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Original Article

Correlation of moderate-to-severe intracranial arterial stenosis load with low cerebral perfusion, white matter hyperintensity, and cognitive dysfunction in patients without strokes

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Abstract: Background: The current study aimed to investigate low cerebral perfusion, white matter hyperintensity, and cognitive dysfunction in stroke-free patients with moderate-to-severe intracranial arterial stenosis. Materials and methods: Patients with hypomnesis were recruited. Vascular risk factors were recorded. Intracranial artery stenosis, stenosis load, blood flow perfusion values, white matter hyperintensity, and cognition were assessed. Results: Patients with arterial stenosis were older and had a higher incidence of hypertension. Patients with arterial stenosis had a significantly higher incidence of cognitive dysfunction, compared with the control group ($P < 0.05$). Correlation analysis showed that intracranial arterial stenosis load was significantly negatively related to total MoCA scores ($P < 0.001$). Cerebral perfusion at the periventricular area in the stenosis group was significantly lower than that in the control group ($P < 0.01$). Arterial stenosis load was negative to blood flow ($P < 0.05$). Incidence of white matter hyperintensity in the frontal lobe, temporal lobe, occipital lobe, and antecornu and peri-ventricular areas in the stenosis group was significantly higher than that in the control group. Arterial stenosis load was positively related to whole-brain white matter hyperintensity ($P < 0.05$). Conclusion: Intracranial arterial stenosis load is negatively related to total MoCA scores and ventricular area blood flow perfusion, but positively associated with whole-brain white matter hyperintensity.

Keywords: Intracranial arterial stenosis, hypertension, cognitive dysfunction, montreal cognitive assessment

Introduction

Computerized tomography angiography (CTA), digital subtraction angiography (DSA), and magnetic resonance angiography (MRA) have been widely used in clinical practice with the development of imaging technology. The detection rate of asymptomatic intracranial and extracranial arterial stenosis has increased over the years [1]. Arteriosclerosis or arterial stenosis-related cognitive impairment is a common type of chronic progressive cognitive impairment in the elderly [2]. Arteriosclerosis may increase the risk of dementia, making it an important risk factor for development of Alzheimer's disease [3]. Controlling risk factors of cerebrovascular disease may prevent and improve cognitive impairment and delay disease progression [4, 5]. Intracranial arterial stenosis (IAS) is one of the direct consequences of vascular risk factors. The relationship between IAS before strokes and cognitive impairment has not paid adequate attention. Of note, interventions administered before strokes may maximize the clinical value. Thus, it is imperative to investigate the relationship between IAS and cognitive impairment.

Some investigators have proposed that chronic hypoperfusion is a major cause of cognitive impairment in patients with IAS [6]. However, available findings are different or even conflicting, due to differences in sample size, course of disease, inclusion criteria, severity of IAS, methods used for measurement of cognition, and educational backgrounds [7]. Although some investigators have conducted studies investigating the correlation between IAS and

cognitive impairment, little is known about the relationship of IAS with brain perfusion and white matter hyperintensity (WMH).

This study aimed to investigate the correlation between moderate-to-severe IAS and cognitive impairment in patients without strokes, detect brain perfusion and WMH in these patients, and further explore potential mechanisms underlying IAS and cognitive impairment.

Methods

Subjects

Patients (n = 132) complaining of memory decline were recruited from the Department of Neurology of Tongji Hospital and Zhoupu Hospital, between November 2015 and December 2016. They had no history of strokes. According to inclusion criteria and exclusion criteria, 70 patients were assigned to the stenosis group, in which there were 31 males and 39 females, with a mean age of 73.01 ± 8.86 years. In the control group, there were 62 patients, including 30 males and 32 females, with a mean age was 65.84 ± 9.67 years. Demographics, hypertension, smoking, drinking, hyperhomocysteinemia, hyperlipidemia, and family histories of dementia were recorded. Informed consent was obtained from each subject before acceptance into the study. This study was approved by the Institutional Review Board of Shanghai Tongji Hospital and conducted according to the Declaration of Helsinki.

