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Cerebrovascular Diseases

Imaging

Cerebrovasc Dis
DOI: 10.1159/000526261

Received: December 30, 2021
Accepted: July 18, 2022
Published online: September 12, 2022

Carotid Artery Stenosis and Progression of Hemispheric Brain Atrophy: The SMART-MR Study

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Keywords
Carotid artery stenosis · Brain atrophy · Cohort studies · MRI

Abstract
Introduction: It has been hypothesized that carotid artery stenosis (CAS) may lead to greater atrophy of subserved brain regions; however, prospective studies on the impact of CAS on progression of hemispheric brain atrophy are lacking. We examined the association between CAS and progression of hemispheric brain atrophy. ***Methods:*** We included 654 patients (57 ± 9 years) of the SMART-MR study, a prospective cohort study of patients with manifest arterial disease. Patients had baseline CAS duplex measurements and a 1.5T brain MRI at baseline and after 4 years of follow-up. Mean change in hemispheric brain volumes (% of intracranial volume [ICV]) was estimated between baseline and follow-up for left-sided and right-sided CAS across three degrees of stenosis (mild [≤29%], moderate [30–69%], and severe [≥70%]), adjusting for demographics, cerebrovascular risk factors, and brain infarcts. ***Results:*** Mean decrease in left and right hemispheric brain volumes was 1.15% ICV and 0.82% ICV, respectively, over 4 years of follow-up. Severe right-sided CAS, compared to mild CAS, was associated with a greater decrease in volume of the left hemisphere (B = −0.49% ICV, 95% CI: −0.86 to −0.13) and more profoundly of the right hemisphere (B = −0.90% ICV, 95% CI: −1.27 to −0.54). This pattern was independent of cerebrovascular risk factors, brain infarcts, and white matter hyperintensities on MRI, and was also observed when accounting for the presence of severe bilateral CAS. Increasing degrees of left-sided CAS, however, was not associated with greater volume loss of the left or right hemisphere. ***Conclusions:*** Our data indicate that severe (≥70%) CAS could represent a risk factor for greater ipsilateral brain volume loss, independent of cerebrovascular risk factors, brain infarcts, or white matter hyperintensities on MRI. Further longitudinal studies in other cohorts are warranted to confirm this novel finding.

Study group listed in acknowledgments.

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Introduction

Brain atrophy is an important hallmark of dementia and is commonly seen in patients with atherosclerotic disease [1, 2]. Although brain volume loss occurs with normal aging, accelerated brain atrophy has been shown to represent an important risk factor for cognitive impairment and dementia [3–5]. The underlying causes that lead to progression of brain atrophy remain largely unknown; however, previous studies suggest that cerebrovascular disease, male sex, and reduced cerebral blood flow may represent potential risk factors [6, 7].

Carotid artery stenosis (CAS) may also represent a risk factor for accelerated brain atrophy and the development of dementia [8, 9]. Several hypotheses linking CAS to accelerated brain atrophy have been formulated. First, CAS can lead to atheroembolic stroke, which is a risk factor for accelerated brain atrophy [10]. Second, CAS may represent a proxy marker for cerebrovascular risk factors, which may negatively impact brain health through greater brain tissue loss over time [9]. Third, high-grade CAS may lead to compromised blood flow through the affected carotid artery that, if not adequately compensated for by collateral circulation, may result in brain tissue loss [11]. Several aspects of the association between CAS and progression of brain atrophy, however, are unclear. For example, it is not known whether CAS represents a risk factor for greater atrophy of the ipsilateral cerebral hemisphere, the contralateral cerebral hemisphere, or both. The limited number of studies on this relationship reported smaller brain volumes ipsilateral to the side of the stenosis [12–15]. The cross-sectional design of these studies, however, precludes establishing a cause–effect relationship, and to our knowledge, no previous longitudinal studies examined the effects of CAS on hemispheric brain volume changes.

Here, we hypothesized that CAS was associated with greater ipsilateral hemispheric brain atrophy. Using data from the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, we examined the longitudinal association of CAS with changes in hemispheric and total brain volumes over 4 years of follow-up, adjusting for demographics, cerebrovascular disease, and its risk factors.

