Relationship between Leukoaraiosis and Atherosclerosis Plaques

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Abstract. The aim of this study was to investigate the relationship between the different kinds of leukoaraiosis (LA) and carotid atherosclerosis (AS) plaques. A total of 208 LA patients were divided into three groups, namely, circumventricular (Group I, n=68), subcortex (Group II, n=66), and mixed types (Group III, n=74). The AS plaques and stenosis of the carotid were detected using color Doppler flow imaging and the magnetic resonance images of patients, respectively. Among the patients enrolled in this study, 67.79% (141/208) had AS plaques, 24.04% of which was detected in Group II (50/66), 25.96% from Group III (54/74), and 17.79% from Group I (37/68), with significant difference among all groups. By contrast, the score of the stable plaques was identical, with all the AS plaques scoring under three grades. The Grades I/II/III plaques of the subjects in Group I were 45/40/47, respectively; Group II had 20/40/47; and Group III had 20/31/34. The Grades I/II/III plaques among the 52 subjects with carotid stenosis (50%) were 15/19/18 without any differences. The carotid AS plaque is one of the risk factors of LA and the fragments of vulnerable plaques related to leukoaraiosis.

Key words: Leukoaraiosis, Carotid atherosclerosis plaque, Relativity

Introduction

Leukoaraiosis (LA), a radiological term introduced by Hachinski in 1987, refers to a disorder of white matter disturbances induced by various causes, and is commonly observed in the elderly through magnetic resonance images (MRI). Traditionally, the severity of LA is indicative of a cerebrovascular disease, although the metabolic syndrome (MetS) in the healthy subjects is significantly associated with the incidence of LA. Thus, MetS is considered as an LA risk, along with the impaired fasting glucose or hypertriglyceridemia that are likewise associated with LA. The main drawback of LA is its ability to accelerate the progress of Alzheimer’s Disease (AD), which has been attributed to the modest but non-significant increase in the frequency of mild cognitive deficiencies and parkinsonism. No effective treatments for LA have been reported yet; thus, performing certain methods of intervention to slow down the progress of LA is highly important to delay cognitive dysfunction. Recently, the relationship between atherosclerosis (AS) and LA has been identified. Our research, which focuses on the influences of carotid AS plaque in different conditions, including stable, unstable, and stenosis on different types of LA, has a positive role both in regressing the evolution of LA and in health economics.

Materials and Methods

Subjects

A total of 208 patients were recruited from the patients admitted to the People’s Hospital of Pudong between December 2007 and April 2009, and had been diagnosed during their three days of hospitalization using MRI. Among the subjects, 123 patients were males (mean age, 67.8±6.8), and 85 patients were females (mean age, 69.1±8.1). Based on their brain MRI, the patients were classified into three groups according to their brain MRI: circumventricular (Group I), subcortex (Group II), and mixed types (Group III) LA. Group I is composed of 68 subjects, with 41 males (mean age, 69.8±7.8) and 27 females (mean age, 68.1±8.3), which presented 21 unilateral and 47 bilateral types. Group II comprises 66 subjects, with 35 males (mean age, 70.3±6.5) and 31 females (mean age, 71.1±7.1), which presented 30 unilateral and 47 bilateral types. Finally, Group III is composed of 74 subjects, with 47 males (mean age, 69.8±7.8) and 27 females (mean age, 69.8±8.1), which presented 22 unilateral and 52 bilateral types. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the People’s Hospital of Pudong. Written informed consent was obtained from all participants.

Grouping

The subjects with LA who have undergone MRI examination were diagnosed according to the diagnostic and exclusion criteria of LA. The subjects were subsequently classified into three groups according to their brain MRI: circumventricular (Group I), subcortex (Group II), and mixed types (Group III). Each group
was further divided into unilateral and bilateral types. In line with the Coto grade system, LA is classified into three grades according to its severity. Less than 2 focuses were categorized as Grade I; 3 to 6 focuses, under Grade II; and confluent focuses, under Grade III.