Inclusion criteria

Stenosis group: Any intracranial artery that had stenosis of ≥ 50% or occlusion; Control group: Any intracranial artery that had stenosis of ≤ 30% [8]. Volume data were input into the package of three-dimensional CT angiography (CTA), followed by vascular subtraction imaging. Next, 3-D image data were obtained. WASID method [9] was used to evaluate IAS.

Exclusion criteria

Patients diagnosed with brain strokes or cerebral hemorrhages by cranial CT or MRI; Patients with a history of severe brain trauma or atrial fibrillation; Patients that had heart, liver, kidney, or lung dysfunction, as well as malignancies or other severe infections; Patients that could not cooperate with examinations due to visual or hearing impairment or aphasia.

CT scanning

Whole-brain perfusion imaging was performed with Toshiba Aquilion ONE 320 CT, with the following parameters: Coverage: 140 mm; Volume scanning; Slice thickness: 0.5 mm; FOV: 220 mm; Matrix: 512 × 512; Tube voltage: 100 kV; Tube current: 150 mA. Next, 50 mL of contrast agent (Iohexol; 350 mg I/mL) was intravenously injected. The first scanning was performed 7 seconds later, then intermittent scanning was performed with an interval of 2 seconds, beginning at 12 seconds. In the arterial phase, imaging was conducted from 12 seconds and peaked at 18-28 seconds. In the venous phase, intermittent scanning was conducted with an interval of 5 seconds, from about 40 seconds and continuing to 60 seconds. A single rotation time was 0.5 seconds. Total scanning time was 60 seconds and a total of 19 volume data was collected.

MRI scanning

Siemens Verio 3.0T MRI instrument (Germany) and standard orthogonal head coils were used for MRI scanning. Patients were placed in the supine position and a standard orthogonal head coil was used. After localization, scanning was performed, with the follow parameters: Axial T1 scanning: TR, 1530 s; TE, 9 ms; Slice thickness, 5 mm, interval, 1 mm; FOV, 230 mm × 230 mm; Axial T2 scanning: TR, 4210 ms, TE, 96 ms, slice thickness, 5 mm; Interval, 1 mm; FOV, 230 mm × 230 mm. FLAIR scanning: TR, 5000 ms; TE, 94 ms, TI, 1800 ms; Slice thickness, 5 mm; Interval, 1 mm; FOV, 230 mm × 230 mm.

Assessment of cognitive function

Montreal Cognitive Assessment (MOCA), Chinese edition, was used for assessment of cognitive function in a quiet environment. The total MoCA score was 30. One was added if the educational length was ≤ 12 years and the cumulative total score was < 30. Thresholds were as follows: Total MoCA score is ≥ 24 for educational levels of primary school or higher; Total MoCA score is ≥ 20 for educational levels lower than primary school.

Assessment of IAS and calculation of IAS load

Bolume data were input into the package of three-dimensional CT angiography (CTA), followed by vascular subtraction imaging. Next,

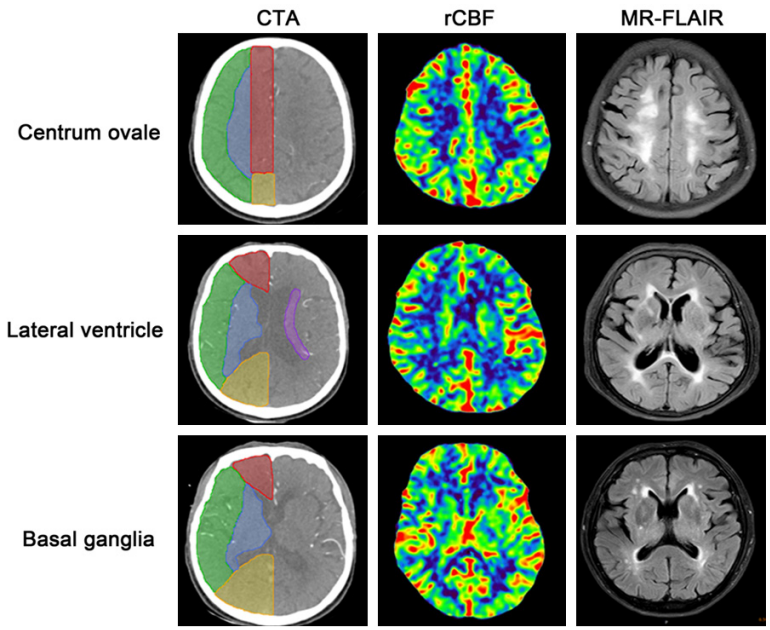

Figure 1. Representative images of CTA, CBF, and FLAIR. In CTA, red represents territory of ACA. Green and blue represent the territory of MCA, yellow represents PCA, blue represents the sub-cortical territory of MCA, and purple represents the territory of peri-ventricular area.

