Correlation of Common Carotid Artery Intima Media Thickness, Intracranial Arterial Stenosis and Post-stroke Cognitive Impairment

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Abstract-

Background and Purpose: Atherosclerosis of the intracranial arteries is a well-recognized cause of ischemic stroke in Asians, and extracranial carotid artery disease is more often seen in western countries. The relationship of common carotid artery intima-media thickness (CCA-IMT), intracranial arteries stenosis (ICS) and vascular cognitive impairment (VCI) after ischemic stroke has not been fully elucidated. In this study, we investigated the relationship between CCA-IMT and the severity of ICS and VCI.

Methods: We recruited patients from December 2004, to June 2005, with the inclusion criteria: (1) first-ever ischemic stroke, (2) admission within 3 days of stroke onset, (3) under 80 years old, and (4) no previous dementia history. We excluded patients with stroke scores greater than an NIHSS of 15; those with recurrent stroke, and those with extracranial internal carotid artery stenosis >50%. All the patients underwent brain MR angiography, carotid ultrasonography and neuropsychological testing during hospitalization and at 3 months after stroke. We defined the percent of ICS using the method of Warfarin-Aspirin Symptomatic Intracranial Disease. Measurement of CCA-IMT was made on the far wall of the common carotid artery, 1.5 cm proximal to the bifurcation at a point free of plaques. Cognitive performance was assessed using the Cognition Assessment State Instrument (CASI).

Results: Thirty patients (21M/9F, mean age 65.97 ± 10.33 years) were studied. The initial CCA-IMT was 1.04 ± 0.59 mm and the initial CASI was 64.73 ± 14.75. The ICS was 70 ± 26%. At 3 months after stroke, the CCA-IMT was 1.06 ± 0.59 mm; and CASI was 70.07 ± 18.50. Compared with patients with CCA-IMT > 0.87 mm, those with CCA-IMT ≤ 0.87 mm had lower ICS (57 ± 23% vs. 81 ± 24%, p = 0.013), but similar initial CASI score (67.92 ± 13.52 vs. 61.93 ± 16.64, p = 0.28). The improvement of CASI score at 3 months was significantly higher in patients with CCA-IMT ≤ 0.87 mm (67.92 ± 13.52 vs. 77.36 ± 14.12, p = 0.001), than those with CCA-IMT > 0.87 mm (61.93 ± 16.64 vs. 63.69 ± 19.89, p = 0.612).

Conclusions: CCA-IMT might be associated with the severity of ICS and VCI at 3 months after the first-ever ischemic stroke. The patients with lower CCA-IMT had a better CASI evaluation at 3 months after stroke. A larger scale of study to explore the association of CCA-IMT, VCI and ICS at 3 months after stroke might help further delineation of these relationships.

Key Words: Common carotid artery intima-media thickness, Intracranial arterial stenosis, Vascular cognitive impairment, Acute ischemic stroke

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INTRODUCTION

Atherosclerotic stenosis of the major intracranial arteries is a well recognized cause of ischemic stroke in Asians, whereas extracranial carotid artery disease is more common in western countries\(^1\)-\(^5\). Recently, common carotid artery intima-media thickness (CCA-IMT) has been identified as a vascular risk factor. Increased CCA-IMT values have been associated with an atherosclerotic process in the intracranial arteries and with stroke\(^6\)-\(^7\). Vascular cognitive impairment (VCI) after a stroke may develop into ‘vascular dementia’\(^8\). The relationship of CCA-IMT, intracranial arterial stenosis (ICS) and VCI after ischemic stroke has not been fully elucidated. We therefore investigated the association of CCA-IMT, ICS and VCI in patients at admission and three months after a first-ever ischemic stroke.

METHODS

Subject

We prospectively recruited from December 2004, to June 2005, using the following inclusion criteria: (1) first-ever ischemic stroke, (2) admission within three days of the stroke symptoms onset, (3) patients under 80 years of age, and (4) patients with no dementia history. We excluded the patients with (1) stroke severity greater than NIHSS of 15), (2) recurrent stroke, and (3) extracranial internal carotid artery (ICA) stenosis >50%. All patients underwent brain magnetic resonance angiography (1.5 Telsa TOF MRA without contrast), carotid ultrasonography and neuropsychological test during admission, and the CCA-IMT and neuropsychological test were repeated at three months after stroke. This study was approved by the hospital’s IRB (Institutional Review Board) and all participating patients had provide informed consent before entering the study.

