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High Agatston Calcium Score of Intracranial Carotid Artery

A Significant Risk Factor for Cognitive Impairment

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Abstract: The effect of intracranial internal carotid artery (ICA) calcification on cognitive impairment is uncertain. Our objective was to investigate whether intracranial ICA calcification is a significant cognitive predictor for cognitive impairment. Global cognition and degrees of intracranial ICA calcification of 579 subjects were assessed with Mini-Mental State Examination (MMSE) and Agatston calcium scoring method, respectively. Other risk factors for cognitive impairment, including age, education level, hypertension, diabetes mellitus, smoking, hyperlipidemia, and body mass index, were documented and analyzed for their associations with cognitive function.

In univariate analyses, older age, lower education level, hypertension, diabetes mellitus, and higher intracranial ICA Agatston scores were significantly associated with cognitive impairment. In ordinal logistic regression, only age and total intracranial ICA Agatston score were significant risk factors for cognitive impairment. After adjustment for the other documented risk factors, subjects were 7% (95% CI: 5–10; $P < 0.001$) and 6% (95% CI: 0–13; $P = 0.04$) more likely to have lower cognitive category with every year increment of age and every 100-point increment of the total intracranial ICA Agatston score respectively. These results suggest an important role of the intracranial ICA calcification on cognitive impairment.

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Abbreviations: CT = computed tomography, ICA = internal carotid artery, ICC = intraclass correlation coefficient, MMSE = Mini-Mental State Examination, ROI = region of interest.

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INTRODUCTION

Cognitive impairment and dementia are common in an aging population with prevalence increasing from 5.0% among people aged 71 to 79 years to 37.4% in those aged 90 and older.[1,2] The clinical presentations of dementia are nonspecific and various aspects of cognition, such as memory, attention, language, and problem solving, could be affected. Although age is a predominant risk factor for cognitive impairment, the associations between diseases of cognition and various cardiovascular risk factors, such as hypertension, hypercholesterolemia, diabetes mellitus, obesity, and smoking, suggest an existence of a common biological mechanism, such as the apolipoprotein E ε4 allele.[3] Atherosclerosis is a systemic disease resulting from prolonged exposure to the risk factors.[4] In a study of Rosano et al, the level of coronary artery calcification is generally higher in people with older age, cognitive impairment or abnormal magnetic resonance imaging findings, including infarcts, white matter changes, and ventricular enlargement, but the calcification itself did not act as an independent risk factor for cognition decline.[5] Compared with the coronary artery, atherosclerotic lesions in the intracranial internal carotid arteries (ICA) may conceivably have more direct effect on cognitive function due to its proximity and close relation to the blood supply of the brain. The atherosclerosis-related luminal stenosis and small platelet aggregates or cholesterol microemboli shed from the diseased arterial wall may play important roles in cognitive decline.[6]

Previous studies on ICA calcification used different scoring methods and focused on the association between the calcification and ischemic cerebrovascular disease with discordant results.[7–11] Some authors considered the calcifications as a stabilizing component of the atherosclerotic plaque and others stated an increased risk of thromboembolic disease associated with the calcifications.[10,11] In addition to the well-known detrimental effect of major ischemic stroke associated with ICA occlusive disease on cognition,[12] systemic reviews showed associations between carotid stenosis and cognitive impairment.[13,14] Possible mechanisms suggested for cognitive impairment associated with carotid stenosis include chronic cerebral hypoperfusion and lacunar infarction. However, it remains uncertain whether the cardiovascular risk factors exert their effect on the cognitive function by mechanisms involving atherosclerotic calcifications of the intracranial ICAs, frequent findings on computed tomography (CT) of the brain.

This study was designed to quantitatively characterize the association between the burden of intracranial ICA calcification and cognitive function using the Agatston calcium scoring method,[15] which was originally applied in assessing calcium burden of the coronary artery. We hypothesized that individuals with higher intracranial ICA Agatston scores are more likely to have declined cognitive function than those with lower scores or no calcium.

