.

It is worth noting that none of the risk factors for IA, i.e., smoking, female sex, and hypertension, were associated with IA in our study, although all had increased OR. Our study participants had similar average age, sex ratio, and average BMI as in the study by Cras and coworkers, which used proton-density weighted MR images from the Rotterdam study to assess IA [25]. Differences were that our participants had lower SBP, DBP, and rate of hypertension and fewer smokers. These differences in sample characteristics may explain the diverging results, as may lower statistical power in our study with 1667 participants compared to 5841 participants in the study by Cras and coworkers.

Comparing our findings with the two previous studies on anatomical variants of the CoW and IA reveals discrepancies and similarities. Key findings in the two previous studies were that a missing A1 segment was associated with IA in the ACoA, while a missing P1 segment was associated with IA in the ICA [22,23]. In our data, all variants with a missing A1 segment had prevalences below 2%, making meaningful comparisons difficult. However, the increased prevalence of ICA aneurysms for the P variant agrees with Horikoshi and coworkers [23]. Unfortunately, further comparisons were impossible due to differences between ours and Horikoshi's classification of the CoW anatomy.

Strengths of the current study include a well-characterized population sample with high-resolution TOF MRA and the use of statistical models adjusted for known risk factors of IA. We also examined multiple incomplete CoW variants in our study, which enabled us to identify specific variants with increased odds of IA. An important limitation of the current study was the moderate sample size, with only 110 participants with IA. This power issue also prevented us from examining less prevalent CoW variants. There is also uncertainty in the CoW anatomy as it was determined from TOF images, which require net flow for the arteries to be visible [36]. The cross-sectional design cannot inform on causality, and an incomplete CoW and IA could develop in parallel over time due to common underlying risk factors.

5. Conclusion

This cross-sectional population-based study shows that incomplete CoW variants are associated with the presence of IAs, suggesting that incomplete CoW variants may contribute to the development of IAs. Further studies are warranted to clarify whether a causal mechanism is behind variations in the CoW and IA.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2023.120740.

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Disclosures

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