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Association between symptomatic intracranial atherosclerotic disease and the integrity of the circle of Willis

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The relationship between the severity of intracranial atherosclerotic disease and the circle of Willis integrity is unclear. In this brief report, we investigate the associations between symptomatic intracranial atherosclerotic disease and the integrity of the circle of Willis. Patients with symptomatic intracranial atherosclerosis were enrolled and underwent intracranial artery magnetic resonance vessel wall imaging and time-of-flight angiography. The presence or absence of an intracranial atherosclerotic plaque and its maximum wall thickness and stenosis were evaluated. The presence or absence of the A1 segment of the bilateral anterior cerebral arteries (from the internal carotid artery to the anterior communicating artery segment is called anterior cerebral artery A1 segment), and anterior communicating artery, the P1 segment of the bilateral posterior cerebral arteries (The P1 segment of the posterior cerebral artery is a horizontally outward segment), and bilateral posterior communicating arteries were determined. The associations of the intracranial plaque features with the integrity of the circle of Willis were analyzed. Of the 110 recruited subjects (57.2 $\pm$ 11.1 years; 65% males), 51 had intracranial plaques, and 44 had stenosis. In patients with bilateral A1 and P1 segments (n = 85), intracranial stenosis was more severe in patients with an anterior communicating artery than those without an anterior communicating artery (19.7% $\pm$ 21.7% vs. 1.4% $\pm$ 3.3%, p = 0.046). In patients with bilateral A1 and P1 segments and an anterior communicating artery (n = 79), intracranial stenosis was more severe in patients with posterior communicating arteries than those without posterior communicating arteries (27.9% $\pm$ 23.7% vs. 13.5% $\pm$ 17.9%, p = 0.007). The odds ratio of intracranial stenosis was 1.214 (95% confidence interval (CI), 1.054--1.398; p = 0.007) in discriminating for the presence of posterior communicating arteries in patients with bilateral A1 and P1 segments and an anterior communicating artery after adjusting for confounding factors. The severity of intracranial atherosclerosis was independently associated with the presence of posterior communicating arteries in patients with a complete anterior part of the circle of Willis.

Keywords

Intracranial artery; Atherosclerosis; Circle of Willis; Magnetic resonance imaging; Vessel wall; Neurovascular

1. Introduction

Intracranial atherosclerosis is the main cause of ischemic stroke in an Asian population, divided into symptomatic and asymptomatic types. Symptomatic intracranial atherosclerosis refers to ischemic stroke or transient ischemic attack occurring in the stenosis area of the supplying artery [1]. It is well established that the progression of the intracranial atherosclerotic disease will decrease blood perfusion and increase the risk of cerebral ischemic events [2–6]. During the progression of atherosclerotic cerebrovascular disease, the compensatory system can be initiated through the collateral circulation to preserve perfusion and stabilize cerebral blood flow [7–11]. As the primary collateral pathway, the circle of Willis (COW) connects the bilateral anterior circulations via the anterior communicating artery (ACoA) or the anterior and posterior circulations via the posterior communicating arteries (PCoAs). The integrity of the COW usually represents the capability of compensation when there is a decline in cerebral blood flow [12, 13]. Since atherosclerosis is a systemic disease that frequently involves multiple vascular beds (including the contralateral carotid artery and basilar artery), knowledge of the dominant communicating arteries is important for developing treatment strategies in patients diagnosed with atherosclerotic diseases multiple vascular beds.

Limited studies have demonstrated that the severity of atherosclerotic carotid disease is associated with the presence of collateral flow in the communicating arteries. Hartkamp *et al.* [14] demonstrated that patients with internal carotid artery (ICA) obstruction were more likely to have complete anterior parts of the COW, such as the presence of bilateral

A1 segments and an ACoA, or an entirely complete COW. Researchers also found that the stenosis of an ICA obstruction was correlated with cross-flow in the ACoA [15, 16]. However, the association between the severity of intracranial artery atherosclerosis and the integrity of the COW (particularly the status of the PCoAs) remains unclear.

It is hypothesized that intracranial atherosclerotic disease may activate the communicating arteries in certain orders that integrate bilateral circulations and/or anterior and posterior circulations as the disease severity increases. This study investigates the associations between the severity of intracranial atherosclerotic disease and the integrity of communicating arteries in the COW using three-dimensional (3D) magnetic resonance (MR) vessel wall imaging.

