Original Article

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DOI: 10.4103/bc.bc_43_19

Demographic age-related variation in Circle of Willis completeness assessed by digital subtraction angiography

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Abstract

OBJECTIVE: Incomplete circle of Willis (CoW) configuration is an important risk factor for cerebrovascular pathology, namely aneurysm formation and ischemic stroke. This study was performed to characterize CoW variation using digital subtraction angiography and to identify demographic and physiologic features that may influence the risk of having an incomplete CoW configuration.

MATERIALS AND METHODS: A retrospective review of 274 patients who underwent cerebral angiography by a single surgeon for any indication was conducted. Each CoW branch was graded as normal, hypoplastic, or aplastic. Univariate and multivariate regression analyses were conducted to assess the impact of age, gender, race, and certain comorbidities on CoW configuration.

RESULTS: A complete CoW was identified in 37.23% of patients. In univariate analysis, patients <40 years old were more likely to have a complete CoW (odds ratio [OR]: 4.973, 95% confidence interval [CI]: 2.610–9.476, $P < 0.001$) as were patients <70 years old (OR: 2.849, 95% CI: 1.131–7.194, $P < 0.05$). Univariate analysis on demographic factors and comorbidities revealed CoW completeness to decrease with hypertension (OR: 0.575, 95% CI: 0.347–0.951, $P = 0.031$) and diabetes mellitus (OR: 0.368, 95% CI: 0.180–0.754, $P = 0.006$). Multivariable logistic regression analysis used to assess the impact of age on CoW completeness showed age to be an independent predictor of complete CoW, with an inverse correlation between increasing age and CoW completeness (OR: 0.955, 95% CI: 0.937–0.973, $P < 0.001$) after controlling for potential confounders including hypertension and diabetes mellitus.

CONCLUSIONS: CoW configuration shows considerable variation with age; however, further investigation is required to elucidate the full impact of other demographic and vascular risk factors on CoW anatomy.

Keywords:

Age, cerebral arteries, circle of Willis, demographic, digital subtraction angiography

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Submission: 30-09-2019
Revised: 31-10-2019
Accepted: 26-11-2019
Published:18-02-2020

Introduction

The Circle of Willis (CoW), the epicenter of cerebral blood flow, provides crucial collateral circulation through its seven major branches. Given its importance in neurovascular physiology, even slight variations to the normal anatomy of this eminent structure can have clinical repercussions. Experimental and computational models suggest that increased flow through an abnormal configuration of patent branches increases wall sheer stress leading to aneurysmal formation.[1-4] Similarly, incomplete configuration increases the risk of ischemic stroke, likely due to reduced collateral circulation.[4,5]

How to cite this article: Eaton RG, Shah VS, Dornbos III D, Zaninovich OA, Wenger N, Dumont TM, Powers CJ. Demographic age-related variation in Circle of Willis completeness assessed by digital subtraction angiography. Brain Circ 2020;6:31-7.

An incomplete CoW as a risk factor for stroke and aneurysm formation continues to be a focus of research in cerebrovascular disease. In 1984, Kayembe *et al*.[6] found aneurysms to be more common in autopsy studies in patients with CoW anatomic variations, a finding suggested by CoW assessment with advanced imaging. Individuals with variations in the CoW are more likely to have aneurysmal recurrence after endovascular treatment[7] and may be at higher risk for aneurysmal rupture.[8,9] Variation of the first segment of the anterior cerebral artery increases the likelihood of having an anterior communicating artery aneurysm[10] and puts individuals at risk for infarct after aneurysmal rupture.[11] Acute ischemic stroke risk is similarly elevated in individuals with variant CoW configurations.[5,12-18] Individuals with good cerebral collateral circulation tend to have smaller infarct size at baseline and higher rates of neurological improvement following acute ischemic stroke.[19,20]

A recent work by Zaninovich *et al*.[21] supports the emerging theory that age and gender have a significant effect on the rates of complete CoW, which subsequently impacts these disease states. Women have a higher lifetime risk of stroke, more frequent recurrences, and higher mortality, whereas men have the risk of first stroke at a younger age.[22] Notably, stroke risk strongly correlates with age in both genders.[22] Ghods *et al*. showed that gender affects aneurysmal location, in which women are more likely to have multiple aneurysms, aneurysms of the internal carotid artery, and tend to present with subarachnoid hemorrhage.[23] With regard to age, middle cerebral artery aneurysms are less common with age >55 years, and women are more likely to present later in life.[23,24]