3-D image data were obtained. WASID method [9] was used to evaluate IAS: IAS = 1 - [diameter of stenotic artery/diameter of distal normal artery] × 100%. Bilateral intracranial common carotid artery, anterior cerebral artery, middle cerebral artery, posterior cerebral artery, vertebral artery, and basilar artery were assessed, in a blind manner, by two experienced physicians in the Department of Neurology, with double-checking. IAS load was calculated as follows: Stenosis of any intracranial artery ≥ 50% or complete occlusion was scored 1; The sum of scores indicates IAS load.

Measurement of cerebral perfusion

Volume data were input into Perfusion Mismatch Analyzer (PMA) (Advanced Medical Science Center, Iwate Medical University, Iwate, Japan) for calculation of cerebral blood flow (CBF). The Willis circle was used as a reference plane, 10 AIFS was automatically selected, and intracranial veins at the upper of skull base were automatically selected as VIFS. Deconvolution method was employed for calculation of perfusion images. The matrix was 512 × 512, slice thickness was 0.1 mm, and defaults were used for other parameters. For quantitation, perfusion imaging after PMA reconstruction were input into Mango (http://rii.uthscsa.edu/mango/). The region of interest (ROI) was delineated at the centrum ovale, top lateral ventricle, and basal ganglia levels. Corresponding CBF was then calculated. Intracranial arterial territory was determined according to methods provided by Moeller et al. [10]. However, the venous sinus, major vessels, and ventricles should be avoided. Mean CBF was calculated at the above three levels. CBF at the side of stenosis was used if unilateral stenosis was present. Mean CBF was calculated if bilateral stenosis was observed. Mean CBF, at the above levels, was compared between the two groups (**Figure 1**).

Assessment of white matter lesions

FLAIR sequence was selected at the centrum ovale, top lateral ventricle, and basal ganglia levels for assessment of WMH, with a modified Schletens scoring system [11]. Antecornu, postcornu, and peri-ventricular areas were assessed as follows: 0, no change; 1, lesion of < 5 mm; 2, lesion of 6-10 mm. WMH was assessed in the deep brain (subcortical) of frontal, parietal, temporal, and occipital lobes, as follows: 0, no abnormality; 1, lesion of ≤ 3 mm and lesion number of ≤ 5; 2, lesion of ≤ 3 mm and lesion number of ≤ 6; 3, lesion of 4-10 mm and lesion number of ≤ 5; 4, lesion of 4-10 mm and lesion number of ≥ 6; 5, lesion of ≥ 11 mm and lesion number of ≥ 1; 6, lesion fusion. White matter intensities of different ROIs, at the above levels, were assessed. The mean score of both sides was calculated. WMH is defined if the score of the deep brain is > 2 and if the score of the peri-ventricular area is > 1. Incidence of WMH was compared between the two groups (**Figure 1**).

Statistical analysis

Statistical analysis was performed with SPSS version 20.0. Demographics are expressed as descriptive data (x ± s; percentage). One-way analysis of variance was used for comparisons between the stenosis group and control group.