2. Methods

2.1 Study sample

In this study, patients with recent (within 2 weeks) ischemic stroke or transient ischemic attack (TIA) in anterior circulation determined by either imaging findings or clinical diagnosis were continuously recruited. All patients underwent MR imaging. The exclusion criteria were as follows: (1) cardiogenic stroke, hemorrhagic stroke; (2) patients who failed to complete MR examination due to contraindication, including pacemaker, artificial valve, nerve stimulator, eyeball foreign body and convulsion with a high fever. Clinical information (age, sex, body mass index, cholesterol level, and blood pressure) was recorded. Each patient collected history of hypertension, diabetes mellitus, smoking, hyperlipidemia, stroke, transient ischemic attack, and coronary heart disease.

2.2 MR imaging

The MR imaging was conducted on a 3.0T MR scanner (Achieva TX, Philips Healthcare; Best, the Netherlands) with a custom-designed 36-channel neurovascular coil. Intracranial arteries were imaged by acquiring images of the vessel wall and angiography with three-dimensional motion-sensitizing driven equilibrium rapid gradient-echo sequence (3D MERGE), 3D T1-volume isotropic turbo spine-echo acquisition (VISTA), and 3D time-of-flight (TOF). The extracranial carotid arteries were imaged by TOF MR angiography. The parameters for 3D MERGE were as follows: fast field echo; repeat time/echo time, 9.2/4.3 ms; flip angle, 6°; field of view, $4.0 \times 16 \times 25$ cm^3; spatial resolution, $0.8 \times 0.8 \times 0.8$ mm^3. The parameters for 3D T1-VISTA were as follows: turbo spin echo; repeat time/echo time, 700/21 ms; field of view, $4.5 \times 20 \times 20$ cm^3; spatial resolution, $0.6 \times 0.6 \times 0.6$ mm^3. The parameters for 3D TOF were as follows: fast field echo; repeat time/echo time, 25/3.5 ms; field of view, $4.5 \times 20 \times 20$ cm^3; spatial resolution, $0.7 \times 0.7 \times 1.4$ mm^3.

2.3 Image review

Two experienced radiologists interpreted the MR images for consensus using an MR workstation (Extended MR WorkSpace 2.6.3.4; Best, the Netherlands). Intracranial atherosclerosis was defined as eccentric wall thickening occurring in the following arterial segments of anterior circulation: internal carotid artery (C3—C7), M1 segment of the middle cerebral artery (MCA) and A1 segment of the anterior cerebral artery (ACA). The vessel wall images determined the presence or absence of intracranial artery plaques. The maximum wall thickness (Max WT) and stenosis of the corresponding intracranial atherosclerotic plaque were measured when a plaque was present. Luminal stenosis was measured on the maximum intensity projection images of TOF MR angiography (MRA) utilizing criteria for warfarin–aspirin symptomatic intracranial disease (WASID) [17] and North American Symptomatic Carotid Endarterectomy Trial NASCET [18] for intracranial arteries and carotid arteries, respectively. The presence or absence of the A1 segment of the bilateral anterior cerebral arteries, an ACoA, the P1 segment of the bilateral posterior cerebral arteries, and bilateral PCoAs was evaluated on the TOF MRA images.

2.4 Statistical analysis

The Shapiro-Wilk normality test tests the normality of the data distribution. Continuous variables were reported as the mean and standard deviation, and discrete variables were described as percentages. The clinical characteristics were compared between patients with and without an ACoA or PCoAs using the Mann–Whitney or chi-square test (where appropriate). When there were multiple plaques in the intracranial arteries of one patient, the most severe plaque burden (including Max WT and stenosis) among all plaques was selected for statistical analysis. It is well evidenced that the severity of plaque burden was associated with plaque vulnerability at the patient level. Thus, an atherosclerotic plaque with the most severe burden may represent the most vulnerable plaque among multiple lesions. For patients with bilateral A1 and P1 segments, the Max WT and stenosis of the intracranial plaques were compared between subjects with and without an ACoA or PCoAs using the non-parametric Mann–Whitney U test. Univariate and multivariate logistic regressions were performed to determine the odds ratios and corresponding 95% confidence intervals (CIs) of the intracranial artery plaque, Max WT, and stenosis in discriminating the presence of an ACoA or PCoAs. The probability of intracranial artery stenosis in predicting the presence of an ACoA or PCoAs before and after adjusting for confounding factors was calculated using C-statistical analysis. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 16.0 (SSPS Inc.; Chicago, IL, USA).