Digital subtraction angiography (DSA) remains the gold standard for assessing cerebral arteries and is particularly successful in identifying hypoplastic vessels when compared to computed tomography angiography (CTA) and magnetic resonance angiography (MRA).[25-27] The primary objective of this study was to describe CoW completeness with respect to age, gender, and race as assessed by DSA, rather than noninvasive imaging, which tends to be less specific. To our knowledge, this is the largest patient cohort to be assessed by DSA, allowing for characterization of anatomic variations of each major vessel, including fetal posterior communicating arteries. The mechanism underlying apparent changes in CoW configuration with age has yet to be elucidated, although this is hypothesized to be secondary to a combination of factors including atherosclerosis.[28,29] As such, this study also seeks to describe the population and patient factors associated with incomplete CoW with respect to known atherosclerotic risk factors, namely blood pressure, low-density lipoprotein, smoking, diabetes mellitus, and body mass index.[30]

Materials and Methods

Patients

The study was approved by the institutional review board with a waiver of consent, given that all data were gathered retrospectively and anonymously. From January 2016 to March 2018, 322 consecutive patients who underwent DSA for any indication by a single surgeon were included in the study. Clinical indications for DSA included ischemic stroke, cerebral aneurysm, suspected vasospasm, intracerebral hemorrhage, vessel dissection, transverse sinus stenosis, severe epistaxis, arteriovenous malformation, and dural arteriovenous fistula. Of the initial 322 patients, 48 were excluded due to (1) incomplete imaging due to either missing internal carotid artery or vertebral artery injections, (2) occlusion or severe stenosis of vasculature proximal to the CoW, or (3) patients with moderate or severe vasospasm. Patients diagnosed with Moyamoya disease were also excluded from the study.

Patient information was gathered via a retrospective review of personal health information. Demographic information was used to compile age, gender, and race. The International Classification of Diseases-9 and International Classification of Diseases-10 codes were used to describe whether patients had any of the comorbidities of interest, including Type II diabetes mellitus, hypertension, coronary artery disease, peripheral artery disease, prior cerebrovascular accident or transient ischemic accident, and obstructive sleep apnea at the time of angiography. Body mass index was calculated using the patients' height and weight measurements. Hyperlipidemia was defined as any preangiography low-density lipoprotein value $\geq$100 mg/dl. Smoking status was determined by evaluating documentation obtained preangiography, with any documented previous smoking history being considered positive.

Image acquisition

DSA images were acquired via transfemoral approach with a 4 Fr or 5 Fr catheter in a fully equipped DSA unit. A catheter was advanced into the right and left internal carotid arteries and a vertebral artery. Contrast was injected manually, and images were captured at 3 frames/s. Anteroposterior and lateral images were obtained with oblique images variably obtained based on pathology identified during angiography.

Image analysis

All DSA images were reviewed by three blinded reviewers. To minimize differences between prior studies on CoW configuration, the major branches of the CoW were considered to be the anterior communicating artery, the first segments of both anterior cerebral

arteries, the first segments of both posterior cerebral arteries, and both posterior communicating arteries.[21,25] Each segment was graded as normal, hypoplastic, or aplastic [Figure 1]. Hypoplastic was defined as vessel size <30% of the size of the ipsilateral distal vessel. For the posterior communicating artery and the first segment of posterior cerebral artery, this was the second segment of the posterior cerebral artery, and for anterior circulation arteries, this was the second segment of the anterior cerebral artery.[25] Aplastic vessels were defined as a vessel that could not be identified on any DSA image.

Statistical analysis

The incidence of each vessel segment of the CoW was tabulated for the entire cohort. The frequency of incomplete CoW was defined as any CoW with at least one aplastic vessel and was calculated for three age groups (ages <40, 40–69, and ≥70 years). The incidence of incomplete CoW was found within each demographic and comorbid disease group of interest including gender, race, diabetes mellitus, smoking status, hypertension, hyperlipidemia, coronary artery disease or peripheral artery disease, prior cerebrovascular accident including transient ischemic accident, obstructive sleep apnea, and obesity. Univariate binary logistic and linear regression analyses were used to assess the impact of categorical and continuous dependent variables, respectively. Finally, a multivariable logistic regression analysis was conducted to assess the potential predictors of CoW completeness with respect to age using co-variants that approached statistical significance ($P < 0.20$) on univariate analysis.

