Cerebrovascular risk factors for patients with cerebral watershed infarction

A case–control study based on computed tomography angiography in a population from Southwest China

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Abstract

To determine cerebrovascular risk factors for patients with cerebral watershed infarction (CWI) from Southwest China.

Patients suffering from acute ischemic stroke were categorized into internal CWI (I-CWI), external CWI (E-CWI), or non-CWI (patients without CWI) groups. Clinical data were collected and degrees of steno-occlusion of all cerebral arteries were scored. Arteries associated with the circle of Willis were also assessed. Data were compared using Pearson chi-squared tests for categorical data and 1-way analysis of variance with Bonferroni post hoc tests for continuous data, as appropriate. Multivariate binary logistic regression analysis was performed to determine independent cerebrovascular risk factors for CWI.

Compared with non-CWI, I-CWI had higher degrees of steno-occlusion of the ipsilateral middle cerebral artery, ipsilateral carotid artery, and contralateral middle cerebral artery. E-CWI showed no significant differences. All the 3 arteries were independent cerebrovascular risk factors for I-CWI confirmed by multivariate binary logistic regression analysis. I-CWI had higher degrees of steno-occlusion of the ipsilateral middle cerebral artery compared with E-CWI. No significant differences were found among arteries associated with the circle of Willis.

The ipsilateral middle cerebral artery, carotid artery, and contralateral middle cerebral artery were independent cerebrovascular risk factors for I-CWI. No cerebrovascular risk factor was identified for E-CWI.

Abbreviations: ACA = anterior cerebral artery, ACA-A1 = precommunicating segment of the ACA, CoW = circle of Willis, CTA = computed tomography angiography, CWI = cerebral watershed infarction, E-CWI = external CWI, FTP = fetal-type PCA, I-CWI = internal CWI, MCA = middle cerebral artery, PCA = posterior cerebral artery, PCA-P1 = precommunicating segment of the PCA, PComA = posterior communicating artery.

Keywords: carotid artery, cerebral infarction, circle of Willis, computed tomography angiography, middle cerebral artery, risk factor

1. Introduction

Cerebral watershed infarction (CWI) (also called border zone infarction) is an ischemic lesion that involves the junction between 2 adjacent arterial territories. It was first reported by Pozzi in 1884. Zulch and Behrend determined its typical locations and hypothesized its pathogenesis in the 1960s. CWI is well known for its particular morphological characteristics and locations. It is reported to account for approximately 12.7% of all cerebral infarcts[1] and may occur in situations involving severe systemic hypotension, such as when a person rises from the supine position, excess exercise, Valsalva's maneuvers, administration of antihypertensive drugs, bleeding, and anemia.[2] The prognosis of CWI is reportedly different from other types of cerebral infarction after intravenous thrombolysis therapy.[3]

The pathogenesis of CWI has been studied for more than 50 years and still remains controversial. It is reported that CWI, especially internal CWI (I-CWI), is typically caused by systemic or local hypoperfusion.[1,4–6] A positron emission tomography study reported that metabolic activity levels, a sign of blood perfusion, significantly decreased around CWI,[7] and an autopsy study reported cholesterol microemboli in external CWI (E-CWI) patients.[8] Some researchers think that CWI is an interplay between microemboli, from the heart or atherosclerotic artery, and a reduction in perfusion.[9] Microemboli favors the watershed zone, but cannot be cleared because of reduced perfusion, blocking distal arteries and resulting in a cerebral infarction.[10–12] Extracranial and intracranial atherosclerotic arteries cannot only reduce blood perfusion through severe vascular stenosis, but also occlude small arteries when unstable

atherosclerotic plaques detach into the bloodstream.[13] Cerebrovascular changes may be critical risk factors in CWI patients.

