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Atherosclerotic calcification relates to cognitive function and to brain changes on magnetic resonance imaging

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Abstract

Background: Increasing evidence suggests a role of atherosclerosis in the pathogenesis of cognitive impairment and dementia. Calcification volume measured with computed tomography (CT) is a valid marker of atherosclerosis. This study investigates associations of atherosclerosis (measured using CT) at four locations with cognition and brain changes on magnetic resonance imaging (MRI).

Methods: To quantify calcification volume, 2414 nondemented people from the Rotterdam Study underwent CT of the coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries. To assess global cognition and performance on memory, executive function, information processing speed, and motor speed, they also underwent neuropsychological tests. In a random subgroup of 844 participants, brain MRI was performed. Automated segmentation and quantification of brain MRI scans yielded brain tissue volumes in milliliters. Diffusion tensor imaging was used to measure the microstructural integrity of the white matter. Relationships of atherosclerotic calcification with cognition, brain tissue volumes, and diffusion tensor imaging measures were assessed with linear regression models and adjusted for relevant confounders.

Results: With larger calcification volumes, lower cognitive scores were observed. When calcification volumes were larger, total brain volumes were also smaller. Specifically, larger coronary artery calcification volumes related to smaller gray matter volumes, and extracranial and intracranial carotid calcification volumes related to smaller white matter volumes. Larger calcification volume in all vessel beds was accompanied by worse microstructural integrity of the white matter.

Conclusions: Larger calcification volume is associated with worse cognitive performance. It also relates to smaller brain tissue volumes and worse white matter microstructural integrity, revealing possible mechanisms through which atherosclerosis may lead to poorer cognition.

Keywords: Arterial calcification; Atherosclerosis; Brain imaging; Cognition; Brain atrophy

1. Introduction

Increasing evidence suggests a role of atherosclerosis in the development of cognitive impairment [1,2] and dementia [3,4]. Vascular brain injury may underlie this association and can be visualized using magnetic resonance imaging (MRI) [5–7]. However, not all studies show consistent results [8,9]. A potential source of discrepancy between studies is the use of different measures of atherosclerosis, of which carotid ultrasonography is the most frequently used.

Computed tomography (CT)–assessed calcification volume is a more novel, observer-independent, and sensitive measure to reliably assess atherosclerosis [10,11]. Two previous studies suggest that CT-assessed calcification is associated with cerebral atrophy on MRI and with poorer cognitive performance [12,13]. However, these studies only examined calcification in the

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coronary arteries. Investigating arteries that supply blood directly to the brain, that is, the extracranial and intracranial carotid arteries, may demonstrate clearer associations and also provide direct etiological clues on the relationship between atherosclerosis and brain pathology. Previous studies showing only moderate correlations indeed suggest differences between calcification across vessel beds [14,15].

Another consideration is that most previous studies assessed brain pathology using visual rating scales. Advances in MRI and postprocessing techniques allow automatic quantification of brain tissue volumes as a more precise measure of brain pathology. Furthermore, novel MRI sequences such as diffusion tensor imaging (DTI) yield information on the microstructural integrity of white matter [16], which is independently associated to cognitive function [17].

Previously, we reported that CT-assessed calcification volume in various vessel beds is strongly associated with focal brain pathology, that is, lacunar infarcts and white matter lesions [18]. In the current study, we investigated, using the Rotterdam Study, the associations between calcification volume on CT (measured in four major vessel beds) and cognitive function and global brain pathology on MRI. Furthermore, we also explored associations with the microstructural brain tissue integrity.

2. Methods

2.1. Study population

This study is based on the Rotterdam Study [19], a prospective, population-based study aimed at investigating determinants of chronic diseases in the elderly population. The original cohort comprised 7983 participants aged 55 years or older and was extended in 2000 to 2001 with an additional 3011 persons. From 2003 onward, all participants who visited the research center were invited to undergo CT of the heart, aorta, and carotid arteries. In total, 2524 participants were scanned. Because of the presence of a pacemaker, six persons did not undergo a cardiac scan, but only an aorta and carotid artery scan. Owing to coronary stent implantation or image artifacts, 110 scans were not gradable, leaving a total of 2414 complete CT examinations.

From August 2005 to May 2006, a random sample of 1073 participants of the cohort extension who had undergone a complete CT examination was invited to undergo brain MRI. Of the 965 MRI-eligible persons (e.g., without claustrophobia), 897 participated. Owing to physical inabilities (e.g. back pain), imaging could not be performed in 12 individuals. All participants with cortical infarcts on MRI were excluded because brain segmentation did not yield reliable results in those cases. This left 844 participants in the current study with both a CT and an MRI examination, with a mean interscan interval of 8 months (±5 months). This study was approved by the Institutional Review Board of the Erasmus MC (Rotterdam, The Netherlands). All participants gave informed consent.

2.2. CT acquisition and processing

A 16-slice (n = 724) or 64-slice (n = 1690) multidetector computed tomography (MDCT) scanner (Somatom Sensation 16 or 64, Siemens, Forcheim, Germany) was used to perform noncontrast CT scanning. Using a cardiac scan and a scan that reached from the aortic arch to the intracranial circulation (1 cm above the sella turcica), the following vessels were scanned: the coronary arteries, the aortic arch, the extracranial carotid arteries, and the intracranial carotid arteries. Detailed information regarding imaging parameters of both scans is described elsewhere [20].

The estimated radiation dose to which participants were exposed was up to 2.1 millisievert (mSv) for the cardiac scan and 2.8 ms for the extracardiac scan. In a minority of persons with a heart rhythm disorder, cardiac scans required somewhat higher dosages (up to 4.1 mSv). Each participant was scanned once.

Dedicated commercially available software (syngo Calcium Scoring, Siemens, Forcheim, Germany) was used to quantify calcification volume at each of the specified regions; this was expressed in cubic millimeters. The aortic arch was measured from the origin to the first centimeter of the common carotid arteries, the vertebral arteries, and the subclavian arteries beyond the origin of the vertebral arteries. The extracranial carotid arteries were measured at both sides, within 3 cm proximally and distally of the bifurcation [15]. The intracranial internal carotid artery comprised the horizontal segment of the petrous internal carotid artery to the top of the internal carotid artery. Automatic calcification quantification in this region was impossible because of the close relationship between calcium in the arterial wall and the skull. A detailed description of the scoring method of calcification in this region can be found elsewhere [18,21]. Briefly, after delineating calcification manually, the volume of the intracranial carotid artery calcification was calculated by multiplying the number of pixels above the threshold (130 HU) [22] with the pixel size and the slice increment.

2.3. Assessment of cognitive function

All participants underwent the following neuropsychological tests: a 15-word verbal learning task, the Stroop test, the Letter–Digit Substitution Task, the Purdue Pegboard test, and a word fluency test. Per participant, *z*-scores were calculated per test. *Z*-scores for the Stroop test were inverted because higher scores indicate worse performance, whereas higher scores on the other tests indicate better performance. On the basis of the individual test scores, we constructed compound scores for memory, executive function, information processing speed, global cognition, and motor speed to obtain more robust outcome measures [17].

2.4. MRI acquisition and processing

MRI scanning was performed on a 1.5-T scanner with an eight-channel head coil (GE Healthcare, Milwaukee, WI),