Results

The overall incidence of patent, hypoplastic, and aplastic vessels for each of the seven major branches of the CoW is listed in Table 1. The overall incidence of a complete CoW in the entire patient cohort was 37.23% when incomplete CoW was defined as any aplastic vessels. The incidence of a complete CoW was 8.03% when an incomplete CoW was defined as any hypoplastic or aplastic vessels. The most common variants were an aplastic left posterior communicating artery (31.75%) and a hypoplastic right posterior communicating artery (29.56%). The incidence of normal vessels in the anterior circulation was 68.25% for anterior communicating artery and 95.26% and 91.24% for the first segments of left and right anterior cerebral arteries, respectively. The left and right posterior communicating arteries were normal in 25.18% and 25.91% of cases, respectively, whereas the left and right posterior cerebral arteries were normal in caliber in 88.32% and 85.77% of cases, respectively. Hypoplastic and aplastic vessels were seen in greatest frequency in the anterior communicating artery and posterior communicating arteries. Fetal posterior communicating arteries were present in 14.60% of patients on the left and 16.79% on the right.

Patients aged <40, 40–69, and ≥70 years had a complete CoW in 67.92%, 31.75%, and 18.75%, respectively [Table 2]. On univariate analysis, patients <40 years old were more likely to have a complete CoW (odds ratio [OR]: 4.973, 95% confidence interval [CI]: 2.610–9.476, $P < 0.001$) as were patients <70 years old (OR: 2.849, 95% CI: 1.131–7.194, $P < 0.05$) compared to patients aged ≥70 years. Overall, increasing age correlates with total aplastic and hypoplastic vessels ($\beta = 0.017$, 95% CI: 0.011–0.024, $P < 0.001$).

Table 1: Original data on the incidence of normal, hypoplastic, aplastic, and fetal circle of Willis branches

	Normal, *n* (%)	Hypoplastic, *n* (%)	Aplastic, *n* (%)	Fetal, *n* (%)
A-CommA	187 (68.25)	56 (20.44)	31 (11.31)	-
Left A1	261 (95.26)	10 (3.65)	3 (1.09)	-
Right A1	250 (91.24)	12 (4.38)	12 (4.38)	-
Left P-CommA	69 (25.18)	78 (28.47)	87 (31.75)	40 (14.60)
Right P-CommA	71 (25.91)	81 (29.56)	76 (27.74)	46 (16.79)
Left P1	242 (88.32)	11 (4.01)	21 (7.66)	-
Right P1	235 (85.77)	20 (7.30)	19 (6.93)	-

A-CommA: Anterior communicating artery, A1: First segment of anterior cerebral artery, P-CommA: Posterior communicating artery, P1: First segment of posterior cerebral artery

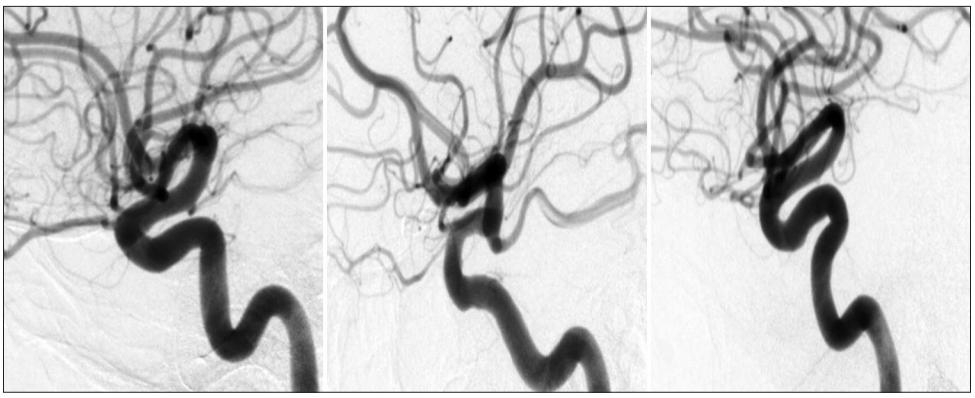

Figure 1: Original digital subtraction angiography image of posterior communicating artery variation. Examples of hypoplastic (left), normal (middle), and aplastic (right) posterior communicating artery