Carotid ultrasonography

All patients underwent carotid ultrasonography during hospitalization and at 3 months post-stroke by one experienced technician using an Agilent SONOS 4500, with a 7.5-MHz linear array transducer manufactured in Andover, Massachusetts. Measurement of intima-media thickness was made on longitudinal B mode images of the far wall of the common carotid artery (CCA), 1.5 cm proximal to the bifurcation, at a point free of plaques. According to Talelli et al. reports of post-stroke cognitive impairment\(^9\), we arbitrarily categorized patients into two groups with CCA-IMT \(\leq 0.87\) mm and CCA-IMT > 0.87 mm to investigate their correlation to the variables.

Assessment of cognition

All patients were administered the Cognition Assessment State Instrument (CASI)\(^10\) during hospitalization and at the third month post-stroke by a single investigator. CASI, scores below 80/100 (educated) and 50/100 (uneducated) are considered to be indicative of cognitive impairment.

Measuring intracranial arterial stenosis

We selected the diseased vessels by measuring the middle cerebral arteries (MCA) and intracranial ICA as the ICS because the intracranial ICA and MCA are the continuation of the CCA, and the cognitive function is more vulnerable with an MCA territory lesion. We defined the percentage of stenosis of an intracranial artery using the WASID method\(^11\)-\(^13\), the equation was as follows: percent stenosis = \([1 - (D_{\text{stenosis}}/D_{\text{normal}})] \times 100\) (Fig.), where \(D_{\text{stenosis}}\) = the diameter of the artery at the site of the most severe degree of stenosis and \(D_{\text{normal}}\) = the diameter of the proximal normal artery. \(D_{\text{normal}}\) was determined by the following criteria: For the MCA, anterior cerebral artery (ACA), posterior cerebral artery (PCA), intracranial vertebral artery (VA) and basilar artery (BA), the diameter of the proximal part of the artery at its widest, non-tortuous, normal segment was chosen (first choice). If the proximal artery was diseased (i.e., MCA origin stenosis), the diameter of the distal portion of the artery at its widest, parallel, non-tortuous normal segment was substituted (second choice). If the entire intracranial artery was diseased, the most distal, parallel, non-tortuous normal segment of the feeding artery was measured (third choice) (i.e., measured at dominant VA if the entire BA was diseased, measured at supraclinoid carotid artery if the entire MCA was dis-
If tandem intracranial lesions were present, the most severe stenosis was selected. For a ‘gap sign’ (i.e., the lumen of the vessel could not be visualized at the site of severe stenosis), the percent stenosis was defined as 99%.

All the measurements of the intracranial arteries were made on the image monitor using computerized scale marked in 0.1-mm increments. Inter-observer agreement in the difference of percent stenosis measured by two readers was less than 10%.

**Statistical analysis**

Between-group comparisons were made with the t-test for continuous variables and Chi-square test for categorical data. Tests were two-tailed and the results were considered significant at P<0.05. Univariate correlates were assessed using Pearson correlation. Analyses were conducted using SPSS version 9.0 for windows (SPSS Inc.).

**RESULTS**

Thirty patients were recruited in this study (21 males and 9 females) with a mean age of 65.97±10.33 years. The initial CCA-IMT was 1.04±0.59 mm. The initial CASI was 64.73±14.75. The ICS was 70±26%. At three months after stroke, the CCA-IMT was 1.06±0.59 mm; and CASI was 70.07±18.50. We divided patients by CCA-IMT into two groups (CCA-IMT ≤ 0.87 mm and >0.87 mm). Compared with patients with CCA-IMT >0.87 mm, patients with CCA-IMT ≤ 0.87 mm had lower ICS (57±23% vs. 81±24%, p=0.013), similar initial CASI score (67.92±13.52 vs. 61.93±16.64, p=0.28) but higher CASI score at 3 months after stroke (77.36±14.12 vs. 63.69±19.89, p=0.041). In comparison, the improvement of CASI score at 3 months was significant higher in patients with CCA-IMT ≤ 0.87 mm (67.92±13.52 vs. 77.36±14.12, p=0.001) than those with CCA-IMT > 0.87 mm (61.93±16.64 vs. 63.69±19.89, p=0.612) (Table 1).

Correlation between the severity of ICS measured with WASID method and CCA-IMT value obtained dur-

![Figure. WASID Method: Warfarin-Aspirin Symptomatic Intracranial Disease. Ds: Diameter of stenotic lumen; Dn: Diameter of normal lumen.](image-url)
ing hospitalization \((r = .51, p = 0.004)\) and three months post-stroke \((r = .49, p = 0.007)\) were significant.

Older age was significantly associated with CCA-IMT \((61.36 \pm 10.7\) vs. \(70.00 \pm 8.4; p = 0.019\)). Gender and vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and smoking) were not associated with CCA-IMT (Table 2).