Detection of Carotid AS Plaque by CDFI

Carotid AS plaques were detected using the model of Logq500 Color Doppler flow imaging (CDFI), with 5 MHz to 10 MHz of linear Probe. The patients were asked to remain in a lying position with a low pillow, and their heads had to be slightly tilted back; that is, lateral to the contralateral side of the inspection area. The sampling sites were located 1 cm and 2 cm from the common carotid artery bifurcation, at the bifurcation, and 1 cm or more from the internal carotid bifurcation. Carotid AS plaque can be defined through the following criteria: any vascular segment of the carotid artery systems protruding into the lumen and/or localized roughness, with increased echogenicity and an area of focal increased thickness (>1.3mm) in the intima-media thickness (IMT). Plaque score, calculated by summing the thickness of all the carotid AS plaques in both carotid arteries, was used in this study. According to the characteristics of ultrasonic materials, carotid AS plaque can be classified as flat, soft, hard, or ulcerous. Among these categories, the soft and ulcerous plaques are the most unstable. The average scores were obtained by calculating the stable and unstable plaque scores.

Detection of Carotid AS Plaque through MRI

MRI was performed using a General Electric Signa (1.5-T) system (General Electric Magnetic Medical Systems), which could accurately display the lipid core, fibrous cap, and the calcium in the AS plaque. Based on its appearance, the plaque was classified under three levels, namely, intact thick fibrous cap (level 1), intact thin fibrous cap (level 2), and ruptured fibrous cap (level 3).

Assessment of Internal Carotid Artery Stenosis

According to the consensus reached by the Society of Radiologists in Ultrasound in 2003, the degree of stenosis should be stratified under the following categories: normal (no stenosis), less than 50% stenosis, 50% to 69% stenosis, 70% to 99% stenosis to near occlusion, near occlusion, and total occlusion. Using the following formula, the degree of internal carotid artery stenosis can be comprehensively diagnosed.

Degree of stenosis = (1-cross-sectional area of residual vascular luminal area/vascular cross-sectional area) × 100%

Statistical Analysis

The data represented by mean±SD was analyzed using SPSS 12.0. The differences in the obtained data were compared through a homogeneity test of variances and a t or t' test.

Results

AS Plaques

After the detection by CDFI, 141 of the 208 LA patients have been found to have carotid AS plaques, with a positive rate of 67.79%. The positive rates of Groups I, II, and III were 54.41% (37/68), 75.76% (50/66), and 72.97% (54/74), respectively, with significant differences among the groups.
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Relationship between LA and AS Plaques

In Group I, 11 cases from the unilateral type LA had carotid AS plaques detected using CDFI, and 6 subjects showed the same side of LA and plaques. For the bilateral type LA from Group I, 26 cases had carotid AS plaques, with 11 subjects expressing both sides of LA and plaques. In Group II, 22 cases of unilateral type LA had carotid AS plaques, with 12 subjects showing the same side of LA and plaques. In addition, 28 cases of bilateral type LA had carotid AS plaques, with 12 subjects showing both sides of LA and plaques. Finally, in Group III, 16 cases of unilateral type LA had carotid AS plaques, with 7 subjects showing the same side of LA and plaques. Among the clients with bilateral type LA, 38 cases had carotid AS plaques, with 13 subjects showing both sides of LA and plaques (Table 1, Fig. 1).

Scores of AS Plaque of different Groups Detected by CDFI

Carotid AS plaque scores of the three groups under the detection of CDFI: The average scores of the stable plaque were 2.32±0.46, 2.65±0.28, and 3.02±0.35 for Groups I, II, and III, respectively, and no significant difference was found among the groups (Table 1, Fig. 1).

Table 3. Different Grades of Carotid Artery Stenosis in Three Groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total(n,%)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tr>
<td>I</td>
<td>36 (52.94)</td>
<td>9</td>
<td>14</td>
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<tr>
<td>II</td>
<td>44* (66.67)</td>
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<td>49** (66.22)</td>
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Note: *P<0.05, Group 1 vs Group 2; **P<0.05, Group 1 vs Group 3

Figure 3. A: Carotid ultrasonography detection: mixed echo plaques on the anterior wall of the initiation of right external carotid artery; B: Carotid ultrasonography detection: 52.9% arteriostenosis in the initiation of right internal carotid artery.

Different AS Plaques Grade for different Groups Detected by MRI

Conditions of the AS plaques for all three groups examined using MRI: Grade I plaques represented 54.88%, 35.71%, and 38.21% (45/82, 40/112, and 47/123) of Groups I, II, and III, respectively. Grade II plaques represented 24.39%, 27.68%, and 27.64% (20/82, 31/112, 34/123) of Groups I, II, and III, respectively. Grade III plaques represented 20.73%, 36.61%, and 34.15% (17/82, 41/112, 42/123) of Groups I, II, and III, respectively (Table 2).

