Original Article
Is incomplete circle of Willis associated with white matter lesion?

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Abstract: Objective: The pathogenesis of cerebral white matter lesion (WML) may be associated with chronic cerebral hypoperfusion. Incomplete circle of Willis (CoW) and cerebral artery stenosis (CAS) may contribute to chronic cerebral hypoperfusion. This study aimed to investigate whether incomplete CoW and CAS were associated with WML by a prospective study. Methods: 102 patients were enrolled in this study. The WML group included 52 patients who had level 2 or 3 WML according to Fazekas scale and no stroke history, and the control group included 50 patients who had normal cranial magnetic resonance images (MRI). All subjects underwent baseline examinations and completed MRI and contrast-enhanced cerebral CT angiography (CTA). CoW morphology was divided into complete and incomplete types according to the CTA results. The extent of CAS was calculated with reference to WASID method. Results: Hypertension, serum creatinine and homocysteine levels were higher in WML group than in control group (P<0.05). There were no significant differences of sex, age, smoking, diabetes, coronary artery disease, serum lipid, and blood glucose or alanine transaminase level between two groups (P>0.05). Although the percentage of CAS and incomplete CoW in WML group was higher than in control group, there was no significant difference between the two groups. Conclusions: CoW is the most important mechanism of cerebral collateral circulation. Incomplete CoW and CAS may impair self-regulation of cerebral blood flow and hemodynamic stability, but there is insufficient evidence to suggest that incomplete CoW and CAS are associated with WML in this study.

Keywords: White matter lesions, circle of Willis, cerebral artery stenosis, magnetic resonance images, CT angiography

Introduction

Leukoaraiosis or white matter lesions (WML) are common neuroimaging findings in the elderly, which distribute symmetrically beside lateral ventricle, semioval area, or corona radiata area. WML can be detected by CT scan which shows low-density changes, but conventional MRI sequences play an essential role in identifying WML. WML is best seen on T2-weighted sequences, and contrast between WML and normal tissue is further increased on Fluid Attenuated Inversion Recovery (FLAIR) sequences. WML has been considered as a cerebral small vessel disease and the pathogenesis was uncertain, it may be associated with chronic cerebral hypoperfusion [1]. However, neither a clear risk factors for cerebrovascular disease nor pathophysiological process of chronic hypoperfusion is observed in WML patients in clinical practice. Circle of Willis (CoW) is the primary intracranial collateral circulation, it has a major role in redistributing the blood in case of diminished supply through the internal carotid artery and the basilar artery, but an entirely intact CoW only exists in 20-45% of the population [2, 3]. It has been hypothesized that incomplete CoW may diminish cerebral autoregulation by weakening anastomosis capacity and reduce flow in middle cerebral artery [4, 5]. The purpose of this study was to investigate whether cerebral artery stenosis (CAS) and morphological abnormalities of CoW were associated with WML from the perspective of vascular disease.

Subjects and methods

Subjects

This study is a single-center prospective cohort study. In the study, a sample of 102 conse-
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Figure 1. A 45-year-old male patient with no prior hypertension, diabetes, hyperlipidemia, smoking history, or family history of hypertension disease. His blood pressure was 200/110 mmHg upon admission. His WML was Grade 3 (Fazekas scale) and old lacunar infarction was indicated by FLAIR; his CoW was complete as indicated by enhanced CTA; and there was no significant stenosis of cerebral arteries.

Figure 2. A 80-year-old male patient with hypertension, complained of long-term dizziness, fatigue, depression, insomnia and memory loss. Grade 3 WML by Fazekas scale was indicated by Flair MRI. His CoW was incomplete, his A1 segment of the left ACA was absent and the right PCA was hypogenesis and many stenoses of cerebral arteries were found by enhanced CTA.

tive Chinese participants were included. All subjects were patients from the Neurology Department of Shanghai Tongji Hospital, with symptoms of mainly dizziness, headache, insomnia, and anxiety. The patients included 2 groups: 1) WML group (n=52) Level 2-3 according to Fazekas scale, with no prior stroke; 2) control group (n=50) with almost normal head MRI examination result. All subjects underwent baseline examinations, including a questionnaire on the presence of cardiovascular disease and classic risk factors, height, weight, blood pressure measurements, blood tests, neuropsychological assessments, ultrasound scanning of the common carotid and internal carotid artery, head contrast-enhanced CT angiography (CTA) and MRI of the brain, including axial T1-weighted, T2-weighted imaging, FLAIR and diffusion-weighted imaging. Subjects were excluded if they met one of the following criteria: 1) with a prior history of central nervous system disease, such as stroke, cancer, infection, poisoning and primary demyelinating disease; 2) with serious organic diseases in other systems; 3) with MRI contraindication; 4) allergic to iodine water; and 5) not able to tolerate or not able to follow study procedures.