### DISCUSSION

Our study found that among patients with first-ever ischemic stroke, those with lower initial CCA-IMT values had better CASI performance three months after stroke. All patients showed improvement in CASI performance at three months after stroke; however, only the group with lower CCA-IMT showed statistically significant improvement compared to the group with higher CCA-IMT. Despite the statistical significance, these results, based on a rather small sample, suggest a larger study for further exploration and validation. To our knowledge, most of the investigations of VCI focus on the trend beyond the period of six months to one year, therefore, we intend to investigate the trend of post-stroke cognitive change from the time of the patients’ hospitalization to the third month after the stroke. Tallelli et al.\(^{(9)}\) reported that increased CCA-IMT was associated with cognitive impairment 1 year after their first ischemic stroke. In a study of non-stroke population, Auperin et al.\(^{(14)}\) reported that increased CCA-IMT was associated with compromised cognitive performance in a subgroup of male patients with carotid atherosclerotic plaques. Cerhan et al. and Knopman et al. found that CCA-IMT was associated with cognitive impairment in the baseline evaluation of non-stroke patients but no association was found 4 years later\(^{(15-16)}\). In our post-stroke patients, study results showed that the post-stroke cognitive impairment might be associated with increased of CCA-IMT - that was consistent with these earlier studies.

Another aspect of our findings is that stroke patients with the lower CCA-IMT values had less severe ICS compared to those with higher CCA-IMT. Establishment of methods for measuring the major ICS in a larger scale of study is necessary for further validation of the finding. CCA-IMT is associated both with stroke\(^{(6)}\) and white matter lesions\(^{(7)}\) and thus has been qualified as a marker of cerebral atherosclerosis. The cerebral atherosclerosis may be more severe in stroke patients with increased CCA-IMT values as our study showed, a condition that provided an additional risk of post-stroke cognitive impairment.

Age is a risk factor of cognitive impairment and increased CCA-IMT value\(^{(9,17)}\). In the present study, the CCA-IMT ranged from 0.38 to 1.27 mm, increases in CCA-IMT with age was variable from 0.009 mm per year from Japanese data\(^{(18)}\) to 0.01 mm per year from US communities\(^{(19)}\). These studies might explain the significant association of higher CCA-IMT and older age in the groups studied. However, the correlation between the age and the initial CCA-IMT, initial CASI and ICS were not significant. Besides, the CCA-IMT values we obtained initially and at three months after stroke were similar \((1.04 \pm 0.59\) mm vs. \(1.06 \pm 0.59\) mm, \(p = 0.88\)). These data suggest that a longer follow-up study beyond one year may be necessary if further exploration of the influence of age on CCA-IMT growth is desired in future studies. The patients with similar CCA-IMT after three months had their improvement in CASI performance generally, these results might imply that other factors beside age may affect post-stroke cognitive function. A larger population and longer term of investigation is needed for further validation of these findings.

### Table 2. The general characteristics of patients stratified by CCA-IMT

<table>
<thead>
<tr>
<th></th>
<th>IMT (\leq 0.87)</th>
<th>IMT (&gt; 0.87)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [mean(S.D.)]</td>
<td>61.36 (10.7)</td>
<td>70.00 (8.4)</td>
<td>0.019*</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>10 (33%)</td>
<td>11 (37%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (27%)</td>
<td>11 (37%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>2 (7%)</td>
<td>5 (17%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1 (3%)</td>
<td>4 (13%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0</td>
<td>1 (3%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 (13%)</td>
<td>5 (17%)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

\(*<0.05, \text{Chi-square test for categorical data, } t\text{-test for continuous variables.}\)

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The limitations of this study should also be considered. A larger scale of study will give a more powerful and less variable results to explore the association of CCA-IMT, VCI, ICS and the conventional vascular risk factors\(^{20-22}\). Assessment of cognition was based on CASI, which is a screening tool and not a diagnostic instrument. The use of more specific diagnostic tools is suggested for future studies. For the measurement of CCA-IMT, measurement of the far wall might be of less value for indication of an atherosclerotic process than measurement at multiple carotid sites. Moreover, establishment of methods for measuring the branches with narrow and tortuous segments, and having all the major ICS including bilateral ACA, MCA, PCA, VA and BA being measured are necessary in our future study. We intend to quantify the ICS by categorizing the ICS as mild, moderate and severe groups and have their association with the correlated variables instead of using ICS as a continuous variable because the sensitivity of MRA to detect a small percentage change of blood vessels lumens may not be reliable.

In conclusion, CCA-IMT was associated with the severity of ICS and VCI at three months after a first-ever ischemic stroke as shown in this study. The patients with lower CCA-IMT had a better CASI performance at three months after stroke. These results suggest a larger scale of study to explore the association of IMT, VCI and ICS three months (and later) after stroke, and help define the study design of any future study with an expanded sample size and more variables to explore.

**APPENDIX**
REFERENCES