Material and Methods

Study Population

Data were used from the SMART-MR study, a prospective cohort study at the University Medical Center Utrecht with the aim of investigating risk factors and consequences of brain changes on magnetic resonance imaging (MRI) in patients with manifest arterial disease. In brief, between 2001 and 2005, 1,309 middle-aged and older patients newly referred to the University Medical Center Utrecht for treatment of manifest arterial disease (manifest coronary artery disease [59%], cerebrovascular disease [23%], peripheral arterial disease [22%], or abdominal aortic aneurysm [9%]) were included for baseline measurements. During a 1-day visit to our medical center, a physical examination, ultrasonography of the carotid arteries, blood and urine samplings, neuropsychological assessment, and a 1.5 T brain MRI scan were performed. Questionnaires were used to assess demographics, risk factors, medical history, and medication use. Between 2006 and 2009, follow-up measurements took place, including a 1.5 T MRI of the brain. In total, 754 patients of the surviving cohort gave written informed consent and participated in the follow-up. The SMART-MR study was approved by the Medical Ethics Committee of the University Medical Center Utrecht according to the guidelines of the Declaration of Helsinki of 1975, and written informed consent was obtained from all patients.

Assessment of CAS

Presence of CAS was assessed at baseline with ultrasonography consisting of color Doppler-assisted duplex. Measurements were performed with a 10 MHz linear-array transducer (ATL Ultramark 9) by ultrasound technicians. The severity of CAS was evaluated on the basis of blood flow velocity patterns [16]. The greatest stenosis observed on the right or the left side of the common or internal carotid artery was taken to determine the severity of CAS. CAS was classified into groups of mild (≤29%; peak systolic velocity [PSV] ≤100 cm/s), moderate (30–69%; PSV >100 to ≤210 cm/s), and severe (≥70%; PSV >210 cm/s) for each side. In addition, to examine the effects of unilateral CAS on brain volumes in the presence of bilateral stenosis, we classified patients into (i) mild-to-moderate CAS on both sides, (ii) severe unilateral left-sided CAS, (iii) severe unilateral right-sided CAS, and (iv) severe bilateral CAS.

MRI Protocol

MR imaging of the brain was performed on a 1.5T whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, The Netherlands) using a standardized scan protocol. Transversal T1-weighted (repetition time [TR] = 235 ms; echo time [TE] = 2 ms), T2-weighted (TR = 2,200 ms; TE = 11 ms), fluid-attenuated inversion recovery (FLAIR) (TR = 6,000 m; TE = 100 ms; inversion time = 2,000 ms), and T1-weighted inversion recovery images (TR = 2,900 ms; TE = 22 ms; inversion time = 410 ms) were acquired with a voxel size of $1.0 \times 1.0 \times 4.0$ mm^3 and contiguous slices.

Brain Infarcts

Brain infarcts were visually rated by a neuroradiologist blinded to patient characteristics on the T1-weighted, T2-weighted, and FLAIR images. Lacunes were defined as focal lesions between 3 and 15 mm according to the STRIVE criteria [17], whereas nonlacunar lesions were categorized into large infarcts (i.e., cortical infarcts and subcortical infarcts not involving the cerebral cortex) and infarcts located in the cerebellum or brain stem.

Brain Volume Measurements

The T1-weighted, the T1-weighted inversion recovery, and FLAIR sequence were used for automated brain segmentation.

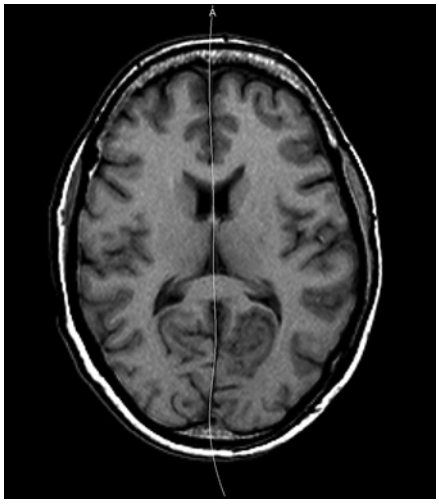

Fig. 1. Illustration of the midsagittal surface (white line) separating the cerebral hemispheres on an axial T1-weighted MR image of a 52-year-old male patient. Note that the midsagittal surface also accounts for the presence of left-right asymmetry of the occipital lobes (i.e., "brain torque") in this patient.

