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Risk factors for atherosclerotic and medial arterial calcification of the intracranial internal carotid artery

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ABSTRACT

Background and aims: Calcifications of the intracranial internal carotid artery (iICA) are an important risk factor for stroke. The calcifications can occur both in the intimal and medial layer of the vascular wall. The aim of this study is to assess whether medial calcification in the iICA is differently related to risk factors for cardiovascular disease, compared to intimal calcification.

Methods: Unenhanced thin slice computed tomography (CT) scans from 1132 patients from the Dutch acute stroke study cohort were assessed for dominant localization of calcification (medial or intimal) by one of three observers based on established methodology. Associations between known cardiovascular risk factors (age, gender, body mass index, pulse pressure, eGFR, smoking, hypertension, diabetes mellitus, hyperlipidemia, previous vascular disease, and family history) and the dominant localization of calcifications were assessed via logistic regression analysis.

Results: In the 1132 patients (57% males, mean age 67.4 years [SD 13.8]), dominant intimal calcification was present in 30.9% and dominant medial calcification in 46.9%. In 10.5%, no calcification was seen. Age, pulse pressure and family history were risk factors for both types of calcification. Multivariably adjusted risk factors for dominant intimal calcification only were smoking (OR 2.09 [CI 1.27–3.44]) and hypertension (OR 2.09 [CI 1.29–3.40]) and for dominant medial calcification diabetes mellitus (OR 2.39 [CI 1.11–5.14]) and previous vascular disease (OR 2.20 [CI 1.30–3.75]).

Conclusions: Risk factors are differently related to the dominant localizations of calcifications, a finding that supports the hypothesis that the intimal and medial calcification represents a distinct etiology.

1. Introduction

Calcifications of the intracranial internal carotid artery (iICA) are an important independent risk factor for stroke in the general population [1]. These calcifications are often interpreted as a proxy for atherosclerosis. However, already in 1965, it was described that calcifications in the siphon of the carotid artery are not only found in the intimal layer of the vascular wall, but also in the medial layer and around the internal elastic lamina [2]. Recently, it was shown that calcification in the iICA is predominantly located around the internal elastic lamina [3]. Calcifications in this area are considered to be medial arterial calcifications [4].

Medial calcifications have been described in multiple arteries, including femoral and breast arteries [5,6]. Breast arterial calcifications (BAC), as visualized on mammography, are thought to be exclusively medial [5]. BAC has a similar incidence in patients with angiographically normal arteries and patients with coronary heart disease [7]. However, the incidence of BAC was found to be higher in patients with an indication for coronary angiography than in the general population [7]. Therefore, is has been hypothesized that BAC shares some, but not all risk factors for atherosclerosis [7].

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Combining previous literature, we know that there is a strong association between iICA calcifications and stroke, and that iICA calcifications are predominantly medial. Furthermore, it is hypothesized that risk factors for medial arterial calcifications can be partly different from risk factors for atherosclerotic vascular disease. Therefore, it is important to determine what risk factors influence the different types of iICA calcifications. If medial arterial calcifications are indeed an important factor in the development of stroke, differences in risk factors could influence current clinical practice regarding risk reduction.

Previous reports described associations between iICA calcifications and age, diabetes, hypercholesterolemia, hypertension, smoking, history of cardiovascular disease and high white blood cell count [8–12]. However, these studies did not take the different localizations of calcification in the vascular wall into account. Based on a comparison with histopathology, we recently described a computed tomography (CT) scoring system that can determine the dominant calcification type in the iICA [13]. This scoring system allows us to evaluate the effect of risk factors on the different dominant calcification types. The aim the current study is to assess whether medial calcification in the iICA is differently related to risk factors for cardiovascular disease, compared to intimal calcification.