Table 1. Characteristics of patients in the two groups at baseline

	Control group (n = 62)	Stenosis group (n = 70)	*P* value
Age (mean ± SD)	65.84 ± 9.67	73.01 ± 8.86	< 0.001***
Sex (male, %)	30 (48.4)	31 (44.9)	0.692
Education years	9.97 ± 4.08	8.57 ± 4.29	0.058
Smoking (%)	14 (22.6)	12 (17.1)	0.433
Alcohol consumption (%)	5 (8.1)	7 (10)	0.699
Hypertension (%)	26 (41.9)	46 (65.7)	0.006**
Diabetes (%)	12 (19.4)	18 (25.7)	0.384
Family history of dementia (%)	4 (6.5)	4 (5.7)	0.859
Hyperlipidemia (%)	23 (48.9)	33 (66)	0.089
Homocysteine (%)	1 (3.7)	4 (11.8)	0.503

Notes: Stenosis group vs Control group, **P < 0.01, ***P < 0.001.

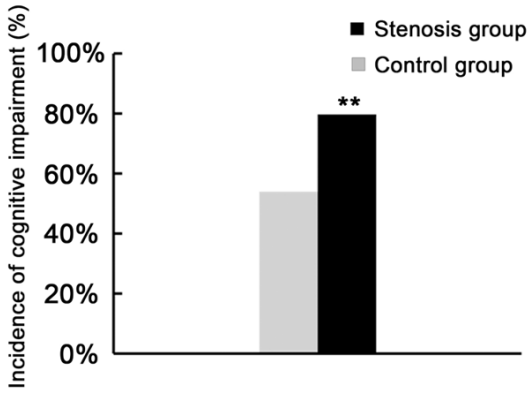

Figure 2. Cognitive impairment in the two groups. Incidence of cognitive impairment was significantly different between the stenosis group and control group (***P* < 0.01).

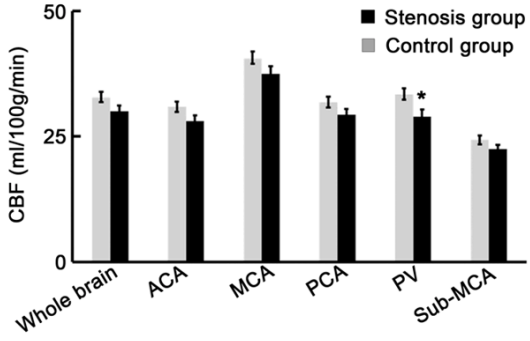

Figure 3. Cerebral perfusion at different areas. Cerebral perfusion at the peri-ventricular area reduced significantly in the stenosis group, compared to the control group (28.91 ± 1.42 vs 34.51 ± 1.49, P < 0.01). However, cerebral perfusion at the territories of ACA, MCA, PCA, and sub-MCA was comparable between the two groups (**P* < 0.05). Note: ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; sub-MCA: sub-cortex of middle cerebral artery; PV: Periventricular region.

Chi-squared test was used for comparisons of rates. Spearman's correlation analysis was employed for evaluation of the relationship of CBF with WMH and cognitive impairment. A value of two-sided P < 0.05 is considered statistically significant. This study was revised by a professor from the Department of Health Statistics, Tongji University.

Results

Demographics and general characteristics

There were significant differences in age and hypertension between the stenosis group and control group (P < 0.05), but no marked differences were observed in gender, education level, smoking, drinking, family history, diabetes, hyperlipidemia, and hyperhomocysteinemia between the two groups (P > 0.05) (**Table 1**).

Correlation between cognitive function and IAS load in the two groups

In the stenosis group, incidence of cognitive impairment was significantly higher than that in the control group (79.7% vs 54.1%, *P* < 0.05) (**Figure 2**). Correlation analysis showed that IAS load was negatively related to total MoCA scores (r = -0.34, P < 0.001) (**Figure 5A**).

Correlation of CBF at different levels with IAS load in the two groups

In the stenosis group, CBF at the peri-ventricular area reduced significantly, compared to the control group (28.91 ± 1.42 vs 34.51 ± 1.49, P < 0.01). CBF at the territories of anterior, middle, and posterior cerebral arteries, as well as the subcortical territory of the middle cerebral artery, was comparable between the two groups (**Figure 3**). Correlation analysis showed that IAS load was negatively related to CBF of the peri-ventricular area (r = -0.21, P < 0.05), but had no relationship with whole-brain CBF (**Figure 5C** and **5D**). IAS load had no correlation with CBF at the territories of anterior, middle, and posterior cerebral arteries, as well as the subcortical territory of the middle cerebral artery.