METHODS

Subjects

The study was approved by the Institutional Review Board of Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan and performed in compliance with the Helsinki Declaration. The written informed consents were obtained from the subjects or the next of kin. All patient records/information was anonymized and deidentified before analysis. Between 2010 and 2011, we prospectively recruited subjects aged 30 or older with noncontrast brain CT obtained for a variety of clinical indications, such as headache, vertigo, sinusitis, head injury, and suspicion of malignancy. Subjects with clinical history or imaging findings of the following conditions were excluded: ischemic stroke, intracranial hemorrhage, brain infections, brain tumors, congenital brain disorders, psychiatric disorders, or poor image quality. Each subject's brain CT scans were assessed from our picture archiving and communication system. An experienced psychologist employed Mini-Mental State Examination (MMSE) to assess the cognitive function. We documented known risk factors for cognitive impairment, including age, education level, hypertension, diabetes mellitus, smoking, plasma cholesterol, and body mass index.[16,17]

Agatston Calcium Scoring of the Intracranial ICA

All CT examinations were performed on a 64-slice multidetector-row CT scanner (Brilliance 64, Philips Medical Systems, Best, the Netherlands) using a standardized noncontrast protocol (120 kVp; 280 mA; collimation, 40 mm × 0.625 mm; table feed, 14.4 mm/rotation; pitch, 0.58). Image reconstructions were made with a field of view of 100 mm; matrix size, 512 × 512; slice thickness, 3.0 mm; increment, 0.5 mm.

For quantification of the calcium burden, all images were transferred to an independent PC-based workstation with Aquarius iNtuition software (TeraRecon, San Mateo, CA). According to the Agatston method,[15] CT density ≥130 Hounsfield units in ≥2 continuous pixels were automatically marked in color by the workstation. Automatic quantification of the calcifications in the intracranial ICA was not feasible due to the close relationship between the calcium in the arterial wall and the bony skull base. Two board-certificated neuroradiologists (27 and 12 years of clinical experience in neuroimaging interpretation, respectively), blinded to clinical information of the subjects, defined the regions of interest (ROIs) by scrutinizing the bilateral intracranial ICAs from cavernous to communicating segments (Figure 1). The calcium score of each ROI in the bilateral intracranial ICAs was summed up to a total intracranial ICA Agatston score for each subject.

Statistical Analysis

The data were reported as median and interquartile range for continuous variables and as frequencies and percentages for categorical variables. The intraclass correlation coefficient (ICC) was used to evaluate interrater reliability of the selected ROIs. Subjects with a MMSE score greater than or equal to 26 points were categorized as normal cognition while scores 21 to 25, 11 to 20, and 0 to 10 were categorized as mild, moderate, and severe cognitive impairment, respectively.[18] Wilcoxon signed-rank test was used to compare the paired Agatston scores of the bilateral intracranial ICAs. The between-group differences in risk factors for cognitive impairment were evaluated for statistical significance with the Kruskal–Wallis test for continuous variables and with the Pearson Chi-squared test for categorical variables. The associations between intracranial ICA calcification and the other risk factors were tested with the Mann–Whitney *U* test for continuous variables and with the Fisher exact test for categorical variables. Significant risk factors in the univariate tests were included as predictors of cognitive decline in an ordinal logistic regression model. The statistical significance was evaluated using the 2-tailed test for both the univariate analyses and parameter estimates in the ordinal logistic regression model with the nominal Type-I error at the 5% level. All the statistical analyses were performed with an IBM SPSS Statistics for Mac (version 20; IBM Corp., Armonk, NY).

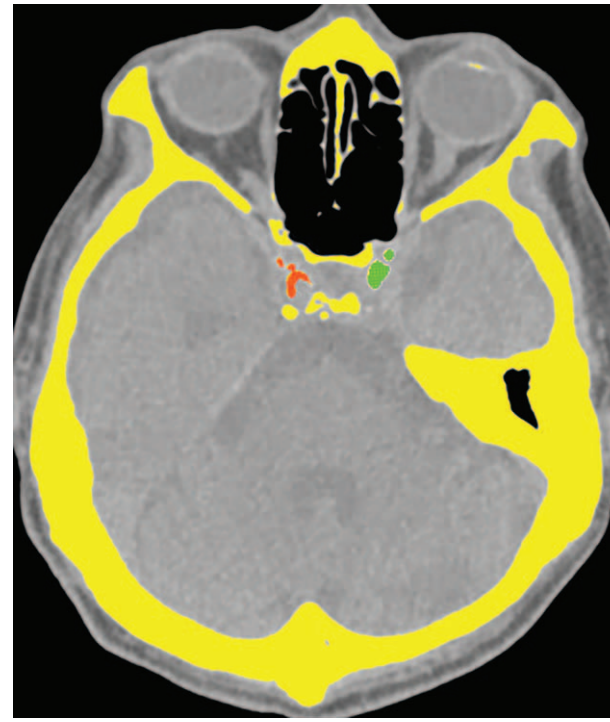

FIGURE 1. Agatston calcium scoring for a 59-year-old man. On the axial noncontrast CT images, the software automatically highlighted densities greater than 130 Hounsfield units in 2 continuous pixels in yellow color. A neuroradiologist selected the regions of interest in the bilateral intracranial internal carotid arteries (labeled in red on the right and in green on the left) for calcium scoring (total ICA Agatston calcium score, 76.8).