3. Results

3.1 Patient characteristics

One hundred ten patients (mean age, 57.2 ± 11.1 years) were recruited from January 2013 to March 2014. Of these patients, 72 (65.5%) were male, 74 (67.3%) had hypertension, 77 (70%) had hyperlipidemia, 58 (52.7%) had a history of smoking, and 35 (31.8%) had a history of diabetes. Ta-

Table 1. Clinical characteristics of the study population.

	Mean ± SD, or n (%)						
	All patients	*ACoA (+)	*ACoA (–)	*p*	#PCoA (+)	#PCoA (–)	*p*
	(n = 110)	(n = 79)	(n = 6)		(n = 34)	(n = 45)	
Age, years	57.2 ± 11.1	56.7 ± 12.2	56.8 ± 6.5	0.976	56.5 ± 11.3	56.8 ± 13.0	0.938
Male sex	72 (65.5)	52 (65.8)	2 (33.3)	0.185	24 (70.6)	28 (62.2)	0.438
BMI, kg/m^2	25.3 ± 3.1	25.3 ± 3.2	25.4 ± 2.3	0.951	25.4 ± 3.0	25.3 ± 3.3	0.864
Smoking	58 (52.7)	42 (53.2)	2 (33.3)	0.423	18 (52.9)	24 (53.3)	0.972
Hypertension	74 (67.3)	48 (60.8)	5 (83.3)	0.402	21 (61.8)	27 (60)	0.874
Hyperlipidemia	77 (70)	55 (69.6)	5 (83.3)	0.756	23 (67.6)	32 (71.1)	0.939
LDL, mmol/L	2.86 ± 1.13	2.94 ± 1.22	2.16 ± 0.93	0.074	3.20 ± 1.59	2.75 ± 0.80	0.323
HDL, mmol/L	1.12 ± 0.36	1.10 ± 0.35	0.99 ± 0.10	0.635	1.19 ± 0.44	1.03 ± 0.25	0.152
TC, mmol/L	4.53 ± 1.15	4.51 ± 1.16	4.00 ± 1.28	0.313	4.63 ± 1.40	4.42 ± 0.96	0.444
TG, mmol/L	1.60 ± 0.89	1.64 ± 0.95	1.62 ± 0.85	0.951	1.46 ± 0.70	1.77 ± 1.09	0.373
DM	35 (31.8)	22 (28.2)	4 (66.7)	0.071	11 (32.4)	11 (25.0)	0.474
Statin use	82 (74.5)	56 (70.9)	6 (100)	0.184	23 (67.6)	33 (73.3)	0.582
History of stroke	62 (56.4)	38 (48.1)	6 (100)	0.026	16 (47.1)	22 (48.9)	0.872
History of CHD	16 (14.5)	12 (15.2)	0 (0)	0.588	5 (14.7)	7 (15.6)	0.917

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, total glyceride; DM, Diabetes mellitus; CHD, coronary heart disease. *For patients with the presence of bilateral A1 and P1 segments. #For patients with bilateral A1 and P1 segments and ACoA.

ble 1 shows the clinical characteristics of the study population among the different COW integrity groups. For patients with bilateral A1 and P1 segments, no significant differences were found in all clinical characteristics except for a history of stroke (48.1% vs. 100%, $p = 0.026$) between patients with and without an ACoA. Similarly, for patients with bilateral A1 and P1 segments and an ACoA, no significant differences were found in all clinical characteristics between patients with and without PCoAs (all $p > 0.05$).

3.2 Association between integrity of the circle of Willis and intracranial atherosclerosis

Of the 110 patients, 51 (46.4%) and 44 (40%) were found to have atherosclerotic plaques and stenosis in the intracranial arteries, respectively. Of all 51 patients with intracranial plaques, 75 plaques were detected, and 45 plaques were located in C3—C7 segments of intracranial internal carotid arteries, 23 plaques were located in the M1 segment of MCA and 7 plaques located in the A1 segment of ACA.

The presence of bilateral A1 segments, bilateral P1 segments, and both bilateral A1 and P1 segments were observed in 100 (90.9%), 92 (83.6%), and 85 (77.3%) patients, respectively. In addition, 91 (82.7%) patients had an ACoA, and 58 (52.7%) patients had PCoAs. The whole anterior part of the COW (presence of bilateral A1 segments and an ACoA) and the whole posterior part of the COW (presence of bilateral P1 segments and PCoAs) were found in 91 (82.7%) and 15 (13.6%) patients, respectively. An entirely complete COW was found in 13 (11.8%) patients.