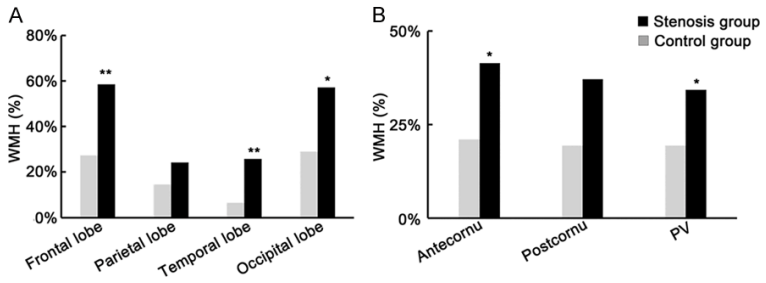

Figure 4. Sub-cortical and peri-ventricular WMH in both groups. A: Incidence of sub-cortical WMH at the frontal lobe (58.6% vs 27.4%, **P < 0.01), temporal lobe (25.7% vs 6.5%, *P < 0.05), and occipital lobe (57.1% vs 29%, **P < 0.01) increased significantly in the stenosis group, compared to the control group. However, there was no marked difference in incidence of subcortical WMH at the parietal lobe between the two groups. B: Incidence of WMH at the peri-ventricular area and antecornu was significantly different between the two groups (antecornu: 41.4% vs 21%, *P < 0.05; peri-ventricular area: 34.3% vs 19.43%, *P < 0.05).

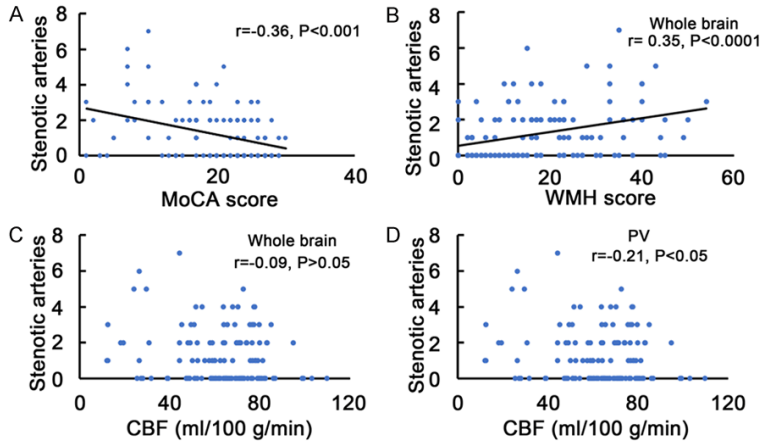

Figure 5. Correlation of IAS load with cognition, WMH, and cerebral perfusion. A: Correlation analysis of IAS load and MoCA scores: IAS load was negatively related to cognitive function (r = -0.36, P < 0.001). B: Correlation analysis of IAS load and whole-brain WMH: Results show that IAS load was positively related to whole-brain WMH (r = 0.35, P < 0.0001). C, D: Correlation analysis of IAS load and cerebral perfusion: Results show that IAS load was not related to whole-brain perfusion but was positively related to cerebral perfusion at the peri-ventricular area (r = -0.21, P < 0.05). WMH: White matter hyper-intensive; PV: Periventricular area.

Incidence of WMH and its relationship with IAS load

Compared to the control group, incidence of subcortical WMH in the frontal, temporal, and occipital lobes increased significantly in the stenosis group (frontal: 58.6% vs 27.4%, P < 0.01; temporal: 25.7% vs 6.5%, P < 0.05; occipital: 57.1% vs 29%, P < 0.01). There were no marked differences in incidence of subcortical WMH in the parietal lobe between the two groups (**Figure 4A**).

Compared to the control group, incidence of WMH at the peri-ventricular area and antecornu increased significantly in the stenosis group (antecornu: 41.4% vs 21%, P < 0.05; peri-ventricular: 34.3% vs 19.43%, P < 0.05) (**Figure 4B**).

Correlation analysis indicated that IAS load was positively related to severity of whole-brain WMH (r = 0.32, P < 0.01) (**Figure 5B**).