Increasingly, researchers are realizing the importance of severe cerebrovascular changes for CWI.[14] Vascular variations (including vascular tortuosity and hypoplasticity) and collateral circulation (including the circle of Willis [CoW], reversed flow in the ophthalmic artery, and collateral flow via the leptomeningeal arteries) may also play important roles in CWI. The CoW is the primary and most important collateral circulation, and a considerable number of CoW variations have been reported among Chinese populations.[15] Yet, no systemic research has looked at all the cerebrovascular changes in CWI patients.

Computed tomography angiography (CTA) is capable of delineating major intracranial vessels, very small arteries, and whole cerebral vasculature.[16] It is a noninvasive vascular examination that does not rely on hemodynamics, and can clearly depict both the intracranial and extracranial vasculature. The sensitivity and specificity of CTA are widely accepted.[17–20]

To better understand the pathogenesis of CWI and provide a basis for its treatment and prevention, we examined the cerebral vasculature of patients with cerebral infarctions and determined cerebrovascular risk factors for CWI using CTA.

2. Methods

2.1. Participants

A total of 1989 consecutive patients with acute ischemic infarctions at the Department of Neurology, the First Affiliated Hospital of Chongqing Medical University between June 2011 and May 2016 met inclusion criteria and were enrolled in the study. Inclusion criteria were clinically diagnosed acute ischemic infarction; magnetic resonance imaging performed within 1 week after the stroke, including a diffusion weighted imaging sequence; and CTA examination was performed within 1 week after the stroke. There were 926 patients who met exclusion criteria and who were excluded. Exclusion criteria were no new infarctions, infarctions in both hemispheres, subtentorial infarctions, or encephalomalacia focus; history of stroke, surgery, injury, or coexisting cerebral diseases (including tumor, vascular malformation, aneurysm, Moyamoya disease, or venous sinus thrombosis); underwent a neurointerventional procedure (including injecting tissue plasminogen activator, mechanical clot removal, angioplasty, or stenting); and poor CTA image quality that prevented visualization of the whole cerebral vasculature.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University and written informed consent was obtained from patients or their guardians. The research protocol was performed in accordance with relevant ethical guidelines and regulations for human studies.

2.2. Demographic characteristics

Patients were categorized into either I-CWI, E-CWI, or non-CWI (patients without CWI) groups according to the criteria defined by Mangla et al[21] (Fig. 1) based on localization determined from diffusion-weighted imaging sequences. Briefly, I-CWI was defined as an infarction of the lenticulostriate-middle cerebral artery (MCA), lenticulostriate-anterior cerebral artery (ACA), Heubner-ACA, anterior choroidal-MCA, and anterior choroidal-posterior cerebral artery (PCA) territories. E-CWI was defined as an infarction located in the frontal cortex (between the ACA and MCA), occipital cortex (between the MCA and PCA), or
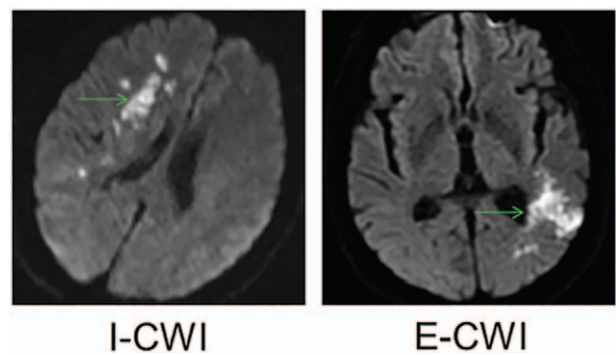
Figure 1. Typical internal and external cerebral watershed infarction showed in diffusion-weighted imaging sequences. E-CWI = infarction localized to the area between the middle cerebral artery and posterior cerebral artery on the left, I-CWI = infarction localized to the area between the lenticulostriate and middle cerebral artery on the right.

paramedian white matter (between the ACA and MCA). Demographic characteristics of all patients were recorded by a third-party neurological physician. All definitions and diagnoses met international criteria.[22,23]