For patients with both bilateral A1 and P1 segments (n = 85), the intracranial stenosis in patients with an ACoA was significantly more severe than in patients without an ACoA (19.7% ± 21.7% vs. 1.4% ± 3.3%, $p = 0.046$) (Table 2). For patients with both bilateral A1 and P1 segments and an ACoA (n = 79), the intracranial stenosis (27.9% ± 23.7% vs. 13.5% ± 17.9%, $p = 0.007$) and the presence of plaques (76.5% vs. 48.9%, $p = 0.013$) in patients with PCoAs were significantly more severe than in those patients without PCoAs (Table 2). For patients who had intracranial plaques, the Max WT of the intracranial artery was similar to patients with and without an ACoA ($p = 0.268$) or PCoAs ($p = 0.748$) (Table 2). An example of a patient with severe intracranial artery stenosis and the presence of bilateral A1 and P1 segments, an ACoA, and PCoAs is shown in Fig. 1.

For patients with bilateral A1 and P1 segments, the presence of an ACoA was not significantly associated with the presence of plaques, Max WT, and stenosis before and after adjusting for the clinical confounding factors of age, sex, body mass index, hypertension, smoking, diabetes mellitus, hyperlipidemia, history of stroke and the stenosis degree of extracranial carotid atherosclerosis (all $p > 0.05$, Table 3). The logistic regression analysis results for patients with bilateral A1, P1, and an ACoA are shown in Table 4. The odds ratio of intracranial stenosis with increments of 5% was 1.174 (95% CI, 1.051–1.313; $p = 0.005$) and 1.214 (95% CI, 1.054–1.398; $p = 0.007$) in discriminating for the presence of PCoAs before and after adjusting for the above confounding factors. The odds ratio of the presence of plaques was 3.398 (95% CI, 1.269–9.095; $p = 0.015$) and 4.374 (95% CI, 1.145–16.701; $p = 0.031$) in discriminating for the presence of PCoAs before and after adjusting for the above confounding factors.

4. Discussion

The results demonstrated a significant difference in stenosis of the intracranial arteries between patients with and

Table 2. Intracranial plaque features in patients with different integrity of COW.

	Mean ± SD, or n (%)					
	*ACoA (+)	*ACoA (–)	*p*	#PCoA (+)	#PCoA (–)	*p*
	(n = 79)	(n = 6)		(n = 34)	(n = 45)	
Presence of plaque	48 (60.8)	3 (50)	0.679	26 (76.5)	22 (48.9)	0.013
Max WT, mm	2.2 ± 0.8	1.7 ± 0.8	0.268	2.2 ± 0.8	2.2 ± 0.7	0.748
Stenosis, %	19.7 ± 21.7	1.4 ± 3.3	0.046	27.9 ± 23.7	13.5 ± 17.9	0.007

*For patients with presence of bilateral A1 and P1 segments. #For patients with presence of bilateral A1 and P1 segments and ACoA.