RESULTS

During the study period, we included a total of 579 subjects (356 women and 273 men; mean age, 62 years; range, 30–90; SD, 14.8 years). Of these, 401 (69.3%) were of normal cognitive function, 116 (20.0%) of mild cognitive impairment, and 62 (10.7%) of moderate cognitive impairment. No subject demonstrated severe cognitive impairment in our study. The paired Agatston scores of the right and left intracranial ICA were not significantly different in each rater's measurements ($P = 0.55$ and 0.83). Since the interrater reliability indices of the intracranial ICA Agatston scores were high (ICC = 0.99), the averaged total intracranial ICA Agatston scores were used for the analysis. A total of 402 out of 579 (69.4%) subjects had intracranial ICA calcifications in a wide range of total Agatston scores (median 69.2; IQR 8.8–261.6).

The baseline characteristics of the study subjects are detailed in Table 1. The univariate analyses showed significant

TABLE 1. Characteristics of the Subjects in the Study

Characteristic	Normal Cognition (n = 401)	Mild Cognitive Impairment (n = 116)	Moderate Cognitive Impairment (n = 62)	*P*-Value
Age	56.2 (47.2–65.5)	72.6 (61.6–79.3)	76.9 (72.1–81.9)	<0.001*
Male	172 (42.9)	48 (41.4)	21 (33.9)	0.41†
Education year	14 (12–16)	12 (9–16)	9 (6–12)	<0.001*
Hypertension	113 (28.2)	56 (48.3)	29 (46.8)	<0.001†
Diabetes mellitus	40 (10.0)	22 (19.0)	18 (29.0)	<0.001†
Smoking	111 (27.7)	34 (29.3)	12 (19.4)	0.33†
Hyperlipidemia	76 (19.0)	20 (17.2)	11 (17.7)	0.91†
Body mass index	24.0 (21.7–26.2)	23.5 (21.5–26.2)	23.7 (21.4–27.4)	0.69*
Total intracranial ICA Agatston score	2.1 (0–48.0)	142.6 (3.9–422.1)	242.9 (72.1–498.8)	<0.001*

Values are presented as median (IQR) or number (%). ICA = internal carotid artery.
* Kruskal–Wallis test.
† Pearson Chi-squared test.

associations of cognitive impairment with older age, lower education level, hypertension, diabetes mellitus, and higher total intracranial ICA Agatston score. Among the documented risk factors for cognitive impairment, older age, lower education year, hypertension, and diabetes mellitus are significantly associated with intracranial ICA calcifications (Table 2).

In an ordinal logistic regression analysis, only age and total intracranial ICA Agatston score were significant risk factors for cognitive impairment (Table 3). After adjustment for the other documented risk factors, subjects were 7% (95% CI: 5–10; $P < 0.001$) and 6% (95% CI: 0–13; $P = 0.04$) more likely to have lower cognitive category with every year increment of age and every 100-point increment of the total intracranial ICA Agatston score respectively.

DISCUSSION

In our study, the burden of intracranial ICA calcification, quantified by the Agatston calcium scoring, was significantly associated with age, education level, hypertension, and diabetes mellitus and was a significant risk factor for cognitive function. A higher intracranial ICA Agatston score was associated with a higher degree of cognitive decline. These associations suggest that Agatston scoring of the intracranial ICA provide additional information over the documented risk factors in relation to cognitive function.