2.3. Image acquisition

CTA examinations were performed using a 64-row multidetector computed tomography scanner (Light-Speed VCT; GE Healthcare, Milwaukee, WI). Scanning parameters were tube voltage, 100 or 120 kV; tube current, 300 mA; pitch, 0.531; matrix, 512×512; section thickness, 5 mm; and reconstruction slice thickness, 0.625. Patients were in the supine position on a computed tomography table with a head holder. Contrast material (80 mL) was injected at 4 mL/s using a power injector through an intravenous cannula. Synchronization of data acquisition was achieved using the real-time bolus tracking method. Images were reconstructed and transferred to a workstation for postprocessing. Images were reformatted as maximum intensity projections and volume-rendered images to evaluate the CoW. Two observers independently reviewed all CTA data. When disagreements occurred, they were resolved via discussion until a consensus was reached.

2.4. Vascular data

The percentage of stenosis was used to score arteries,[24] and was calculated as: percentage of stenosis $= 1 - D_{stenosis}/D_{normal}$, where $D_{stenosis}$ indicated the diameter of the most severe site of the artery and D_{normal} was the diameter of a proximal normal artery. A score of 0 was given for stenosis percentage <50%, a score of 1 was given for stenosis percentage ≥50% and <70%, a score of 2 was given for stenosis percentage ≥70% and <100%, and a score of 3 was given when the artery was occluded (Fig. 2). The following arteries were examined in bilateral hemispheres: internal carotid artery or common carotid artery, vertebral artery, basilar artery, ACA, MCA, and PCA. Arteries associated with the CoW were categorized as absent, hypoplastic, or normal. Hypoplastic indicated that the diameter was <1 mm and had a string-like appearance. The anterior communicating artery and the posterior communicating arteries (PComA) were regarded as normal upon observation if their diameters were small. The following cerebral vessels associated with CoW
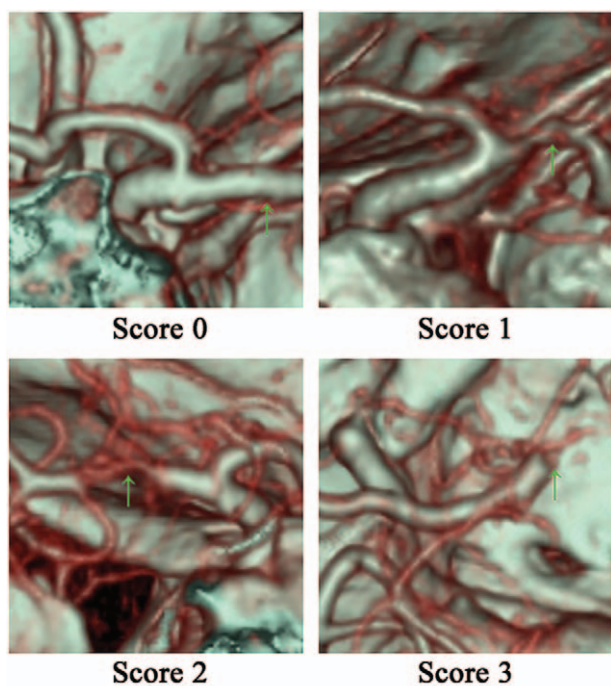
Figure 2. Scores based on the steno-occlusion degree of the MCA. MCA = middle cerebral artery, Score 0 = the right MCA is nearly normal or <50% occluded, Score 1 = the right MCA was ≥50% but <70% occluded, Score 2 = the left MCA was ≥70% but was not completely occluded, Score 3 = the right MCA was completely occluded.

were examined: anterior communicating artery, PComA, precommunicating segments of the ACA (ACA-A1), and precommunicating segments of the PCA (PCA-P1). Fetal-type PCA (FTP) was defined as an artery that originated at the internal carotid artery and continued as a PCA (Fig. 3). Uni-FTP was defined as a unilateral FTP and bi-FTP as a bilateral FTP.

