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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.

Keywords: Carotid Atherosclerosis, Leukoaraiosis, Silent Brain Infarction, Brain Atrophy, Meta-Analysis.

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.

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/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 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 plaque independently from the modality used, including 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. 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 grey 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,[23] and using rank correlation test.[24] 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.[25] 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. Figure 1 summarizes articles' selection process.

3.2 Carotid atherosclerosis and WMH

Ten population-based studies explored the relation between carotid atherosclerosis and WMH [26-35]. Of those, six, comprising 5306 subjects, fulfilled the criteria for inclusion in the meta-analysis.[26-31] 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 Figure 2. No evidence of significant heterogeneity was present (Q-test $p = 0.38$; $I^2 = 0.0\%$). Visual inspection of the funnel plot (Supplementary Figure 1) showed some potential for publication bias, despite a nonsignificant rank correlation test ($p = 0.47$). In particular, the study by Fazekas et al. [26] 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.[32-35] 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.[32] 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.[32]

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.[35] 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.[35]

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.[34] At multivariable regression, plaque score was independently associated to the severity of WMH both in periventricular and deep white matter.[34]

Finally, Landi et al. assessed the association between carotid atherosclerosis and total WMH volume in a cohort of 94 subjects with a mean age of 71 years.[33] At multivariable analysis, they found a significant association between age and WMH, but not between carotid stenosis and WMH.[33]

A single, prospective study reported an increased risk (OR=1.76) for severe WMH at 4 years of follow up in patients with carotid atherosclerosis.[28]

3.3 Carotid atherosclerosis and SBI

Seven studies examined the relationship between carotid atherosclerosis and the presence of SBI at brain MRI.[29, 30, 32, 36-39]. Two[29, 32] referred to subgroups of the population of larger studies,[36] and [39] respectively, thus, in order to avoid duplications, only the latter were included in the present analysis. Four studies, including 3586 participants, fulfilled the criteria for the inclusion in the meta-analysis[30, 36-38] (Table 4). They demonstrate a significant association between carotid atherosclerosis and the presence of SBI, with a pooled OR of 1.89 (95% CI: 1.46-2.45, $p<0.0001$), as shown in Figure 3.

No evidence of significant heterogeneity was detected (Q-test $p=0.23$, $I^2=15.5\%$). The study by Giele et al. [38] was identified as a potential source of bias, since the definition of carotid atherosclerosis markedly differed from other studies (i.e., presence of a stenosis $\geq 70\%$ in the work by Giele et al. [38], imaging evidence of carotid plaques in all other studies). After the exclusion of this study from the analysis, a small increase in effect size was observed, with a pooled OR of 1.94

(95% CI: 1.45-2.60, $p < 0.0001$; Q-test $p = 0.15$, $I^2 = 35.3\%$). Visual inspection of the funnel plot (Supplementary Figure 2) was not suggestive of publication bias, as was rank correlation test ($p = 1$). One further study, not suitable for the meta-analysis, was identified through the search.[39] In particular, at multivariable analysis, Longstreth et al. described a significant association between SBI and ipsilateral carotid plaque with a stenosis of at least 50% in 3244 subjects aged 65 years or more.[39]

3.4 Carotid atherosclerosis and brain atrophy

Only three studies assessing the relationship between carotid atherosclerosis and brain volume were identified,[29, 32, 40] none of which fulfilled the criteria for inclusion in the meta-analysis. Romero et al. observed a highly significant association between the presence of a carotid plaque determining a stenosis $\geq 25\%$ and lower total brain volume to total cranial volume ratio in 1971 subjects.[29] Manolio et al. described an association between sulcal widening, bifrontal distance and ventricular size, all MRI markers of brain atrophy, and the presence of carotid atherosclerosis in a population of 3502 elderly subjects.[32] The association remained significant after adjustment for age, sex, aspirin use and hypertension. Finally, Muller et al. reported an association between carotid atherosclerosis, with a stenosis of at least 50% in diameter, and lower total brain and cortical gray matter volume, normalized for intracranial volume, in a population-based cohort of 1232 subjects.[40] Interestingly, follow up data at 4 years were available for 663 participants, and showed a significant association between severe, i.e., stenosis $\geq 70\%$, or bilateral carotid atherosclerosis and progression of global, cortical and subcortical atrophy.[40]