Our results add to findings of previous studies by using Agatston scoring method in the quantification of the intracranial ICA. In a large group of community-dwelling people excluding participants with cortical infarcts, Bos et al[19] found a marginal association between intracranial ICA calcification volume and cognitive decline after adjustment for cardiovascular risk factors. In a different study of Bos et al[20], intracranial ICA calcification volume is associated with a decline of MMSE score in a middle-aged and elderly population but the association is not significant after excluding stroke subjects from the analysis. These findings suggest an intermediary role of atherosclerosis to stroke, which is a significant factor for cognitive decline.[21] In our sample of nonstroke subjects, however, the intracranial ICA Agatston score, comprising information on both volume and CT density of the calcification, was found to be a significant factor for cognitive impairment. Our finding is in line with a community-based study of Reis et al[22], in which higher Agatston scores of the coronary artery are associated with lower cognitive function in subjects free of known coronary and cerebrovascular disease. Our results extend this

TABLE 2. Associations Between Intracranial ICA Calcification and Other Risk Factors for Cognitive Impairment

Risk Factors	Subjects Without Intracranial ICA Calcification (n = 177)	Subjects With Intracranial ICA Calcification (n = 402)	*P*-Value
Age	48.9 (39.4–56.0)	68.3 (57.8–77.9)	<0.001*
Male	68 (38.4)	173 (43.0)	0.32†
Education year	16 (12–16)	12 (9–16)	<0.001*
Hypertension	32 (18.1)	166 (41.3)	<0.001†
Diabetes mellitus	10 (5.6)	70 (17.4)	<0.001†
Smoking	49 (27.7)	108 (26.9)	0.84†
Hyperlipidemia	31 (17.5)	76 (18.9)	0.73*
Body mass index	23.9 (21.5–25.9)	23.8 (21.6–26.4)	0.58*

Values are presented as median (IQR) or number (%). ICA = internal carotid artery.
* Mann–Whitney *U* test.
† Fisher exact test.

TABLE 3. Relationship Between the Risk Factors and Cognitive Impairment in Ordinal Logistic Regression Analysis

Risk Factors	OR (95 % CI)	*P*-Value
Age	1.07 (1.05, 1.10)	<0.001
Education year	0.97 (0.93, 1.02)	0.28
Hypertension	0.93 (0.61, 1.41)	0.73
Diabetes mellitus	1.45 (0.87, 2.42)	0.15
Total ICA Agatston score/100	1.06 (1.00, 1.13)	0.04

CI = confidence interval, ICA = internal carotid artery, OR = odds ratio.

evidence to intracranial ICA and support a systemic effect of cardiovascular risk factors,[23] by which calcified atherosclerosis influences cognitive function.

The exact underlying mechanism for the association between intracranial ICA calcification and cognitive function in our study is uncertain. In a semiquantitative study of intracranial arterial calcifications, Kassab et al[24] found a positive correlation between the morphological degree of arterial calcification on CT and luminal stenosis on angiography. With participants free of stroke and dementia, the Framingham Offspring Study showed a significant association between carotid stenosis and cognitive performance.[25] Although we did not perform CT angiography to measure the arterial lumen in our subjects, the burden of the intracranial ICA calcification may decrease the arterial caliber and reduce the cerebral blood flow, which in turn affect cognitive function in the long run. The intracranial ICA Agatston score increased with older age, hypertension, and diabetes mellitus in our subjects who were prone to have concomitant multiple risk factors for the cognitive decline. This finding suggests that the risk factors exert their effect on the cognitive function by mechanisms involving atherosclerotic calcifications of the intracranial ICA. However, the significant role of the intracranial ICA Agatston score on cognitive decline may imply the importance of other risk factors, such as inflammatory factors and oxidative stress, mediating the effect of calcified atherosclerosis on cognitive function.[26–28]

There are limitations in this study. First, calcified plaques are only part of the atherosclerosis. On noncontrast CT images, it is difficult to evaluate the whole atherosclerotic plaque. Furthermore, we did not evaluate other vascular factors associated with atherosclerosis of the intracranial ICA, such as blood flow rate and degree of stenosis. Nonetheless, calcified plaques represent a certain characteristic of the atherosclerosis in their effect on cognition. Second, residual confounding may present in this observational analysis. However, our results were robust after adjustment for classic risk factors for cognitive decline. Third, subtle structure and functional alterations documented in the aging brain observed on magnetic resonance images were not available in our analysis.[29] Finally, the Agatston calcium scoring of the intracranial ICA is semi-automatic and requires radiation exposure, which limited its clinical feasibility as a routine screening tool. Future development of an automatic segmentation technique may help stratify the risk of cognitive decline in adjunct to the evaluation of intracranial arterial stenosis on CT angiography.

In conclusion, the burden of intracranial ICA calcification, assessed with Agatston scoring method, is a significant risk factor for cognitive impairment. The precise underlying mechanism of the association requires further investigation.

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