There was no significant difference in the frequency of CoW completeness with respect to gender or race [Table 3]. On univariate regression analysis [Table 4], both hypertension (OR: 0.575, 95% CI: 0.347–0.951, $P = 0.031$) and diabetes mellitus (OR: 0.368, 95% CI: 0.180–0.754, $P = 0.006$) correlated with decreased CoW completeness. Multivariate regression analysis showed age to be an independent predictor of complete CoW with an inverse correlation between increasing age and CoW completeness (OR: 0.955, 95% CI: 0.937–0.973, $P < 0.001$) when controlling for potential confounding variables including African-American race, other race, hypertension, history of cerebrovascular accident, and diabetes mellitus. Importantly, when controlling for age, diabetes mellitus and hypertension did not significantly correlate with CoW completeness status.

Discussion

CoW completeness has varied considerably in imaging[31-42] and autopsy[6,43-50] studies. The completeness rate in this study replicates a recent large sample study with a similar focus using CTA.[21] The functional assessment afforded by DSA allows for accurate characterization of small-diameter vessels into aplastic versus hypoplastic. This nuanced evaluation of hypoplastic vessels altered the completion frequency considerably when hypoplastic vessels were considered incomplete. The largest DSA CoW analysis, a 117-patient series conducted by Han *et al*.[25] previously with an analogous vascular grading scale, showed high variability in the communicating segments relative to the first segments of both the anterior and posterior cerebral arteries. This high degree of variation was replicated in this study, with the anterior and posterior communicating arteries showing considerable variation, an anomaly that has known significant clinical ramifications in cerebrovascular pathology.[10,11] To our knowledge, this is the first dedicated DSA assessment of fetal posterior circulation, which has been cited as a potential risk factor for ischemic strokes.[16] The incidence of approximately 15% overall in this study was comparable to an incidence of 11%–46% documented in a recent review.[51]

The degree of environmental and genetic contributions to CoW configuration remains unclear.[52] In a mouse model,[28] both aging and hypertension were found to reduce posterior communicating artery diameter. However, it has been demonstrated that posterior communicating artery variations occur more often within a family.[29] In this study, younger patient age was highly predictive of CoW completeness, a relationship becoming increasingly well established in literature.[21,32,37-39] The results of this study strengthen this association, finding age to be an independent predictor of complete CoW, even after controlling for hypertension and diabetes mellitus.

The two other demographic variables assessed (gender and race) showed no significant difference in CoW completeness. Previous studies have found a higher female preponderance;[32,34,38] however, others[39,53] have reported opposite findings, with men having a slightly higher completeness. Racial and ethnic differences in configuration have been a recent research focus, in which a Sri Lankan autopsy study[46] demonstrated that CoW configuration varied among ethnicity. MRA evaluation of CoW in Ecuadorian Mexicans,[54] Turkish,[42] and Pakistani[41] populations yielded variable completeness incidence of 65.10%, 85%, and 22.2%, respectively. Due to challenges in assessing ethnic background via the personal health information system, this study estimated differences in ethnicity using race, and thus it is possible that a more refined categorization with respect to ethnic background may show a difference and should be a consideration for similar studies in future.

Atherosclerosis follows an analogous age-based trajectory to CoW completeness frequency changes

Table 2: Original data on the impact of age on circle of Willis completeness

Age (years)	Patients (*n*)	Completion frequency (%)	Mean age (SD)	Univariate analysis for complete CoW, OR (95% CI); *P*	Univariate analysis for total hypoplastic and aplastic vessels, β coefficient (95% CI); *P*
<40	53	67.92	28.94 (6.08)	4.975 (2.611-9.434); <0.001	−0.571 (−0.833-−0.309); <0.001
40-69.99	189	31.75	55.77 (8.15)	2.101 (1.244-3.546); <0.01	0.315 (0.087-1.848); <0.01
≥70	32	18.75	74.72 (4.19)	0.351 (0.139-0.884); 0.026	0.211 (−0.121-0.543); 0.211
Total	274	37.23	52.79 (15.08)	0.954 (0.937-0.972); <0.001	0.017 (0.011-0.024); <0.001

