Intracranial Vascular Calcification is Protective from Vasospasm after Aneurysmal Subarachnoid Hemorrhage

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Vasospasm after aneurysmal subarachnoid hemorrhage was noted in some studies to be less frequent and less severe in older age. One hypothesis is that atherosclerosis makes arteries too stiff to spasm. The objective of this study was to assess the association between intracranial calcification, a marker for atherosclerosis, and vasospasm. Charts and nonenhanced computed tomography scans of patients with subarachnoid hemorrhage were retrospectively reviewed. Transcranial Doppler studies were used to categorize vasospasm using mean flow velocity: mild vasospasm 120-199 cm/second and severe ≥200 cm/second. Calcification of the intracranial internal carotid artery was quantified by calculating the volume and density of the calcified lesions. A total of 172 patients met study criteria (mean age, 54 ± 13 years; 88 women). Patients who had calcification (n = 90; 52%) were significantly older (61 ± 12 years vs. 46 ± 10 years; $P < .0001$). Mean calcification score was 532 ± 853. Calcification score was directly associated with age ($P < .0001$) and inversely associated with mean flow velocity ($P = .0027$). Only the highest tertile was independently associated with less vasospasm (odds ratio, .34; 95% confidence interval, .12-.93). There was an interaction between calcification score and age in which age greater than 65 years was only protective of vasospasm when combined with the highest calcification tertile. We conclude that intracranial calcification is associated with lower rates of vasospasm. The amount of visualized calcification inversely influences the severity of vasospasm. Calcification, and the underlying presumed atherosclerosis, maybe 1 mechanism by which vasospasm has lower frequency and severity in older age. **Key Words:** Subarachnoid hemorrhage—vasospasm—calcification—atherosclerosis.

Introduction

Angiographic vasospasm occurs in 66% of patients who suffer aneurysmal subarachnoid hemorrhage (SAH).[1] Symptomatic vasospasm is the second most important cause of morbidity and mortality in SAH after rebleeding. It accounts for up to 50% of morbidity and mortality after SAH in patients who survive to aneurysm treatment.[2] The amount of blood in the subarachnoid space, as quantified by Fisher[3] and modified Fisher[4] grades, was associated with occurrence and severity of vasospasm. Mean flow velocity (MFV) measured by transcranial Doppler (TCD) is a noninvasive bedside test that has shown good correlation with angiographic vasospasm.[5] Other predictors of vasospasm include poor initial neurologic state as quantified by the Glasgow Coma Scale (GCS) and early rise in MFV of the middle cerebral artery (MCA) by TCD.[6]

Previous studies suggested that older age is associated with lower rate of vasospasm after SAH. Based on their retrospective review of 81 patients with SAH, Torbey

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Received May 4, 2014; accepted June 13, 2014.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.06.013

et al[7] observed that older patients (≥68 years) had lower MFV of MCA and internal carotid artery (ICA) and lower incidence of symptomatic vasospasm than younger patients (44% vs. 66%; $P = .05$). Kale et al[8] noticed the same association in a sample of 108 SAH patients, dichotomized by age (≥50 vs. <50 years). Younger age was an independent predictor for any vasospasm (odds ratio [OR], 5.83; 95% confidence interval [CI], 2.41-14.12) and symptomatic vasospasm (OR, 2.66; 95% CI, 1.008-7.052). One possible explanation of this phenomenon is that atherosclerosis and subsequent arterial stiffness has a protective effect.[8] However, a post hoc analysis of a randomized trial found no association between age and overall incidence of angiographic vasospasm; although symptomatic vasospasm was more frequently reported in the older age groups.[9]

In this study, we aim to assess whether there is an association between the occurrence and severity of vasospasm and the presence and quantity of vascular intracranial calcification, a known marker of atherosclerosis.[10]

Materials and Methods

We retrospectively reviewed charts and images of consecutive patients (≥18 years) admitted to our institution with SAH between the years 2002 and 2010. Exclusion criteria were nonaneurysmal causes of SAH, nonvisualized aneurysm, death or transfer within 1 week, lack of TCD data, and incomplete clinical information.