Discussion

Risk factors of moderate-to-severe IAS

Studies have shown that age, hypertension, diabetes, hyperhomocysteinemia, hyperlipidemia, smoking, and drinking are risk factors of IAS [12]. In the present study, results showed significant differences in age and hypertension between the stenosis group and control group (P < 0.05). Moderate-to-severe IAS was related to age and hypertension. Previous studies have shown that the most important risk factors of IAS are age and hypertension [13], consistent with present results. Patients in the stenosis group had stenosis of ≥ 50%, while patients in the control group had stenosis of < 30%. There were no patients without IAS completely. This might have caused non-significant differences in other risk factors. Compared to other risk factors of cerebrovascular diseases, control of hypertension is of great importance.

Correlation between IAS and cognitive impairment

To date, few studies have been conducted investigating cognitive function in patients with IAS [14]. Some investigators have shown that IAS may cause cognitive impairment [15], but

the study of Cui et al. revealed that severity of IAS had no relationship with severity of cognitive impairment [16]. This discrepancy might be ascribed to the small sample size and differences in methods for cognition assessment. Current results showed that incidence of cognitive impairment was as high as 79.7% in patients with moderate-to-severe IAS, markedly higher than that in the control group. This was consistent with findings from most studies [17]. Results indicate that patients with moderate-to-severe IAS may develop cognitive impairment before strokes and stroke-free older patients may also develop cognitive dysfunction. Thus, early identification and early intervention of IAS should be paid adequate attention.

Correlation between IAS and cerebral perfusion

Mild vascular stenosis may fluctuate cerebral perfusion pressure, but brain blood flow may remain stable via the compensatory effects of collateral circulation, arterioles, and capillaries. Schuff et al. [18] investigated CBF with ASL, finding that patients with subcortical VaD had significantly reduced cerebral perfusion at the cortex of frontal and parietal lobes, which was mainly found in the white matter. In China, Han et al. [19] employed SPECT to assess cerebral perfusion. They found that VCI had developed cerebral hypoperfusion at the focal frontal lobe before the presence of cognitive impairment. In the present study, CT perfusion imaging was used to assess cerebral perfusion. Results showed cerebral hypoperfusion at the territory of peri-ventricular. However, cerebral perfusion remained unchanged at the territory of anterior, middle, and posterior cerebral arteries. This might be ascribed to the distribution of cerebral vessels. White matter at the peri-ventricular area is supplied by perforator arteries and has no or less collateral circulation. Thus, it belongs to the perfusion edge. This indicates that it is susceptible to the influence of cerebral hypoperfusion. It was speculated that the territory of peri-ventricular area is susceptible to hypoperfusion and that cerebral perfusion, in this territory, reduces with an increase in the number of stenotic vessels. However, the territories of anterior, middle, and posterior cerebral arteries are not likely to be influenced by cerebral hypoperfusion. This is due to the compensation of the above arteries, Willis cycle, and pial collateral circulation, even if these arteries become stenotic. This has been confirmed in some clinical trials [20, 21].

Correlation between IAS and WMH

Currently, the relationship between intracranial/extracranial atherosclerosis and WMH remains unclear. Duan et al. [22] found that WMH at the peri-ventricular area was independently related to extracranial arterial stenosis and that IAS was comparable between patients with mild white matter lesions and those with moderate-to-severe white matter lesions. Zhong et al. [23] found that IAS is an independent risk factor of WMH. It could increase the risk for WMH and deteriorated with an increase in the number of stenotic intracranial vessels. There is evidence showing that IAS is more closely related to WMH, compared to extracranial arterial stenosis, and IAS may deteriorate with an increase in the number of stenotic intracranial vessels [24]. This is consistent with present findings. Liu et al. and Zhong et al. employed the Fazekas scoring system [25] to determine WMH. In the current study, a modified Schletens scoring system was used to quantify lesions, making results more objective. In addition, in the studies of Liu et al. and Zhong et al., patients with acute stroke were also included. However, white matter lesions may also be affected by stroke events. Thus, in the present study, patients with brain strokes or hemorrhages, confirmed by cranial CT or MRI, were excluded. The relationship between IAS and WMH was further evaluated, making present results more convincing.