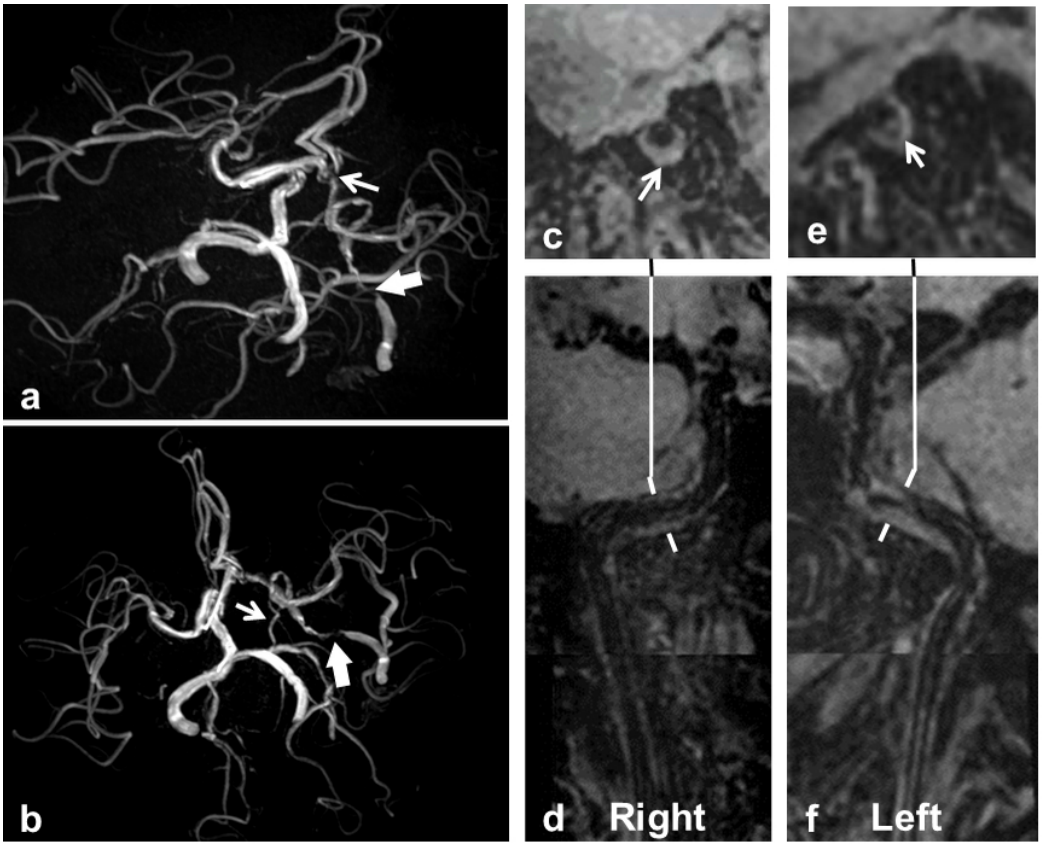

Fig. 1. MR images of a 60-year-old man with severe intracranial artery stenosis who also had an anterior and posterior communicating artery (ACoA and PCoA, respectively). (a) and (b) represent the MIP images of TOF MRA. ACoA and left PCoA are present (thin white arrows in a and b), and severe stenosis in the C2 segment of the left internal carotid artery was observed (thick arrows in a and b). (d) and (f) represent the curved reconstructed images of MERGE. Two plaques in the C2 segments of the bilateral internal carotid arteries (arrows in c and e) are shown.

without an ACoA and PCoAs. It was also determined that characteristics of intracranial artery atherosclerosis, including the presence of plaques, and stenosis, were independently associated with PCoAs in patients with bilateral A1 and P1 segments and an ACoA. The findings indicate that the severity of intracranial artery atherosclerosis may be an independent indicator of the integrity of the COW.

A complete COW was only found in 11.8% of the patients. The data showed that 82.7% and 13.6% of the patients had complete structures of the anterior and posterior parts of the COW, respectively. Two previous studies reported similar results regarding the prevalence of a complete anterior part of the COW (78%–80.95%) [19, 20]. In the present study, the prevalence of whole complete and complete posterior structures of the COW was slightly lower than that reported in the two former studies; one study reported a prevalence of 20.9% and 16.6%, respectively, whereas the other reported a prevalence of 21.0% and 33.0%, respectively. These differences may be due to this study's smaller sample size. In addition, the findings are consistent with a previous study for the presence of bilateral A1 (this study's data vs. previous data: 90.9% vs. 95.0%) and bilateral P1 (this study's data vs. previous data: 83.6% vs. 86.7%) segments.

In patients diagnosed with bilateral A1 and P1 segments, intracranial stenosis was more severe in patients with the presence of an ACoA than those without, and a marginal as-

Table 3. Association between atherosclerosis and presence of ACoA.

	Presence of ACoA*					
	Univariate regression			Multivariate regression#		
	OR	95% CI	*p*	OR	95% CI	*p*
Presence of plaque	1.548	0.294–8.166	0.606	0.455	0.045–4.618	0.505
Max WT, mm	2.588	0.406–16.494	0.314	1.823	0.132–25.274	0.654
Stenosis†, %	1.692	0.792–3.617	0.175	2.087	0.768–5.675	0.149

*For patients with the presence of bilateral A1 and P1 segments. #Adjustment for age, gender, BMI, hypertension, smoking, diabetes mellitus, hyperlipidemia, history of stroke and stenosis of the extracranial carotid artery. †With increment of 5%.

Table 4. Association between atherosclerosis and presence of PCoA.