2.5. Statistical analysis

Statistical analyses were performed using a commercially available software package (SPSS, ver. 22.0; IBM, New York, NY). Categorical data are exhibited as absolute numbers and percentage (%) and continuous data are exhibited as mean ± standard error. Data were compared among groups using
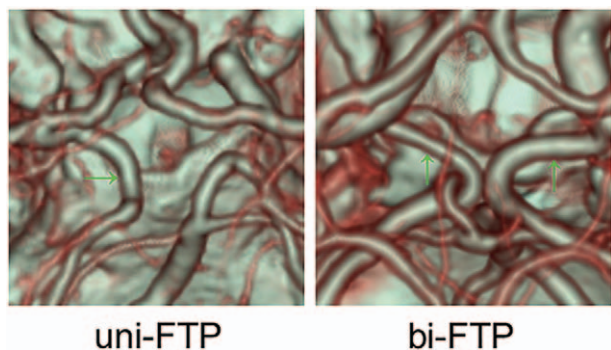
Figure 3. Fetal-type PCA showed in computed tomography angiography. bi-FTP = patient had a bilateral FTP with the PCA-P1 absent on both sides, PCA = posterior cerebral artery, uni-FTP = patient had a unilateral FTP with an absent PCA-P1 on the left.

Pearson chi-squared tests or Fisher exact tests for categorical data and 1-way analysis of variance with Bonferroni post hoc tests for continuous data, as appropriate. Multivariate binary logistic regression analysis was performed to determine independent cerebrovascular risk factors for CWI. A P value < .05 was considered statistically significant.

3. Results

3.1. Demographic characteristics

In total, 1063 patients with cerebral infarction were included. CWI was present in 112 (10.5%) patients, which is approximately equal to the 10% reported in the literature.[1] Forty-seven patients had E-CWI and 65 had I-CWI. Demographic characteristics are shown in Table 1. The 3 groups were sex and age matched ($P > .05$). There were no significant differences in demographic characteristics among the groups ($P > .05$).

3.2. Vascular steno-occlusion

Vascular steno-occlusion data are shown in Table 2. Compared with non-CWI, I-CWI had higher degrees of steno-occlusion of the ipsilateral MCA, contralateral MCA, and ipsilateral carotid artery. There was no statistical significant difference with E-CWI ($P > .05$). Multivariate binary logistic regression analysis indicated that all 3 arteries were independent cerebrovascular risk factors for I-CWI ($P < .05$) (Table 3). I-CWI showed more severe degrees of steno-occlusion of the ipsilateral MCA compared with E-CWI ($P < .05$).

3.3. Variations in arteries associated with the CoW

The variations in arteries associated with the CoW are shown in Table 4. There were no significant differences among groups ($P > .05$). FTP was common among the Chinese population with cerebral infarction (uni-FTP = 21.9%, bi-FTP = 8.5%) but there were no differences among the groups ($P > .05$).

4. Discussion

CWI is recognized for its particular morphological characteristics and locations. It usually occurs in specific situations and is a result of unique risk factors. In the present study, we did not find any risk factors for CWI from the demographic characteristics. This may be because we only examined persistent risk factors rather than transient inducements. Transient inducements, including rising from a supine position, Valsalva's maneuvers, administration of antihypertensive drugs, and bleeding, for example, may be critical risk factors for CWI.

A study from the Netherlands used magnetic resonance angiography combined with magnetic resonance spectroscopy and found that CWI patients with severe carotid stenosis had a significantly reduced blood flow in both the common carotid artery and MCA, and decreased N-acetyl aspartate/choline ratios in noninfarct regions,[25] indicating that severe carotid stenosis might be an important risk factor for CWI in western populations. To the best of our knowledge, western populations are more susceptible to extracranial vascular diseases, while intracranial atherosclerotic diseases are more common among Asians.

In the present study, we confirmed that the ipsilateral carotid artery was an independent risk factor for I-CWI. However, we

Table 1

Demographic characteristics of patients with different types of cerebral infarction.