A probabilistic brain segmentation method consisting of *k*-nearest neighbor classification was performed to segment cortical gray matter, white matter and deep gray matter, sulcal and ventricular cerebrospinal fluid, and white matter hyperintensities (WMH) [18]. The kNN segmentation method has been shown to be suitable for detecting longitudinal brain volume changes [19]. Brain infarcts were manually segmented, and the other segmentations were corrected for the presence of infarcts. All WMH segmentations were visually checked by an investigator (RG) using an image processing framework (MeVisLab 2.7.1., MeVis Medical Solutions AG, Bremen, Germany) to ensure that brain infarcts were correctly removed from the WMH segmentations [20].

Total brain volume was calculated by summing the volumes of cortical gray matter, white matter, WMH, and, if present, the volume of brain infarcts. The total intracranial volume (ICV) was calculated by summing the total brain volume and the volume of cerebrospinal fluid. Hemispheric brain volumes were obtained using an automated method based on the extraction of the midsagittal surface [21]. An illustration of the midsagittal is shown in Figure 1. Infratentorial volumes were automatically subtracted from the volumes to obtain hemispheric cerebral volumes that were used in analyses.

Cerebrovascular Risk Factors

At baseline, age, sex, smoking habits, and alcohol intake were assessed using questionnaires. Height and weight were measured, and the body mass index (BMI) was calculated (kg/m^2). Systolic blood pressure (mm Hg) and diastolic blood pressure (mm Hg) were measured twice with a sphygmomanometer, and the average of these measures was calculated. Hypertension was defined as a mean systolic blood pressure of >160 mm Hg, a mean diastolic blood pressure of >95 mm Hg, self-reported use of antihypertensive drugs, or a known history of hypertension at inclusion. An overnight fasting venous blood sample was taken to determine glucose and lipid levels. Diabetes mellitus was defined as the use of glucose-lowering drugs, a known history of diabetes mellitus, or a fasting plasma glucose level of ≥7.0 mmol/L. Hyperlipidemia was defined as a total cholesterol of >5.0 mmol/L, a low-density lipoprotein cholesterol of >3.2 mmol/L, use of lipid-lowering drugs, or a known history of hyperlipidemia.

Study Sample

Of the 1,309 patients included, 15 had no MRI and 12 had no FLAIR sequence. Furthermore, brain volume data were missing due to motion or artifacts in 39 patients. Of the remaining 1,243 patients, 695 patients underwent a follow-up MRI. Of these, 16 patients had missing brain volume data due to motion or artifacts and CAS measurements were missing in 25 patients on one or both sides. As a result, the analyses were performed on 654 patients.

Statistical Analysis

To examine the relationship of sidedness of CAS with total and hemispheric brain volume changes at follow-up, we chose a mixed model approach using the MIXED procedure of SAS (SAS Institute, Cary, NC, USA). We used this statistical approach because mixed models can estimate the effects of CAS on hemispheric brain volumes while taking into account the effects on the contralateral cerebral hemisphere. Degrees of left-sided and right-sided CAS at baseline were entered as independent variables, whereas total brain volume and hemispheric brain volumes at follow-up were entered as dependent variables.

Next, to examine the effects of severe unilateral CAS on brain volumes in the presence of severe bilateral CAS, we entered a categorical variable with mild to moderate CAS on both sides, severe unilateral left-sided CAS, severe unilateral right-sided CAS, and severe bilateral CAS as outcomes as the independent variable. Mild to moderate CAS on both sides was chosen as the reference category. Total and hemispheric brain volumes at follow-up were entered as the dependent variables.

All of the abovementioned models were run in two steps. In the first model, we adjusted for age, sex, and baseline brain volumes. In the second model, we added covariates indicating hypertension, diabetes mellitus, BMI, smoking pack years, alcohol use, and number of infarcts (including lacunes) and WMH volume on baseline and follow-up MRI.

As a supplementary analysis, we used analysis of covariance (ANCOVA) to estimate changes in hemispheric brain volumes for degrees of left-sided and right-sided CAS. Age, sex, and the abovementioned cerebrovascular risk factors were added as covariates in addition to the number of infarcts and WMH volume on baseline and follow-up MRI in the cerebral hemisphere ipsilateral to the side of stenosis. This supplementary analysis allowed us to estimate changes in hemispheric brain volumes while specifically taking into account cerebrovascular lesions on the side of the stenosis. We excluded patients with severe bilateral CAS from these analyses. Estimates were considered statistically significant when their 95% confidence intervals (CIs) excluded zero.