Relationship between Carotid Artery Stenosis and Grades of AS Plaque

A total of 129 patients were diagnosed with carotid artery stenosis. In Group I, 36 patients had carotid artery stenosis, and the mild/moderate/severe cases were 9, 14, and 13, respectively. In Group II, 44 patients had carotid artery stenosis, and the mild/moderate/severe cases were 12, 14 and 18, respectively. Finally, in Group III, 49 patients had carotid artery stenosis, and the mild/moderate/severe cases were 14, 14, and 21 (Table 3). Among the 52 patients with severe carotid artery stenosis (e”50%) and has

Figure 4. A: Magnetic Resonance Angiography (MRA) result. arteriostenosis was found in the initiation of right internal carotid artery; B: MRI (T2WI) result suggested: arteriostenosis plaque of II grade.

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undergone MRI examination, 15 patients had a Grade I plaque, 19 subjects had Grade II plaque, and 18 subjects had Grade III plaque conditions (Table 2). No significant difference was found among these groups (Figs. 2, 3 and 4).

Discussion
In this study, the relationship between AS plaque and LA was partly determined. More than half of the patients enrolled in our study had carotid AS plaques as detected through CDFI, and the ratio was greater in the subcortex type than with the circumventricular type, as well as the average scores of unstable plaques. Thus, in the subcortex and mixed types, more AS plaques were classified under either Grades II or III. However, the AS plaques under the circumventricular type were defined as Grade I, as detected through MRI. With the AS plaques, carotid artery stenosis occurred in 129 of the 208 subjects, although the severity of the stenosis had no relationship with the grade of the plaque. In additional, the ratio of LA and AS plaques that appeared on the same side was only about half the total, occurring less of in both sides for LA plaques compared with the AS plaques.

Cerebral white matter changes, called LA, appear in the areas of circumventricular and centrum semiovale. The plaque grade may contribute to the development of leukoaraiosis, particularly smaller individual lesions (LA), which generally reflects covert vascular brain injury, is classified either as circumventricular or subcortex type based on MRI detection. Previous studies showed that the most common causes of LA include small-artery diseases (such as atherosclerosis and restenosis) that are associated with hypertension and diabetes mellitus, and cerebral hypoperfusion, which is associated with low blood pressure.

Recently, some studies have suggested that thrombotic plaques have specific correlation in the development of LA. The severity of LA has been associated with the existence of carotid artery stenosis, as chronic atherosclerotic diseases have been found to be related to the pathophysiology of leukoaraiosis and its progression. In Korea, a study showed the significant association between leukoaraiosis and the stroke subtypes, although this area has not been investigated in China. The mechanisms, including the impacted parts and the formation of blood vessels between these types, needs further study.

In anatomy, the white matter adjacent to the cerebral cortex is called U-fibers, which are supplied by the long perforating branch artery and the short perforating branch across the white matter and adjacent cortex. Thus, the U-fibers cannot be easily damaged. The blood supplies of the periventricular white matter originate from the subependymal arteries of the choroidal arteries. Meanwhile, the terminal branches of the striatum arteries match poorly or absent with the arteries originating from the brain surface, making the periventricular white matter more vulnerable to cerebral hypoperfusion and arteriosclerosis. In the pathophysiological perspective, atherosclerosis, carotid AS plaque, and stenosis can directly decrease the regional cerebral blood flow in the white matter, followed by the induction of hyalinization, tortuosity, and extension. These pathophysiological processes intensify the hemodynamic disorder of the white matter, making it loose and extensively demyelinated, with edema and glial cell proliferation. Therefore, the periventricular white matter is more vulnerable than the subcortical white matter.

Nevertheless, the present research showed that the positive rate of carotid AS plaque in the subcortical LA was significantly higher than that of periventricular LA (75.76 % and 54.41 %, respectively), suggesting that the subcortical LA and carotid AS plaque may be more closely related. In recent years, the Medical Research Council Cognitive Function and Ageing study utilized MRI to detect LA in dead brain slices. Studies on the histopathology and the molecular markers of hypoxia were also conducted in these LA regions. During the study, researchers found that obvious hypoxia occurred in the subcortical white matter, and not in the loose periventricular white matter due to the loss in ependymal cells, similar to the findings of the current research. Thus, the different parts and types of LA may have various risk factors; hence, treatment preferences will be different accordingly. Nevertheless, the specific process of pathogenesis needs to be studied further.

