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Atherosclerotic calcification is related to a higher risk of dementia and cognitive decline

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Abstract

Background: Longitudinal data on the role of atherosclerosis in different vessel beds in the etiology of cognitive impairment and dementia are scarce and inconsistent.
Methods: Between 2003–2006, 2364 nondemented persons underwent computed tomography of the coronaries, aortic arch, extracranial, and intracranial carotid arteries to quantify atherosclerotic calcification. Participants were followed for incident dementia (n = 90) until April 2012. At baseline and follow-up participants also underwent a cognitive test battery.
Results: Larger calcification volume in all vessels, except in the coronaries, was associated with a higher risk of dementia. After adjustment for relevant confounders, extracranial carotid artery calcification remained significantly associated with a higher risk of dementia [hazard ratio per standard deviation increase in calcification volume: 1.37 (1.05, 1.79)]. Additional analyses for Alzheimer's disease only or censoring for stroke showed similar results. Larger calcification volumes were also associated with cognitive decline.
Conclusions: Atherosclerosis, in particular in the extracranial carotid arteries, is related to a higher risk of dementia and cognitive decline.

Keywords: Atherosclerosis; Arterial calcification; Epidemiology; Imaging; Dementia; Cognitive decline

1. Introduction

Dementia, including Alzheimer's disease, is a devastating condition with a huge societal impact, both in terms of patient suffering and financial cost [1,2]. An important feature of dementia is the long preclinical phase, during which subtle cognitive deficits develop that can only be measured using dedicated neuropsychological tests [3]. The underlying etiology of dementia and cognitive decline is multifactorial and involves different pathologies which interact and accumulate over the course of years [4]. In addition to beta-amyloid and tau pathology, the role of vascular pathology in the etiology of dementia and Alzheimer's disease is increasingly being recognized [5,6].

Atherosclerosis is highly frequent in the aging population and is considered the most important hallmark of vascular pathology [7]. Thus far, most studies have focused on atherosclerosis in the carotid bifurcation in relation to dementia [8–10]. Indeed, both carotid intima-media thickness and carotid plaques have been associated with dementia, including Alzheimer's disease [8–10].

However, several important questions remain unanswered. First, atherosclerosis is a systemic disease, but its burden differs considerably across vessel beds [7,11,12]. It is therefore conceivable that the contribution of atherosclerosis to dementia may vary depending on the vessel bed. Such differential contribution of atherosclerosis in various vessel beds to disease risk has already been demonstrated for stroke, and even for mortality [13,14]. Second, the study of vascular factors in dementia is often complicated by stroke, which can act as intermediate factor [9,10]. It is therefore

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important to also investigate the role of atherosclerosis in dementia independent from stroke. Finally, given that both atherosclerosis and dementia develop over the course of years, it is important to study how atherosclerosis affects the preclinical phase of dementia, namely the period of cognitive decline without overt clinical disease.

Disentangling the exact role of atherosclerosis in dementia is important, because this knowledge may then serve as basis to develop opportunities for therapeutic or preventive intervention. Against this background, we aimed to study the relationship of atherosclerosis in the coronary arteries, aortic arch, extracranial and intracranial internal carotid arteries with incident dementia, including Alzheimer's disease and the potential influence of stroke on these associations. Finally, we focused on the relationship of atherosclerosis with cognitive decline.

2. Methods

2.1. Setting

This study is based on the Rotterdam Study, a prospective, population-based study aimed at investigating determinants of chronic diseases in the elderly [15]. The original cohort comprised 7983 participants aged 55 years or older and was extended in 2000–2001 with 3011 persons. At study entry and every 3–4 years, all participants are re-examined in a dedicated research center.

Between 2003 and 2006, all participants visiting the research center were invited to undergo non-enhanced computed tomography (CT). Therefore for this study, 2003–2006 is taken as baseline. In total, we scanned 2524 participants (response rate 78%). Both during the 2003–2006-visit and the following visit in 2008–2012 persons underwent cognitive testing. The cohort was screened for dementia at baseline to exclude persons with prevalent dementia. From then onwards, the dementia-free cohort was followed-up for dementia through in-person screening at the follow-up visit and through continuous monitoring for dementia via computerized linkage between the study database and medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care, from baseline until April 27, 2012. The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants.

2.2. Sample for analysis

Fig. 1 shows the composition of the study population. Due to the presence of a pacemaker, coronary stent implantations or image artifacts, 111 examinations from the 2524 were not gradable, leaving a total of 2413 participants with a complete CT examination. From these, 2364 participants were at risk for developing dementia (incorrect dementia-screening or prevalent dementia excluded), encompassing the study population at baseline.

From these 2364 participants, 437 refused a second cognitive examination or had died during follow-up, 38 were incapable of follow-up visit (e.g. physical limitations), 16 had been institutionalized or moved, 10 could not be reached, for seven participants the appointment was postponed for logistical reasons, and in nine participants the cognitive assessment was incomplete and could not be used. This left 1847 participants with data on cognitive change (Mini-Mental State Examination, MMSE, or at least one cognitive test).

2.3. CT Acquisition and processing

We used a 16-slice (n = 785) or 64-slice (n = 1739) multidetector CT scanner (Somatom Sensation 16 or 64, Siemens, Forchheim, Germany) to perform noncontrast CT-scanning. Using a cardiac scan and a scan that reached from the aortic arch to the intracranial vasculature (1 cm above the sella turcica), we scanned the following vessel beds: the coronary arteries, the aortic arch, the extracranial carotid arteries, and the intracranial carotid arteries (Fig. 2). Detailed information regarding imaging parameters of both scans is described elsewhere [12].

We used dedicated commercially available software (Syngo Calcium Scoring, Siemens, Germany) to quantify calcification volume in the coronary arteries, aortic arch, and extracranial carotid arteries [12]. For calcification in the intracranial carotid arteries we used a semiautomated scoring method which is described in detail elsewhere [16]. Briefly, we delineated calcification in the intracranial carotid arteries manually in every CT slice. Next, we calculated the volume of intracranial carotid artery calcification by multiplying the number of pixels above the threshold of 130 Hounsfield units [17] with the pixel size and slice increment.

The interrater reliability of this method is very good (intraclass correlation coefficient, 0.99) [16]. Calcification volumes in each vessel bed are expressed in cubic millimeters. Correlations between calcification across the four vessel beds ranged from 0.5 to 0.6 [12,18].

2.4. Ascertainment of dementia

We screened participants for dementia at baseline and follow-up using a three-step protocol [19,20]. The first screening step consisted of the MMSE and the Geriatric Mental Schedule (GMS) organic level. If participants were screen-positive (MMSE $<$ 26 or GMS organic level $>$ 0), they entered the second step which consisted of the Cambridge Examination for Mental Disorders in the Elderly [20]. Additionally, persons underwent history taking, assessment of activities of daily living, informant interview, retrieval of relevant medical records, and additional neuropsychological testing. When information on neuroimaging was available (38/90 dementia cases; 42%), it was