Methods

Morphological changes of CoW and intracranial arterial stenosis in all participants were analyzed (Figures 1 and 2). Two experienced neuroradiologists (blinded for peer review) evaluated WML on MRI and the shape of CoW on contrast-enhanced CT angiograms in consensus. WML on MRI was defined as ill-defined hyperintensities greater than 5 mm on both T2 and FLAIR images. Fazekas scale was used to assess WML [6], which is divided into Grades 0-3. Grade 0: absent or only 1 dot; Grade 1: punctate foci; Grade 2: beginning confluence of foci; Grade 3: large confluent areas. Grades 0-1 WML may be physiological, so excluded from the WML group. Only Grade 2 and Grade 3 were included in the group. The seven arteries of CoW were evaluated: the anterior communicating artery (AcoA), the two A1 segments of the anterior cerebral arteries (ACA), the two P1 segments of the posterior cerebral arteries (PCA), and the two posterior communicating arteries (PcoA). The morphology of CoW was divided
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Table 1. Comparisons of general characteristics, cerebrovascular stenosis, and CoW between the WML group and the control group

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>WML (n=52)</th>
<th>Control (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>28</td>
<td>21</td>
<td>0.243</td>
</tr>
<tr>
<td>Age</td>
<td>69.35±8.22</td>
<td>65.94±11.53</td>
<td>0.088</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40</td>
<td>21</td>
<td>0.001*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16</td>
<td>12</td>
<td>0.509</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>20</td>
<td>8</td>
<td>0.080</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>22</td>
<td>18</td>
<td>0.548</td>
</tr>
<tr>
<td>Smoking history</td>
<td>20</td>
<td>14</td>
<td>0.298</td>
</tr>
<tr>
<td>CAS</td>
<td>20 (38.46%)</td>
<td>13 (26%)</td>
<td>0.208</td>
</tr>
<tr>
<td>Incomplete CoW</td>
<td>22 (42.31%)</td>
<td>16 (32%)</td>
<td>0.311</td>
</tr>
</tbody>
</table>

*P<0.05, WML vs control group.

Table 2. Comparisons of the levels of chemistry parameters between the WML group and the control group

<table>
<thead>
<tr>
<th></th>
<th>WML (n=52)</th>
<th>Control (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase</td>
<td>15.98±3.50</td>
<td>15.56±4.07</td>
<td>0.577</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>70.27±9.65</td>
<td>64.14±7.43</td>
<td>0.001*</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>4.31±0.90</td>
<td>4.60±0.79</td>
<td>0.078</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>3.03±0.63</td>
<td>3.12±0.54</td>
<td>0.416</td>
</tr>
<tr>
<td>Lipoprotein a</td>
<td>63.82±53.28</td>
<td>55.55±40.31</td>
<td>0.378</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>14.26±6.22</td>
<td>11.16±2.87</td>
<td>0.002*</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>5.54±0.93</td>
<td>5.39±1.20</td>
<td>0.490</td>
</tr>
<tr>
<td>Glycated hemoglobin</td>
<td>6.11±0.85</td>
<td>6.27±1.19</td>
<td>0.425</td>
</tr>
</tbody>
</table>

*P<0.05, WML vs control group.

into 2 types, including complete and incomplete morphology. Complete morphology means an entirely intact CoW, incomplete morphology includes incompleteness of the blood vessels, change in vessel diameter (eg, vessel diameter <1 mm) and fetal-type posterior cerebral artery. The fetal configuration of CoW is a morphologic variant in which the P1 segment is smaller than the posterior communicating artery segment and the internal carotid artery supplies blood to the ipsilateral P2 segment of the posterior cerebral artery via the posterior communicating artery. The extent of CAS was determined by CTA indirect method, calculated with reference to WASID method [7]: stenosis% = (1 - [D_{stenosis}/D_{normal}]) × 100%, where D_{stenosis} represents the narrowest diameter of the stenosis, D_{normal} represents normal diameter of proximal artery. Diameter was measured by Image J software. The severity of stenosis was divided into 2 groups: mild or no stenosis when stenosis% was <50%; obvious or occlusion when stenosis% was ≥50%.

Statistical analysis

Results were analyzed using SPSS soft software (version 18.0, SPSS Inc.). Data in normal distribution were expressed as mean ± standard deviation. t test was used to analyze homogeneity of variance of the variable of group data and chi-square test was used to analyze categorical data. A 2-sided p value <0.05 was considered statistically significant.

Results

There were no statistical differences (P>0.05) in patient number, age, gender ratio, smoking status, and diabetes between the 2 groups. The proportion of patients with hypertension was significantly greater in the WML group compared with the control group (P=0.001) (Table 1). The levels of chemistry parameters homocysteine and serum creatinine were significantly higher in the WML group than in the control group (Table 2).

The proportion of patients with CAS and incomplete CoW as analyzed by CTA was higher in the WML group than in the control group; however, the difference did not reach statistical significance (P>0.05, Table 1).

Discussion

WML is highly associated with age, with the incidence of WML increasing with age. The incidence of WML doubles with increase of 10 years in age. In the general population, the prevalence of WML ranges from 11-21% in adults aged around 64 to 94% at age 82 [8]. Previous studies found that the risk factors of WML are similar to ischemic cerebrovascular disease, including hypertension, diabetes, aging, and carotid artery stenosis [9]. This study also indicates that WML is associated with hypertension, high level of homocysteine and serum creatinine. Higher level of serum creatinine in WML group may be associated with renal arteriosclerosis caused by hypertension, but high homocysteine, as hypertension, may be a risk factor for WML. Our finding is in accord with those of two other studies that have inves-
tigated leukoaraiosis patients similar to ours [10, 11].