Variable (SE/%)	Non-CWI* (951)	I-CWI† (65)	E-CWI‡ (47)	P
Mean age, y	63.70 ± 0.68	65.45 ± 1.44	65.43 ± 1.66	.434
Gender, male	626 (65.8%)	38 (58.5%)	33 (68.1%)	.470
Smoking history	398 (41.9%)	21 (32.3%)	22 (46.8%)	.247
Alcohol consumption	177 (18.6%)	11 (16.9%)	9 (19.1%)	.942
Hypertension	650 (68.3%)	47 (72.3%)	35 (74.5%)	.616
Hypercholesterolemia	449 (47.2%)	31 (47.7%)	25 (53.2%)	.743
Diabetes mellitus	272 (28.6%)	22 (33.8%)	12 (25.5%)	.595
Atrial fibrillation	92 (9.7%)	6 (9.2%)	9 (19.1%)	.135
Coronary atherosclerotic disease	98 (10.3%)	6 (9.2%)	8 (17.0%)	.346

SE = standard error.
* Patients without cerebral watershed infarction.
† Patients with internal cerebral watershed infarction.
‡ Patients with external cerebral watershed infarction.

Table 2

Vascular steno-occlusion degree of the mainly supplying arteries in different types of cerebral infarction.

Variable (SE)	Non-CWI* (951)	I-CWI† (65)	E-CWI‡ (47)	P (I-CWI/non-CWI)	P (E-CWI/non-CWI)	P (E-CWI/I-CWI)
ACA						
Ipsi	0.236 ± 0.040	0.169 ± 0.075	0.213 ± 0.086	.484	.832	.747
Contra	0.080 ± 0.022	0.031 ± 0.031	0.149 ± 0.074	.371	.270	.126
MCA						
Ipsi	0.664 ± 0.061	1.200 ± 0.151	0.702 ± 0.152	.001	.828	.022
Contra	0.086 ± 0.022	0.246 ± 0.093	0.128 ± 0.058	.012	.567	.190
PCA						
Ipsi	0.209 ± 0.034	0.169 ± 0.071	0.319 ± 0.106	.639	.266	.217
Contra	0.109 ± 0.024	0.092 ± 0.052	0.170 ± 0.082	.785	.390	.372
CA						
Ipsi	0.333 ± 0.046	0.723 ± 0.132	0.489 ± 0.145	.001	.264	.174
Contra	0.089 ± 0.022	0.154 ± 0.067	0.106 ± 0.064	.261	.789	.563
VA						
Ipsi	0.369 ± 0.044	0.554 ± 0.120	0.468 ± 0.139	.108	.452	.598
Contra	0.407 ± 0.045	0.446 ± 0.105	0.383 ± 0.124	.730	.853	.693
BA	0.024 ± 0.010	0.031 ± 0.022	0.064 ± 0.047	.795	.205	.397

ACA = anterior cerebral artery, BA = basilar artery, CA = carotid artery, Contra = contralateral artery to the infarction, Ipsi = ipsilateral artery to the infarction, MCA = middle cerebral artery, PCA = posterior cerebral artery, SE = standard error, VA = vertebral artery.
* Patients without cerebral watershed infarction.
† Patients with internal cerebral watershed infarction.
‡ Patients with external cerebral watershed infarction.

also found that both ipsilateral and contralateral MCA were independent cerebrovascular risk factors for I-CWI. Ipsilateral MCA has been confirmed as a risk factor in a positron emission tomography study from Japan[4] and a magnetic resonance angiography study from South Korea[26] in Asian populations. The involvement of the contralateral MCA, however, is a novel

Table 3

Multivariate binary logistic regression analysis of cerebrovascular risk factors for internal cerebral watershed infarction.

Variable	Odds ratio	95% Confidence interval	P
MCA			
Ipsi	1.381	1.113–1.714	.003
Contra	1.579	1.013–2.461	.044
CA			
Ipsi	1.427	1.102–1.846	.007

CA = carotid artery, contra = contralateral artery to the infarction, ipsi = ipsilateral artery to the infarction, MCA = middle cerebral artery.

finding of the present study. It is thought that the contralateral MCA may indicate extensive cerebrovascular changes in I-CWI, leading to persistent hypoperfusion of brain tissue through collateral circulation at different levels, with I-CWI arising if any transient inducements occur during such conditions.

