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Carotid atherosclerosis, silent ischemic brain damage and brain atrophy: A systematic review and meta-analysis

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ABSTRACT

Background: The widespread use of brain imaging has led to increased recognition of subclinical brain abnormalities, including white matter hyperintensities (WMH) and silent brain infarctions (SBI), which have a vascular origin, and have been associated to a high risk of stroke, disability and dementia. Carotid atherosclerosis (CA) may be causative in the development of WMH, SBI and eventually brain atrophy. Aim of the present systematic review and meta-analysis was to assess the existing evidence linking CA to WMH, SBI and brain atrophy.
Methods: The relation between CA and WMH, SBI and brain atrophy was investigated through the systematic search of online databases up to September 2015 and manual searching of references and related citations. Pooled estimates were calculated by random-effects model, using restricted maximum likelihood method with inverse variance weighting method.
Results: Of the 3536 records identified, fifteen were included in the systematic review and 9 were found to be eligible for the meta-analysis. CA was significantly associated with the presence of WMH (Odds Ratio, OR 1.42, confidence interval, CI 1.22–1.66, $p < 0.0001$) and of SBI (OR 1.89, CI 1.46–2.45, $p < 0.0001$). No meta-analysis could be performed for the relation between CA and brain atrophy due to the lack of suitable studies.
Conclusions: CA was found to be associated to WMH and SBI. While no causative association can be inferred from the available data, the presence of carotid plaque may be considered a significant risk factor for subclinical cerebral damage.

1. Introduction

Asymptomatic carotid stenosis is common in the general population, with prevalence estimates being as high as 6% in elderly men and 4.4% in elderly women [1], while presence of carotid artery plaque may be even higher, reaching up to 40% of free living subjects [2]. The widespread use of brain magnetic resonance imaging (MRI) has enabled an increased recognition, especially in elderly subjects, of cerebral alterations in apparently healthy individuals. A causative role for carotid atherosclerosis, however, cannot, to date, be ruled out. MRI detected alterations include white matter hyperintensities (WMH), defined as patchy areas of signal hyperintensity on T2-weighted and/or fluid attenuated inversion recovery (FLAIR) sequences [3,4], and silent brain infarctions (SBI), i.e., focal areas of at least 3 mm in diameter showing high signal intensity on T2-weighted, or having the same signal intensity as cerebrospinal fluid in FLAIR images, and low intensity on T1-weighted images, in the absence of corresponding neurological signs and symptoms and with no clinical history of stroke [5,6]. WMH and SBI are not innocuous, since they have been associated with brain atrophy [7] and confer a significant risk of incident stroke [8], mood and gait disturbances [9], cognitive decline and dementia [8,9]. As a consequence, they could be considered as markers of "brain frailty" [10]. Both types of lesions are thought to have a vascular origin [6,9], but their precise etiology remains controversial. Local microvascular alterations, embolic occlusion of arterioles or chronic cerebral hypoperfusion have all been implicated [6,11]. Advanced age, cardiovascular risk factors, in particular hypertension, atrial fibrillation and patent foramen ovale have been associated with WMH and SBI [6,12–17]. Carotid atherosclerosis, as a source of microemboli [18] or by causing ischemia in case of flow limiting

Abbreviations: CA, carotid atherosclerosis; WMH, white matter hyperintensities; SBI, silent brain infarctions; OR, odds ratio; CI, confidence interval; MRI, magnetic resonance imaging; US, ultrasound; FLAIR, fluid attenuation inversion recovery; IMT, intima-media thickness.

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stenosis, may contribute to WMH and SBI, and ultimately to brain atrophy [19]. The aim of the present systematic review and meta-analysis was to investigate the association between the presence of carotid atherosclerotic plaques and WMH, SBI or brain atrophy in the general population, largely including asymptomatic subjects.

2. Methods

The present study was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [20] guidelines for its design, implementation, analysis and reporting.

2.1. Search strategy

We searched for studies assessing the relation between carotid atherosclerosis and WMH, SBI or brain atrophy detected with brain MRI. Specific inclusion criteria were: MRI field strength of at least 1.0 Tesla, assessment of WMHs on T2-weighted or FLAIR images and definition of SBI as focal lesions of at least 3 mm in diameter that appeared hyperintense on T2-weighted or FLAIR images and hypointense on T1-weighted images, with no associated neurological symptoms, in compliance with recently defined neuroimaging standards [4]. In the absence of a consensus on how to assess brain WMH involvement [4,21], we did not apply restrictions on the methods used. Similarly, no restriction was applied for brain atrophy evaluation method. We included only studies providing imaging evidence of carotid artery atherosclerosis, defined as carotid involvement by a fully developed atherosclerotic lesion. We did not apply restrictions for the specific definition of plaque and for the modality used for carotid assessment, which could include ultrasound (US), digital subtraction angiography, computed tomography angiography or magnetic resonance angiography. Studies concerned with the association between carotid intima-media thickness (IMT) and WMH, SBI or cerebral atrophy were excluded, since IMT, while generally considered an early stage of atherosclerotic disease, appears to be biologically distinct from carotid atherosclerosis, and its relation to carotid plaques is incompletely understood [22]. Studies focusing selectively on stroke patients were excluded to avoid the confounding effect of the expected high ischemic burden in these subjects. Since recent evidence suggests that periventricular and deep WMH are to be considered as part of a continuous pathology [3], we excluded those studies selectively reporting on either of the two. Finally, we considered an article regarding brain atrophy suitable for meta-analysis if it provided mean and standard deviation values of standardized total brain volumes both in patients with carotid atherosclerosis and healthy controls.