The rupture of the carotid AS plaques leads to the release of tissue factors, which in turn results to thrombosis, the obstruction of distal artery, and the pathophysiologic changes in white matter eventually resulting to LA. Based on our findings, no significant differences have been observed in the incidence between ipsilateral and contralateral carotid AS plaques, suggesting that no ipsilateral relationship has been identified between the carotid AS plaque and LA. Through our analyses, we determined that the carotid AS plaque thrombosis caused by the presence of the human-specific circle of Willis may lead to the obstruction of the ipsilateral or contralateral arteries, as well as the bilateral obstruction of the distal arteries, followed by ischemic changes in the white matter.

When carotid artery stenosis is caused by plaque, the cerebral perfusion can be affected in varying degrees, as well as the occurrence and development of LA. However, Rothwell et al. discovered that patients with more severe artery stenosis had no apparent kinetic and hypoperfusion injuries after the examinations, such as positron emission tomography (PET). Unless systemic blood pressure is declined, hypoperfusion injuries may occur. In our study, we have proven the hypothesis that no relationship exists between the severity of LA and the degree of carotid artery stenosis. Based on our analysis, LA can be related to various factors, including age, gender, genetics, blood pressure, small artery diseases, collateral circulation, and the severity of LA; that is, LA results from the combined effect of multiple factors.

In recent years, scholars have conducted in-depth study on
the vascular pathophysiology, the molecular biology of endothelial cell, and the rapid development of new imaging techniques\(^9\). These studies have suggested that an unstable plaque rupture may lead to thrombus formation, and easily results to distal microembolization. With the force of blood pressure, unstable, lipid-rich carotid AS plaques rupture more easily. As a consequence, the surface roughness and exposure to procoagulant phospholipids result to the activation of the coagulation cascade of the secondary mural thrombus formation, which in turn facilitates thrombus formation in ischemic events. The present study showed that the average scores of the unstable plaque in Groups I, II, and III, as detected by CDFI, were 3.29±0.42, 7.68±0.37, and 6.97±0.51, respectively, with the scores of Groups II and III significantly higher compared with the scores of Group I. The carotid AS plaque detected through MRI showed that the number of Grade III plaques was significantly higher in Groups II and III compared with Group I, thereby suggesting that the instability of the carotid AS plaque is important in the development of LA, particularly in subcortical LA.

With regard to the methods used in detecting carotid AS plaque, the present research utilized CDFI and MRI. We found that CDFI has a higher sensitivity, thus can detect the early signs of atherosclerosis and provide a rough estimate of the degree of stenosis caused by carotid AS plaques. Nevertheless, the CDFI results of the assessment of plaque size, as well as the morphology of internal carotid artery and its branches, have been considerably restricted. Compared with CDFI, MRI was able to identify good soft tissue contrasts and arbitrary scan orientations, without other influences, such as calcifications. After the application of white- and black-blood technology, MRI can clearly determine various changes in the outer wall and the luminal in blood vessels, indicate the extent and distribution of the AS plaque, and accurately measure the total volume of lesion vessel walls and the plaque burden. Moreover, MRI can also estimate the extent of stenosis more accurately. Hence, CDFI provides a more simple and dynamic technique for carotid AS plaque screening, whereas MRI can be used to analyze the stability of carotid AS plaque further. Through these methods, a more scientific evaluation of the correlation between carotid AS plaque and LA could be acquired.

In conclusion, this preliminary research showed that carotid AS plaque is a risk factor for LA, and is closely related to subcortical LA, given the important role of plaque instability. With the circle of Willis, the carotid AS plaque rupture can result to ipsilateral, contralateral, or even bilateral LA. However, no relationship has been observed between the severity of LA and the degree of carotid artery stenosis. Previous studies showed that Carotid artery disease and leukoaraiosis are associated with features indicating plaque instability; whereas the degree of stenosis had no effect to plaque.\(^9\) Therefore, patients with LA, particularly those with subcortical LA, should undergo routine examination for carotid AS plaque, as well as active intervention for unstable plaques, because such procedures will significantly prevent or slow down the development of LA.

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**Conflicts of Interest Disclosure:** The authors have no conflicts of interest to report.

**References**

8. Park K, Nakagawa Y, Kumagai Y and Nagahara M. Leukoaraiosis, a common brain magnetic resonance imaging finding, as a predictor of traffic crashes. PLoS One 8: e57255, 2013
Leukoaraiosis on magnetic resonance imaging correlates with worse outcomes after spontaneous intracerebral hemorrhage. Stroke 44: 642-646, 2013