Table 1. Baseline characteristics of the study sample and stratified according to the highest degree of CAS

	Total sample (*n* = 654)	Mild CAS (*n* = 541)	Moderate CAS (*n* = 49)	Severe CAS (*n* = 64)
Age, years	57±10	57±10	61±7	60±8
Sex, % men	81	82	74	84
History of stroke, %	22	16	28.6	70.3
BMI, kg/m^2	27±3	27±4	26±3	27±3
Smoking, pack years[a]	22 (0, 49)	20 (0, 48)	12 (0, 72)	26 (0, 54)
Alcohol intake, % current	77	78	79	78
Hypertension, %	46.8	43.4	55.1	68.8
Diabetes mellitus, %	15	13.5	22.4	26.6
Large infarcts on MRI, %	10	6.1	6.1	20.8
Lacunes on MRI, %	17	14.2	12.2	46.9
Infarcts on MRI, *n*[b]				
Total	0.6±1.3	0.4±1.1	0.6±1.2	2.0±2.1
Left hemisphere	0.2±0.7	0.2±0.6	0.2±0.6	0.8±1.4
Right hemisphere	0.3±0.8	0.2±0.6	0.2±0.7	1.1±1.7
WMH volume on MRI, mL				
Total	2.2±5.1	2.2±5.3	2.3±3.2	2.5±3.4
Left hemisphere	1.1±2.6	1.1±2.6	1.2±1.8	1.4±2.5
Right hemisphere	1.1±2.6	1.1±2.7	1.1±1.6	1.1±1.5
Brain volumes, % ICV				
Total	79.4±2.6	79.6±2.5	78.7±2.4	78.1±2.7
Left hemisphere	78.8±2.7	79.0±2.6	78.1±2.5	77.6±2.9
Right hemisphere	79.9±2.6	80.1±2.6	79.1±2.2	78.6±2.7
CAS, *n* (%)				
Left-sided CAS				
Mild (≤29%)	580 (88)	–	–	–
Moderate (30–69%)	37 (6)	–	–	–
Severe (≥70%)	37 (6)	–	–	–
Right-sided CAS		–	–	–
Mild (≤29%)	576 (88)	–	–	–
Moderate (30–69%)	35 (5)	–	–	–
Severe (≥70%)	43 (7)	–	–	–

Characteristics are presented as mean ± SD, *n* (%), or %. ICV, intracranial volume; WMH, white matter hyperintensity; CAS, carotid artery stenosis. [a] Median (10th percentile, 90th percentile). [b] Including large infarcts, lacunes, cerebellar infarcts, and brain stem infarct.

Results

Baseline characteristic of the study sample (*n* = 654, 57 ± 10 years, 81% male) and stratified according to the highest degree of CAS are shown in Table 1. At baseline, the mean total brain volume of the study sample was 79.4 ± 2.6% ICV. The mean right hemispheric volume was 79.9 ± 2.6% ICV, whereas the mean left hemispheric volume was 78.8 ± 2.7% ICV. Severe CAS was present in 64 patients (left-sided CAS: 37 [6%], right-sided CAS: 43 [7%]) (Table 1). Patients with moderate or severe CAS were on average older, had a worse cardiovascular profile, and showed more infarcts and a greater WMH volume on MRI compared to patients with mild CAS (Table 1). The mean decrease of total brain volume was 0.97% ICV, of left hemispheric brain volume 1.15% ICV, and of right hemispheric brain volume 0.82% ICV over 3.9 years of follow-up for the study sample.