SD: Standard deviation, OR: Odds ratio, CI: Confidence interval, CoW: Circle of Willis

Table 3: Original data on the influence of demographic factors on circle of Willis completeness

	Patients (*n*)	Age, mean (SD)	Completion frequency (%)	OR (95% CI); *P*
Female	175	51.21 (14.84)	38.29	1.134 (0.679-1.894); 0.630
Male	99	55.59 (15.10)	35.35	-
Caucasian	217	52.98 (15.42)	36.41	1.165 (0.635-2.135); 0.622
African-American	55	52.14 (13.50)	40.00	0.570 (0.295-1.098); 0.093

OR: Odds ratio, CI: Confidence interval, SD: Standard deviation

Table 4: Original data on the impact of risk factors for atherosclerotic vascular disease on circle of Willis completeness

	Patients (*n*)	Completion frequency (%)	OR (95% CI); *P*
Smokers	161	34.78	0.801 (0.486-1.318); 0.382
Nonsmokers	108	40.74	
Hyperlipidemia	42	30.95	0.614 (0.270-1.396); 0.245
LDL <100 mg/dL	64	42.19	
Hypertension	170	32.35	0.575 (0.347-0.951); 0.031
No hypertension	103	45.63	
CAD or PAD	49	40.82	1.186 (0.631-2.232); 0.597
No CAD or PAD	224	36.61	
Prior CVA	56	46.43	1.597 (0.881-2.890); 0.123
No prior CVA	217	35.02	
Diabetes mellitus	53	20.75	0.368 (0.180-0.754); 0.006
No diabetes mellitus	220	41.36	
OSA	20	35.00	0.895 (0.335-2.326); 0.821
No OSA	253	37.55	
BMI >30	106	36.79	0.986 (0.595-1.631); 0.956
Normal BMI	167	37.13	

LDL: Low-density lipoprotein, CAD: Coronary artery disease, PAD: Peripheral artery disease, CVA: Cerebrovascular accident, OSA: Obstructive sleep apnea, BMI: Body mass index, OR: Odds ratio, CI: Confidence interval

and is heavily affected by blood pressure, low-density lipoprotein, smoking, diabetes mellitus, and body mass index.[30] One study found no relationship between cerebral small-vessel disease and CoW completeness,[55] supporting a potential hypothesis that configuration changes require continuous vascular demand on large-diameter arteries. This study showed that hypertension and diabetes mellitus were associated with an increased odds of having an incomplete CoW. However, when included in a multivariate analysis, age was found to be the primary mechanistic driver impacting CoW vessel anatomy, rather than these confounding comorbidities. Interestingly, other comorbidities analyzed which are also strongly associated with age such as hyperlipidemia, coronary artery disease or peripheral artery disease, and prior cerebrovascular accident did not reach significance in the regression analysis. It is certainly possible that this study was underpowered to adequately evaluate the impact of the conditions and thus a larger review may be helpful in further establishing this relationship.

The population of patients undergoing cerebral angiography is weighed toward individuals with cerebrovascular conditions, specifically evaluation of stroke and aneurysm, which is known to decrease CoW completeness.[21,56] Unfortunately, this problem is inherent to assessments made by DSA which is an invasive test, requiring appropriate indications. Using a study population more representative of a healthy population using CTA or MRA imaging would potentially produce different results. Finally, this study is of descriptive and retrospective nature and future work should focus on prospectively following a health population over time to further solidify the effect of age on CoW configuration.

Conclusions

CoW anatomy, as assessed by DSA, shows considerable variation. Complete CoW is closely and inversely related to age. The relationship between CoW completeness and other demographic factors, such as race and gender, did not reach significance in this study. Furthermore, comorbid conditions commonly associated with atherosclerosis and cerebrovascular disease did not significantly affect CoW completeness when controlling for age. Further work is needed to elucidate the mechanism behind the age-related decline in CoW completeness and to anticipate which individuals are at risk of CoW incompleteness and its associated pathologic effects.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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