	Presence of PCoA*					
	Univariate regression			Multivariate regression#		
	OR	95% CI	*p*	OR	95% CI	*p*
Presence of plaque	3.398	1.269–9.095	0.015	4.374	1.145–16.701	0.031
Max WT, mm	0.883	0.421–1.851	0.742	1.108	0.433–2.832	0.831
Stenosis†, %	1.174	1.051–1.313	0.005	1.214	1.054–1.398	0.007

*For patients with the presence of bilateral A1, P1 segments and ACOA. #Adjustment for age, gender, BMI, hypertension, smoking, diabetes mellitus, hyperlipidemia, history of stroke and stenosis of the extracranial carotid artery. †With increment of 5%.

sociation was found between the stenosis and the presence of an ACoA. The results are consistent with previous studies [14, 21]. Hartkamp *et al.* [14] demonstrated that patients with an ICA obstruction had a significantly higher percentage of entirely complete COW configurations (55% vs. 36%, $p = 0.02$) and complete anterior configurations (88% vs. 68%, $p = 0.002$) when compared with control subjects. Furthermore, patients with an ICA occlusion were found to have a higher prevalence of collateral flow through the anterior COW.

Kablak-Ziembicka *et al.* [21] reported that the ACoA was instrumental in maintaining collaterals within the COW. Similar results were found in patients with carotid occlusion [22]. Zhu *et al.* [23] demonstrated that the flow of ACoA is the most sensitive index to the morphology change of ipsilateral ICA *in-vitro* study. These results revealed that communicating arteries (as collateral pathways of cerebral blood flow) might play a key role in the compensational capability of cerebral arteries, and their presence may be associated with the severity of stenosis.

In addition to the ACoA, collateral circulation through the PCoAs was reported in previous studies [14, 21, 24, 25]. However, the ACoA was more likely to be present than PCoAs when unilateral ICA stenosis occurred [14, 21, 25]. This study's data demonstrated that for patients with bilateral A1 and P1 segments and an ACoA, intracranial stenosis was more severe in those with PCoAs. Hartkamp *et al.* [14] also found that patients with an ICA obstruction had a significantly higher percentage of complete posterior COW configurations than the control group. As such, it is suggested that the COW tends to be complete, and collateral circulation seems to integrate from the anterior to posterior communicating arteries with an increase in the severity of intracranial stenosis. This hypothesis can be evidenced in part by previous *in vitro* or model studies [23, 26, 27]. For example, investigators reported the reduction of ipsilateral blood flow from the ICA, which is most sensitively detected by the flow of ACoA. The collateral function of the PCoAs will not be activated until severe stenosis in the ICA occurs.

This study had several limitations. First, this was a cross-sectional study lacking the dynamic changes of the COW with the progression of cerebral vascular stenosis. Second, the integrity of the COW was analyzed with TOF MRA that is insensitive to blood flows with slow velocities; therefore, the absence of communicating arteries may have been overestimated. Contrast CTA or MRA are superior to TOF MRA for evaluating the morphology of cerebral vasculatures because of a contrast agent. TOF MRA measures luminal stenosis, and the criteria used to define luminal stenosis are originally digital subtraction angiography (DSA). Third, the logistic regression analysis could not represent the general population since the conditions of Circle of Willis are complicated. Utilizing one regression model could not stratify different conditions of Circle of Willis. Fourth, although the degree of extracranial carotid atherosclerosis slightly affected the association between intracranial plaques and COW morphology, the carotid stenosis in this study population was dominantly mild to moderate, suggesting further investigation by including individuals with a broader range of luminal stenosis in future studies for minimizing patient selection bias. In addition, only the most severe plaque burden was assessed in patients with multiple intracranial plaques, ignoring differences in atherosclerotic burden among patients.

5. Conclusions

In conclusion, the severity of intracranial artery atherosclerosis is independently associated with the presence of PCoAs for patients with a complete anterior part of the COW. Future prospective studies are warranted to determine the causal relationship between the increase of severity of intracranial artery atherosclerosis disease and the time course of integration of collateral circulation.

Author contributions

YLX searched the literatures, analyzed the data and drafted the manuscripts. DYL and WD collected and analyzed the data. ZZZ and XHZ provide supervision, analyzed the data and edited the manuscript.

Ethics approval and consent to participate

The local ethics committee approved the study, and these patients obtained informed consent. The Ethics Committee of our hospital reviewed and approved this study (No. 20110017), and all involved patients provided written consent forms.

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Conflict of interest

The authors declare no conflict of interest.

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