Sidedness of CAS and Brain Volume Changes

Compared to mild right-sided CAS, moderate right-sided CAS was associated with a greater decrease in total brain volume (B = −0.20% ICV, 95% CI: −0.55 to −0.14), left hemispheric volume (B = −0.20% ICV, 95% CI: −0.58 to 0.18) and, more strongly, in right hemispheric volume (B = −0.37% ICV, 95% CI: −0.76 to 0.02), although these estimates did not reach statistical significance (Table 2). Stronger associations, but in a similar pattern, were ob-

Table 2. Associations between degrees of CAS according to the sidedness and changes in total and hemispheric brain volumes after a median of 3.9 years of follow-up compared to mild (≤29%) stenosis on the same side

	Change in total brain volume (% ICV)		Change in brain volume left hemisphere (% ICV)		Change in brain volume right hemisphere (% ICV)	
	B	95% CI	B	95% CI	B	95% CI
Left-sided CAS						
Moderate (30–69%)						
Model 1	0.22	−0.11 to 0.55	0.32	−0.06 to 0.69	0.21	−0.16 to 0.59
Model 2	0.27	−0.07 to 0.61	0.32	−0.05 to 0.70	0.22	−0.16 to 0.60
Severe (≥70%)						
Model 1	−0.14	−0.50 to 0.22	−0.32	−0.71 to 0.06	0.09	−0.30 to 0.49
Model 2	0.03	−0.33 to 0.40	−0.16	−0.55 to 0.23	0.27	−0.13 to 0.67
Right-sided CAS						
Moderate (30–69%)						
Model 1	−0.20	−0.55 to 0.14	−0.20	−0.58 to 0.18	−0.37	−0.76 to 0.02
Model 2	−0.30	−0.65 to 0.05	−0.22	−0.60 to 0.16	−0.38	−0.77 to 0.01
Severe (≥70%)						
Model 1	−0.69	−1.02 to −0.37*	−0.49	−0.86 to −0.13*	−0.90	−1.27 to −0.54*
Model 2	−0.59	−0.93 to −0.25*	−0.36	−0.72 to 0.00	−0.78	−1.15 to −0.41*

Model 1: Adjusted for age, sex, and baseline brain volumes. Model 2: model 1 with adjustment for hypertension, diabetes mellitus, BMI, smoking pack years, alcohol use, number of infarcts on baseline and follow-up MRI, and white matter hyperintensity volume on baseline and follow-up MRI. ICV, intracranial volume; CI, confidence interval; CAS, carotid artery stenosis. * $p < 0.05$.

served for severe right-sided CAS in relation to change in total brain volume (B = −0.69% ICV, 95% CI: −1.02 to −0.37), left hemispheric volume (B = −0.49% ICV, 95% CI: −0.86 to −0.13), and right hemispheric volume (B = −0.90% ICV, 95% CI: −1.27 to −0.54). Estimates slightly attenuated after adjusting for cerebrovascular risk factors and the number of infarcts and WMH volume on baseline and follow-up MRI (Table 2).

For left-sided CAS, a severe stenosis was associated with a greater decrease in volume of the left hemisphere (B = −0.32% ICV, 95% CI: −0.71 to 0.06); however, this estimate did not reach statistical significance and attenuated after additionally adjusting for the abovementioned covariates (Table 2). No associations were observed between degrees of left-sided CAS and change in total or right hemispheric volumes (Table 2). Repeating the analyses after exclusion of patients with large infarcts showed a similar pattern (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000526261), with severe right-sided CAS being significantly associated with a greater decrease in brain volumes compared to mild right-sided CAS, most profoundly of the right hemispheric volume (B = −1.19% ICV, 95% CI: −1.68 to −0.69).

Unilateral and Bilateral Severe CAS and Brain Volume Changes

Consistent with the previous analysis, a severe unilateral right-sided CAS was associated with a greater decrease in total brain volume (B = −0.72% ICV, 95% CI: −1.09 to −0.35) and more profoundly in the right hemispheric volume (B = −0.97% ICV, 95% CI: −1.39 to −0.55), compared to mild-to-moderate CAS on both sides. These estimates attenuated but remained significant after adjusting for cerebrovascular risk factors, number of infarcts, and WMH volume on baseline and follow-up MRI (Table 3). A severe unilateral right-sided CAS was also associated with a greater decrease in the left hemispheric volume; however, this relationship lost significance after adjusting for the abovementioned covariates (B = −0.27% ICV, 95% CI: −0.69 to 0.15; Table 3).

Compared to mild-to-moderate CAS at both sides, a severe unilateral left-sided CAS was associated with a greater decrease in volume of the left hemisphere (B = −0.41% ICV, 95% CI: −0.88 to 0.04); however, this relationship did not reach statistical significance and attenuated after adjusting for the abovementioned covariates (Table 3). No significant associations were observed between a severe unilateral left-sided CAS and decrease in total and right hemispheric brain volumes (Table 3).