Current results indicate that cerebral hypoperfusion was found at the peri-ventricular area and incidence of WMH, at this area, increased significantly. It has been confirmed that the peri-ventricular area is more likely to develop WMH and WMH, compared to other areas [26]. This was confirmed in the current study. When intracranial arterial sclerosis is present, this area may develop hypoperfusion earlier, causing WMH. This may partially explain the high incidence of WMH in the peri-ventricular area. Of interest, it was found that incidence of WMH at the deep brain of frontal, temporal, and occipital lobes, as well as the antecornu, was significantly different between the two groups. However, cerebral perfusion remained unchan-

ged at these areas. This indicates that cerebral hypoperfusion is an important cause of WMH. However, other factors, such as blood brain barrier dysfunction and inflammation, may also affect occurrence of WMH. Cerebral perfusion may not completely reflect ischemic injuries of the brain. More studies with advanced techniques are necessary to further evaluate cerebral perfusion in patients with white matter lesions.

WMH is a common finding on imaging in the elderly. It was speculated that moderate-to-severe IAS is a cause of WMH that cannot be ignored. There is evidence showing that early improvement of cerebral perfusion is able to delay and attenuate, or even reverse, white matter lesions [27]. Monitoring of intracranial vessels, as well as early assessment and intervention, in patients with WMH is crucial in improving prognosis.

Correlation of moderate-to-severe IAS with CBF, WMH, and cognitive impairment

Stenosis of a single intracranial artery may not cause hypoperfusion and abnormal WMH at the corresponding territory. IAS load involves the number of intracranial stenotic vessels and may reflect the influence of IAS on focal cerebral perfusion and WMH. Current results suggest that IAS was negatively related to total MoCA scores and cerebral perfusion at the peri-ventricular area, but positively related to severity of whole-brain WMH. Although present results should be confirmed in more studies with large sample sizes, they indicate that IAS load may provide a valuable reference for clinicians. Moreover, calculation of IAS is simple and practical.

Current results suggest that IAS load was negatively related to cerebral perfusion at the peri-ventricular area ($r = -0.21$, $P < 0.05$) (**Figure 5C**). Cerebral perfusion may be automatically regulated. Changes in cerebral perfusion overwhelming the capability of autoregulation of the brain may cause a rapid reduction in cerebral blood flow. Thus, arterial stenosis related hypoperfusion is only found in patients with severe stenosis and incomplete compensation of extracranial arteries. This was confirmed by current findings. Results show that IAS load was negatively related to total MoCA ($r = -0.34$, $P < 0.01$) (**Figure 5A**), which may be ascribed to wider areas affected by multi-vessel stenosis, as multi-vessel stenosis may affect collateral circulation of the Willis cycle, influencing cerebral perfusion.

Dementia patients usually have focal or diffuse white matter lesions. There is evidence showing that chronic hypoperfusion due to changes in cerebral blood flow is an important cause of WMH [28]. Studies, in which different techniques were used to detect cerebral blood flow, have shown hypoperfusion at the white matter loose area. Cognitive impairment might be ascribed to cerebral hypoperfusion and subsequent WMH. In this study, risk factors of vascular diseases, images, and behaviors were analyzed for cognitive impairment. Results are helpful for the early diagnosis of cognitive impairment. There were some limitations to the current study, however: (1) This was a cross-sectional study with a small sample size. More longitudinal studies with large sample sizes are needed to confirm current findings; (2) Collateral circulation was not assessed in this study. Thus, it failed to evaluate the influence of collateral circulation on whole-brain perfusion. In future studies with large sample sizes, assessment of collateral circulation should be further investigated.

Conclusion

Advanced age and hypertension are high risk factors of moderate-to-severe IAS. Patients with moderate-to-severe IAS are more likely to develop cognitive impairment. IAS load is negatively related to total MoCA scores and cerebral perfusion at the peri-ventricular area. It is also negatively related to severity of whole-brain WMH. Cognitive impairment in patients with moderate-to-severe IAS may be related to cerebral hypoperfusion and WMH.

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Disclosure of conflict of interest

None.

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