We did not identify any cerebrovascular risk factors for E-CWI. E-CWI patients shared the same degrees of cerebrovascular steno-occlusion compared with non-CWI. The degree of steno-occlusion of the ipsilateral MCA in E-CWI was found to be milder than in I-CWI. This may be because E-CWI is mainly associated with potential cardiac embolic disease while I-CWI is mainly associated with atherosclerotic MCA disease, a suggestion consistent with a magnetic resonance angiography study from South Korea.[27]

Not all severe vascular steno-occlusions lead to ischemic stroke. Many patients with severe common carotid artery or MCA stenosis do not show any clinical symptoms until they undergo a physical examination. This is because collateral circulation in the brain plays an important role in preventing stroke.[28]

Table 4

Variations of the arteries associated with circle of Willis.

Variable (%)	Non-CWI* (951)	I-CWI† (65)	E-CWI‡ (47)	P
ACA-A1 unilateral absence	107 (11.3%)	10 (15.4%)	5 (10.6%)	.589
ACA-A1 unilateral hypoplastic	140 (14.7%)	10 (15.4%)	5 (10.6%)	.728
PCA-P1 unilateral absence	123 (12.9%)	10 (15.4%)	5 (10.6%)	.755
PCA-P1 bilateral absence	39 (4.1%)	2 (3.1%)	0 (0%)	.342
PCA-P1 unilateral hypoplastic	109 (11.5%)	7 (10.8%)	4 (8.5%)	.815
PCA-P1 bilateral hypoplastic	6 (0.6%)	1 (1.5%)	0 (0.7%)	.551
AComA absence	123 (12.9%)	9 (13.8%)	8 (17.0%)	.711
PComA unilateral absence	233 (24.5%)	18 (27.7%)	11 (23.4%)	.829
PComA bilateral absence	513 (53.9%)	33 (50.8%)	29 (61.7%)	.498
Unilateral FTP	208 (21.9%)	13 (20.0%)	12 (25.5%)	.779
Bilateral FTP	81 (8.5%)	7 (10.8%)	2 (4.3%)	.425

ACA-A1 = precommunicating segment of anterior cerebral artery, AComA = anterior communicating artery, FTP = fetal-type posterior cerebral artery, PCA-P1 = precommunicating segment of posterior cerebral artery, PComA = posterior communicating artery.
* Patients without cerebral watershed infarction.
† Patients with internal cerebral watershed infarction.
‡ Patients with external cerebral watershed infarction.

The CoW is the primary and most important collateral circulation, and understanding its involvement in stroke is very important. The absence of PComA was common in the population of the present study. PComA is reported to prevent infarction upon occlusion of the common carotid artery.[29] However, no significant differences were found among the arteries associated with the CoW in the present study. The CoW did not seem to have any unique compensatory functions in CWI patients from Southwest China. A probable explanation for this result is that CWI in people from Southwest China is mainly related to MCA while MCA is distal to the CoW. Considering ethnic differences, the function of the CoW in western populations with CWI requires further research as extracranial atherosclerotic disease is more common these populations.[30,31]

This study had some limitations. First, we did not investigate the clinical symptoms in CWI patients and their relationship to the cerebrovascular changes. Second, we only included patients from 1 hospital in Southwest China. A multicenter study is required. Third, CTA is reported to overestimate vascular stenosis compared with digital subtraction angiography; therefore, the epidemiological results of cerebrovascular changes should be treated with caution.

5. Conclusions

Ipsilateral MCA, carotid artery, and contralateral MCA were independent cerebrovascular risk factors for I-CWI. No cerebrovascular risk factor was identified for E-CWI. The CoW had no relationship with CWI.

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