Studies reporting the odds ratio (OR) of patients with carotid atherosclerosis for extensive WMH or for the presence of SBI were included in the quantitative synthesis. If the study reported both adjusted and unadjusted ORs, we included in the analysis the value adjusted for age and sex, and, if available, cardiovascular risk factors. We decided to include age and sex adjusted ORs due to the known effect of both these variables on CA [23] and WMH prevalence and burden [3]. If no OR was available, the article was still included if the OR could be manually calculated from the data reported.

Searches were performed of literature published through September the 30th, 2015 using MEDLINE and Embase. Additional records were identified on the gray literature database OpenSIGLE, related article feature on PubMed and hand searching of reference lists.

2.2. Data extraction

Data concerning the imaging technique used to assess the presence of carotid artery plaque, MRI field strength, total number and mean age of participants and the proportion of participants with history of cerebrovascular disease were collected from each study. For studies on WMH or SBI, contingency tables and ORs were extracted. For studies on brain volume, mean and standard deviation of standardized total brain volumes were extracted.

2.3. Statistical analysis

Continuous variables are reported as mean (standard deviation) or median (1st–3rd quartile). Categorical variables are expressed as percentages. The summary effect size was calculated with the random-effect models, using restricted maximum likelihood method with inverse variance weighting. Between-study heterogeneity was assessed with Q test and I^2. Potential publication bias was assessed by inspecting a funnel plot of effect sizes versus standard errors [24], and using rank correlation test [25]. A meta-analysis was carried out if at least three studies were available for the same outcome. All analyses were performed using the metafor package in R [26]. Associations with $p < 0.05$ were considered significant.

3. Results

3.1. Articles selection

The search strategy for Embase is shown in Table 1. For other databases, we applied the same strategy with variations based on database structure. Of the 3536 articles identified, 3426 records were excluded upon title screening. Abstracts of the remaining 110 records were reviewed, which led to the exclusion of further 42 articles. Full text was evaluated in 68 articles, and 15 were found to match our inclusion and exclusion criteria. Of those, 9 were found suitable for meta-analysis. Fig. 1 summarizes articles' selection process.

Table 1
Search strategy for Embase. For other databases, i.e. MEDLINE and OpenSIGLE, we applied variations based on database structure.

#1	'carotid artery disease'/exp
#2	'white matter lesion'/exp
#3	'leukoaraiosis'/exp
#4	white AND matter AND hyperintensit*
#5	2# OR #3 OR 4#
#6	'brain atrophy'/exp
#7	silent OR occult
#8	'cerebrovascular accident'/exp
#9	#7 AND #8
#10	'lacunar stroke'/exp
#11	#9 OR #10
#12	#5 OR #6 OR #11
#13	#1 AND #12
#14	Filter #13 for "English and Humans"

3.2. Carotid atherosclerosis and WMH

Ten population-based studies explored the relation between carotid atherosclerosis and WMH [27–36]. Of those, six, comprising 5306 subjects, fulfilled the criteria for inclusion in the meta-analysis [27–32]. Table 2 reports data extracted from these studies. Combining all studies, the pooled OR for WMH in patients suffering from carotid atherosclerosis was 1.42 (95% confidence interval [CI]: 1.22–1.66, $p < 0.0001$), as shown in Fig. 2. No evidence of significant heterogeneity was present (Q-test $p = 0.38$; $I^2 = 0.0\%$). Visual inspection of the funnel plot (Supplementary Fig. 1) showed some potential for publication bias, despite a nonsignificant rank correlation test ($p = 0.47$). In particular, the study by Fazekas et al. [27] appeared as an outlier in terms of sample size and OR. However, the exclusion of this study led to marginal changes in the results, yielding a pooled OR of 1.40 (95% CI: 1.20–1.63, $p < 0.0001$; Q-test $p = 0.58$; $I^2 = 0.0\%$).

Four additional studies were identified through the systematic search, which could not be included in the quantitative synthesis [33–36]. Table 3 summarizes the main findings and reasons for exclusion from the meta-analysis. Manolio et al. investigated the association between carotid atherosclerosis and the extent of cerebral WMH involvement assessed using a visual scoring system in a cohort of 3502 subjects older than 65 years of age [33]. These Authors report a significant association between carotid atherosclerosis and the severity of white matter changes that was stronger with increasing stenosis severity and remained significant after adjustment for age and sex [33].

De Leeuw et al. described the relation between the number of atherosclerotic plaques in the carotid arteries bilaterally and brain WMH, assessed semi-quantitatively, in a cohort of 1077 individuals aged 60 to 90 years [36]. They found a significant association between the number of plaques and the severity of WMH in the periventricular white matter, but not in the subcortical region. Such an association remained significant after adjustment for hypertension [36].

Shrestha et al. explored the association between the number of carotid plaques and carotid plaque score, i.e., the sum of the heights of all the plaques detected bilaterally using ultrasound, and the extent of WMH assessed by Fazekas score in a cohort of 179 subjects, with a mean age of 66 years [35]. At multivariable regression, plaque score was independently associated to the severity of WMH both in periventricular and deep white matter [35].

Finally, Landi et al. assessed the association between carotid atherosclerosis and total WMH volume in a cohort of 94 subjects with a mean