4. Discussion

The main finding of the present systematic review and meta-analysis was the demonstration of a significant association between carotid atherosclerosis and a higher risk of both WMH and SBI. The association appears to be particularly robust, since it derives mainly through the analysis of either multivariate OR or from directly calculated OR, which are believed to reduce spurious associations due to reporting bias. Secondly, we found records concerning the relation between carotid

atherosclerosis and brain volumes: surprisingly few studies were identified, [29, 32, 40], but all appeared to suggest an association between carotid plaque and brain atrophy.

As the use of brain MRI has become increasingly widespread, clinicians often have to cope with the incidental finding of silent cerebral alterations, particularly in patients with asymptomatic carotid artery plaques. WMH and SBI are frequently discovered in healthy subjects, and their prevalence depends on age.[41-43] These lesions were shown to associate with brain atrophy, a marker of accumulating cerebral damage.[7, 44] Both WMH and SBI appear to have a vascular pathogenesis [6, 9, 45] and both are strongly associated with cardiovascular risk factors and atrial fibrillation.[6, 12, 13] However, the precise etiology is yet to be defined. Indeed, local vascular degenerative processes leading to hypoperfusion or acute ischemia with tissue necrosis,[9] distal embolization from the heart[13] or from a large vessel,[46] or chronic reduction in cerebral perfusion, have all been implicated.[19, 47] Carotid atherosclerosis may thus contribute to the pathogenesis of both WMH and SBI as a source of microemboli [48] or through the reduction of cerebral blood flow.[49] While some of the studies eligible for the present systematic review and meta-analysis reported an increasing cerebral involvement proportional to the degree of the carotid stenosis,[29, 32] many of the studies did not report stenosis severity.[26-28, 30, 31] In others, patients with hemodynamically significant stenosis, i.e., $\geq 50\%$, were absent or under-represented.[36, 37] These data support a potential etiologic role for carotid atherosclerosis in the development of WMH and SBI, but possibly suggest that the presence of a flow limiting stenosis is not required, making the chronic ischemia hypothesis less likely. Furthermore, some reports associated the presence of vulnerability features within the plaque to a higher burden of silent ischemic brain damage, suggesting a direct role for atherothrombosis and subsequent distal embolization.[29, 50, 51] A recent meta-analysis showed a significant association between atrial fibrillation and presence of SBI, with a pooled OR of 2.62, which supports an embolic origin for these lesions.[52] A direct causative role for carotid atherosclerosis with an embolic mechanism would imply a higher burden of silent ischemic lesions ipsilateral to the site of carotid artery disease. Research in this field, however, yielded mixed

results.[53-55] Indeed, the association may be accounted for by the risk factors shared by carotid atherosclerosis, WMH and SBI, including age, hypertension, dyslipidemia, smoking and diabetes.[9, 12] Carotid atherosclerosis may be considered a marker of higher ischemic vulnerability of the brain. This may allow the clinician to identify subjects at risk of stroke and dementia, and prompt an aggressive correction of cardiovascular risk factors, eventually including the initiation of treatment which were shown to effectively slow the progression of cerebral ischemic damage, including antiplatelet medications, as aspirin[56] or cilostazol[57] and lipid lowering medications such as statins.[58]

5. Conclusions

Carotid atherosclerosis appears to be strongly associated to the presence of WMH (OR=1.42, $p<0.0001$) and SBI (OR=1.89, $p<0.0001$). The few available studies concerning the relation between carotid atherosclerosis and brain volumes suggest that carotid plaques and cerebral atrophy may be associated. While any speculation about the causative role of carotid atherosclerosis for WMH, SBI and subsequently brain atrophy cannot be made from the available literature, carotid atherosclerosis can be proposed as a marker for susceptibility to ischemic cerebral damage.

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7. Conflicts of interest

None

8. References

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Figures

Figure 1. Study selection flow diagram

Figure 2. Meta-analysis of the studies evaluating the association between carotid atherosclerosis and white matter hyperintensities. OR: odds ratio; CI: confidence interval.