2. Materials and methods

2.1. Cohort

The patients were derived from the DUtch acute Stroke Study (DUST) cohort; a multi-center cohort study of 1393 patients with suspected acute ischemic stroke. Patients were included if the following criteria were met: 1) older than 18 years, 2) National Institutes of Health Stroke Scale ≥2, or 1 if an indication for intravenous thrombolysis with recombinant tissue type plasminogen activator was present, 3) acute neurological deficit of less than 9 h of duration. Patients were excluded from the study if another diagnosis on admission non-contrast Computed Tomography (CT) explained the neurological deficits, and in case of a known contrast allergy or previously known renal failure at the time of admission. At the time of admission, patient characteristics were collected, including blood pressure, height, weight, smoking, and family history of vascular diseases (1 or more first degree relative <60 years). Information about the medical history of the patients was collected, including previously diagnosed hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg), hyperlipidemia (cholesterol ≥5–8 mmol/l) or diabetes mellitus (fasting glucose ≥7.0 mmol/l and/or glucose ≥11.1 mmol/l) and previous vascular disease (including previous diagnosis of myocardial infarction, transient ischemic attack, stroke and peripheral vascular disease or previous vascular intervention). Furthermore, laboratory tests, including serum creatinine and glucose, and an non-contrast CT-scan were performed. DUST was approved by the Medical Ethical Committee of the participating hospitals under protocol number 08–373. Informed consent was obtained from all patients for use of the data [14].

2.2. CT imaging

Multiple CT scanners were used in the participating centers. The number of detectors ranged from 40 to 320 (LightSpeed VCT, GE Healthcare, Milwaukee, Wisconsin; Brilliance 40, Brilliance 64, and Brilliance iCT 256, Philips Healthcare, Best, the Netherlands; Sensation 64, Siemens, Erlangen, Germany; Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan) at 120 kV and 300–375 mA s. Patients were scanned from the skull base to the vertex and scans were reconstructed with a slice thickness ranging from 0.625 to 1 mm.

2.3. CT scoring

For all patients, the presence, morphologic characteristics and severity of iICA calcifications were scored on the thin slice CT data by one of three readers with at least 2 years of experience reading CT images. (PdJ, JdV, RK) The agreement between the readers was previously found to be good, with kappa's ranging from 0.70 to 0.80 [13]. The readers were blinded to the clinical data. Using the previously developed scoring model points were awarded for different morphologic aspects of the calcifications (0–4 points for circularity, 0–3 points for thickness of calcifications, and 0–4 points for continuity of calcification over a longer arterial segment). Based on the total score (range 0–11 points) the calcifications were defined as dominantly intimal (score <7 points), dominantly medial (score ≥7 points), indistinguishable (continuity of calcification unclassifiable, due to the presence of only very small amounts of calcification), or absent (Fig. 1) [13]. Furthermore the severity of the calcifications was scored in a four-tier system (none, mild, moderate, severe) as previously described by Woodcock and colleagues [15].

2.4. Clinical and laboratory characteristics

Body mass index (BMI) was calculated using the collected weight and height of the patients. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16]. This formula calculates the eGFR based on gender, age, serum creatinine and race. Since information regarding race was not available in the dataset, we calculated the eGFR as if we only included white patients. Given the localization of the study, we assumed the majority of patients to be white.

2.5. Statistical analysis

Characteristics (age, gender, body mass index, systolic blood pressure, diastolic blood pressure, pulse pressure, serum creatinine, eGFR <60 mL/min/1.73 m^2, glucose, smoking, hypertension, diabetes mellitus, hyperlipidemia, previous vascular disease, and family history) were expressed according to the location of

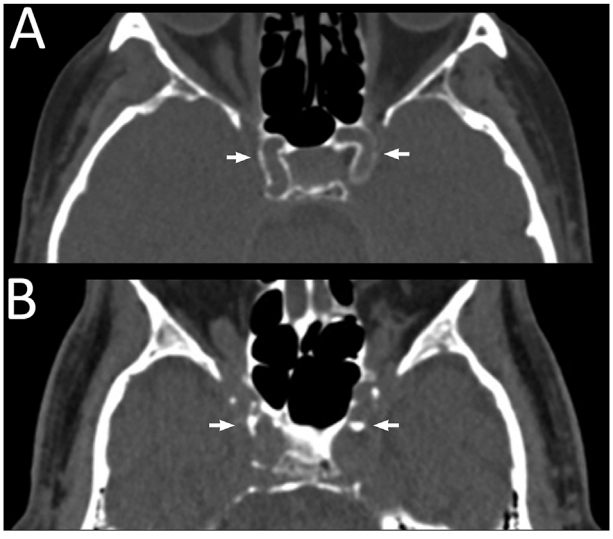

Fig. 1. Examples of predominant intimal and predominant medial calcification on CT. (A) An example of predominant medial calcification: a thin continuous line of calcification (arrows). (B) An example of predominant intima calcification: thick dots of calcification (arrows).