Data collected included age, gender, GCS, Hunt and Hess grade,[11] modified Fisher grade,[4] whether aneurysm was clipped or coiled, length of stay, discharge modified Rankin Scale, and MFV of intracranial vessels as measured by TCD in the first 14 days from onset.[12] Vasospasm was defined according to MFV as follows: mild 120-199 cm/second and severe ≥200 cm/second.

Calcification of the cavernous and supraclinoid segments of bilateral intracranial ICA was quantified using published methodology.[13] The bone window of noncontrast computed tomography (CT) scan was reviewed after a magnification of 400%-600%. Areas of calcification were visually identified. Region of interest was manually drawn around each area. Surface area, average and maximum Hounsfield units (HU) were automatically calculated (Fig 1). We excluded areas that were less than 1 mm^2 or had HU <130. HUs were categorized as follows: 130-199 HU = score 1, 200-299 HU = score 2, 300-399 HU = score 3, and ≥400 HU = score 4. Calcification volume was calculated as the product of the sum of surface areas of calcification pieces and the slice thickness. Calcification score was calculated as the product of calcification volume and maximum HU.[13]

Univariate analysis was initially performed to compare patients with and without calcification. Chi-square, *t* test, and analysis of variance test were used for parametric variables, whereas Wilcoxon rank sum test was used for nonparametric variables. Logistic regression was performed to assess whether age is an independent predictor of vasospasm, after correcting for relevant variables. Then calcification was added to the model. The interaction between age and calcification was studied in a separate model. Statistical analysis was performed using JMP software (SAS Corp, Cary, NC).

Results

We identified 250 patients 18 years of age or older admitted with SAH. After exclusion of 78 patients (nonaneurysmal etiology/other diagnoses [n = 41]; inadequate TCD data [n = 25]; and transfer or death <7 days from onset [n = 12]), 172 patients were included in this analysis (mean age, 54 ± 13 years; 88 women).

Vasospasm was identified in 116 patients (67%), of which 86 patients had mild vasospasm, whereas 29 patients had severe vasospasm. There was an inverse association between age and MFV. Compared with those without vasospasm, patients who developed vasospasm were significantly younger (51 ± 12 years vs. 60 ± 14 years; $P < .0001$), had higher rate of Hunt and Hess grades IV and V (61% vs. 41%; $P = .013$), higher rate of initial modified Fisher grades III and IV (61% vs. 45%; $P = .045$), and a trend toward longer hospital stay (20 ± 10 vs. 16 ± 11 days; $P = .17$). Gender and initial GCS were not significantly different between the 2 groups.

Calcification was visualized in 90 patients (52%). Patients with calcification were significantly older (61 ± 12 years vs. 46 ± 10 years; $P < .0001$), had significantly lower median MFV (129 vs. 134 cm/second; $P = .0009$; Table 1) and lower rate of vasospasm (58% vs. 68%; $P = .006$; Fig 2). There was a nonsignificant trend toward poor functional outcome on discharge in patients with calcification compared with those without calcification (Table 1).

Calcification Score

For those who had visualized calcification, the mean calcification score was 532 ± 853, and the median was 165 (58-733). Higher calcification score was associated with older age ($P < .0001$; Fig 3) and with lower MFV ($P = .0027$; Fig 4)

Logistic regression models examined the independent effect of calcification on occurrence of vasospasm. After adjusting for age, gender, and modified Fisher grade, lack of calcification was an independent predictor of vasospasm (OR, .38; 95% CI, .16-.871). Age less than 65 years had the opposite effect (OR, 3.37; 95% CI, 1.38-8.45). Modified Fisher grade was predictive of vasospasm whereas gender was not (Table 2).

To study the effect of the quantity of calcification, the calcification score was trichotomized into tertiles (first