Figure 3. Meta-analysis of the studies evaluating the association between carotid atherosclerosis and silent brain infarctions. OR: odds ratio; CI: confidence interval.

Tables

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"

Table 2. Data extracted from the studies evaluating the relation between carotid atherosclerosis and white matter hyperintensities.

Author	Year	CA Imaging	MRI	N	CA and WMH	Reported OR	Calculated OR	Age (years)	Proportion of symptomatic subjects (%)
Fazekas	1988	US	1.5T	52	19	NA	3.56	58	0
Bots	1993	US	1.5T	111	8	NA	1.04	74	0
Pico	2002	US	1.0T	640	46	1.35 [†]	1.56	62	0
Romero	2009	US	1.0T	1971	NA	1.76 [‡]	-	58	NA [§]
Yoshida	2012	US	1.5T	790	90	NA	1.25	61	0
Brisset	2013	US	1.5T	1742	NA	1.37 [†]	-	72	NA

Proportion of symptomatic subjects reports the number of subjects with symptomatic cerebrovascular disease. MRI = magnetic resonance imaging; CA = carotid atherosclerosis; WMH = white matter hyperintensities; OR = odds ratio; US = ultrasound. [†]Adjusted for age, sex and cardiovascular risk factors; [‡]Adjusted for age and sex; [§]Overall manifest cardiovascular disease (including cerebrovascular disease, coronary artery disease, heart failure and peripheral artery disease) 7.5%; ^{||}Overall manifest cardiovascular disease (including cerebrovascular disease, coronary artery disease, heart failure and peripheral artery disease) 6%.

Table 3. Studies concerned with the relation between carotid atherosclerosis and white matter hyperintensities not included in the meta-analysis.

Author	Year	n	Main findings	Reasons for exclusion
Manolio	1999	3502	WMH severity assessed with an Authors' defined visual scoring system increased with increasing stenosis severity. The association remained significant after age and sex adjustment.	Both WMH and CA treated continuously. No variances reported. OR was not reported or calculable.
DeLeeuw	2001	1077	Significant association between number of plaques in the carotid arteries and a semiquantitative measure of WMH severity in the periventricular, but not in the subcortical, white matter.	Not reported the number of subject without CA. WMH treated as a continuous variable. Distinction between periventricular and subcortical WMH.
Shresta	2007	179	Plaque score, i.e. the sum of the thickness of all plaques identified bilaterally in the carotid arteries, significantly correlated with WMH assessed with Fazekas score.	CA and WMH treated as continuous variables. Insufficient data for OR calculation.
Landi	2015	94	No association between the degree of stenosis and cerebral WMH in a multivariate analysis including age and cardiovascular risk factors	Number of subjects without CA was not reported. Insufficient data to calculate OR.

Table 4. Data extracted from the studies evaluating the relation between carotid atherosclerosis and silent brain infarctions.

Author	Year	CA Imaging	MRI	N	CA and SBI	Reported OR	Calculated OR	Age (years)	Proportion of symptomatic subjects (%)
Giele	2003	US	1.5T	308	1	NA	0.84	58	0
Inoue	2006	US	1.5T	448	19	NA	3.28	51	0
Das†	2008	US	1.0T	2040	NA	1.62‡	.	58	0
Yoshida	2009	US	1.5T	790	93	NA	1.84	61	0

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Proportion of symptomatic subjects reports the number of subjects with symptomatic cerebrovascular disease. MRI = magnetic resonance imaging; CA = carotid atherosclerosis; SBI = silent brain infarction; OR = odds ratio; US = ultrasound. †Presence of plaque defined for carotid stenosis of at least 25%; ‡Adjusted for age and sex.

Online Figures Captions

eFigure1. Funnel Plot for the meta-analysis on the relation between carotid atherosclerosis and white matter hyperintensities. The visual inspection of the Funnel Plot is suggestive for the presence of small study effect, i.e. the study with the smallest sample size appears to be the one with the largest effect size (bottom right), despite a non significant rank correlation test ($p=0.47$).

eFigure2. Funnel Plot for the meta-analysis on the relation between carotid atherosclerosis and silent brain infarctions. The visual inspection of the funnel plot does not suggest the presence of small study effect, which is supported by a non significant rank correlation test ($p=1$).