WML is regarded as a cerebral small vessel disease, and the diameters of these vessels are often smaller than 0.1 mm, located in the junction of white matter and gray matter. Most of the blood supply of the white matter of the cerebral hemisphere is from long deep perforating artery, and the blood supply of white matter of lateral ventricle wall is from subependymal ventricular artery distal vessel. The artery itself is the terminal branch of the choroid plexus artery. The white matter of the lateral ventricle wall locates between anterior cerebral artery and arteria cerebri media. Imaging findings include WML, lacunar infarction and remote cerebral microhemorrhage, which may exist alone or concomitantly. The pathological feature of WML manifests diffuse white matter demyelination, mainly around the lateral ventricles deep white matter, semiovale area or corona radiata area, usually with silent lacunar infarctions in basal ganglia, thalamus and subcortical white matter region. There are no demyelinating changes in the arcuate fibers and corpus callosum [1]. The etiology of WML is unclear. The pathophysiology mechanism may be chronic hypoperfusion of white matter and blood-brain barrier damage causing chronic leakage of plasma into white matter [1]; however, other studies report nonischemic causes for WML [12, 13].

The association between low regional cerebral blood flow and WML has been described in many studies and some studies reported an association with white matter hypoperfusion [14-18]. We supposed WML was a result of vascular lesions, and then explored the association between WML and CAS and anomaly of CoW.

CoW is comprised of A1 segment of former cerebral artery of both sides, P1 segment of posterior cerebral artery of both sides, terminal of carotid arteries on both sides, anterior communicating artery and posterior communicating artery. Carotid arteries on both sides are connected at the basis encephali by anterior communicating artery, connecting vertebrobasilar artery system via posterior communicating artery. CoW is the most important mechanism of cerebral collateral circulation, which connects hemisphere and anterior and posterior circulation. Complete CoW and balanced development of the various vessels occur in a small population. The structure variation rate is high, which differs in studies due to different assessment methods. Currently in clinical practice, the most common evaluation methods for collateral circulation include MRA, CTA and digital subtraction angiography (DSA), of which, DSA is considered as golden standard. CTA method has high sensitivity and specificity in assessing the anatomic variations of the CoW (>90%), and is simple to operate, non-invasive and economic and practical, therefore it is widely used in clinical practice [19].

About 20%~45% individuals had complete CoW. In an autopsy study including 1,000 patients, the variation rate of CoW was found to be 54.8% [20]. Variation of CoW included incompleteness of its comprising vessels and changes in vessel diameter. Vessel is considered dysplastic when the diameter is less than 1 mm [14]. Study has shown that higher variation rate observed in posterior circulation compared with anterior circulation. The variation in anterior circulation is mainly absence vessel, while the variation in posterior circulation is mainly dysplastic [20]. It is unclear whether WML associated with anomaly of CoW, because there was few control studies with large sample size to determine whether WML is associated with anomaly of CoW. Ryan et al. reported that the prevalence of CoW variants strongly correlated with WML, patients with absent anterior vessels exhibited more frontal white matter disease than those with intact anterior vessels, patients with absent posterior vessels exhibited more occipital white matter disease than those with intact posterior vessels [21]. Interestingly, a previous study found that a fetal configuration of CoW in atherosclerotic subjects was associated with a decreased WML load, thus, they surmised this altered vascularization could be protective for lesions in the white matter [22]. Chuang et al. reported that the incidence of incomplete CoW was 77.4% in 106 patients with carotid artery stenosis; WML was positively associated with the number of missing vessels of CoW; and WML significantly worsened with dysplasia of merging anterior communicating artery [23]. Saba et al. investigated 47 patients with carotid stenosis undergoing carotid endarterectomy surgery and found the volume of WML was associated with structure anomaly of CoW [24]. Previous stud-
ies were mainly restricted to WML patients with carotid artery stenosis, which were insufficient to draw a conclusion. Our research has the advantage of design by a prospective cohort study and all participants without definite history of cerebrovascular disease, so it can avoid the defect about selective bias. This study found that there was higher incidence of anomaly of CoW in WML patients, but there was no obvious correlation between anomaly of CoW and WML.

In the recent 2 decades, studies have shown that the severity of carotid stenosis is associated with WML; however, there are few studies investigating the association between cerebral stenosis and WML. Two Chinese studies found that there were no significant association between cerebral stenosis and WML [25, 26]. In our study, the proportion of patients with CAS was numerically higher in the WML group; however, there was no significant association between CAS and WML.

In our study, hypertension and high plasma homocysteine is a risk factor for WML. CoW is the most important mechanism of cerebral collateral circulation, incomplete CoW and CAS can affect the auto-regulation of cerebral blood flow and hemodynamic stability, but there is insufficient evidence to suggest that CAS and morphological abnormalities of CoW are associated with WML.

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Disclosure of conflict of interest

None.

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