Table 3. Associations between sidedness of ≥70% CAS and changes in total and hemispheric brain volumes after a median of 3.9 years of follow-up compared to <70% stenosis at both sides

	Change in total brain volume (% ICV)		Change in brain volume left hemisphere (% ICV)		Change in brain volume right hemisphere (% ICV)	
	B	95% CI	B	95% CI	B	95% CI
Severe (≥70%) unilateral left-sided CAS						
Model 1	−0.31	−0.73 to 0.11	−0.41	−0.88 to 0.04	−0.18	−0.64 to 0.29
Model 2	−0.10	−0.53 to 0.32	−0.20	−0.66 to 0.26	0.05	−0.42 to 0.52
Severe (≥70%) unilateral right-sided CAS						
Model 1	−0.72	−1.09 to −0.35*	−0.45	−0.86 to −0.04*	−0.97	−1.39 to −0.55*
Model 2	−0.56	−0.95 to −0.17*	−0.27	−0.69 to 0.15	−0.80	−1.22 to −0.37*
Severe (≥70%) bilateral CAS						
Model 1	−0.72	−1.20 to −0.25*	−0.81	−1.34 to −0.28*	−0.64	−1.17 to −0.10*
Model 2	−0.54	−1.04 to −0.05*	−0.60	−1.13 to −0.07*	−0.42	−0.96 to 0.12

Model 1: Adjusted for age, sex, and baseline brain volumes. Model 2: model 1 with adjustment for hypertension, diabetes mellitus, body mass index, smoking pack years, alcohol use, number of infarcts on baseline and follow-up MRI, and white matter hyperintensity volume on baseline and follow-up MRI. Number of patients with <70% CAS at both sides (reference): 590 (91%), ≥70% unilateral left-sided CAS: 21 (3%), ≥70% unilateral right-sided CAS: 27 (4%), and ≥70% bilateral CAS: 16 (2%). ICV, intracranial volume; CI, confidence interval;. CAS, carotid artery stenosis. * $p < 0.05$.

Severe bilateral CAS, compared to mild-to-moderate CAS at both sides, was significantly associated with a greater decrease in total brain volume (B = −0.72% ICV, 95% CI: −1.20 to −0.25), right hemispheric volume (B = −0.64% ICV, 95% CI: −1.17 to −0.10), and more profoundly in left hemispheric volume (B = −0.81% ICV, 95% CI: −1.34 to −0.28). These estimates slightly attenuated after additionally adjusting for the abovementioned covariates (Table 3).

Supplementary Analysis

Change in the right hemispheric brain volume differed significantly among degrees of right-sided CAS (ANCOVA $p = 0.002$). Consistent with the primary analysis, moderate and severe right-sided CAS were associated with a greater decrease in right hemispheric volume (mean difference −0.29% ICV, 95% CI: −0.66 to 0.08; −0.74% ICV, 95% CI: −1.18 to −0.30, respectively) compared to mild right-sided CAS, adjusting for demographics, cerebrovascular risk factors, and number of infarcts and WMH volume in the right hemisphere on baseline and follow-up MRI (online suppl. Table 2).

Change in left hemispheric brain volume did not differ significantly among degrees of left-sided CAS (ANCOVA $p = 0.36$). Similarly, change in left hemispheric brain volume did not differ between degrees of right-sided CAS (ANCOVA $p = 0.19$), and change in right hemispheric brain volume did not differ significantly between degrees of left-sided CAS (ANCOVA $p = 0.88$).

Discussion

In this cohort of patients with manifest arterial disease, we found that severe right-sided CAS was associated with a greater decrease in right hemispheric brain volume over 4 years of follow-up. This relationship was independent of age, sex, cerebrovascular risk factors, and brain infarcts and WMH on baseline and follow-up MRI. A severe left-sided CAS however was not associated with a greater decrease of left hemispheric volume.

As noted in the introductory section, several hypotheses have been formulated that may explain the relation between CAS and progression of brain atrophy. First, brain infarcts may mediate the association between carotid atherosclerosis and brain atrophy [22]. Second, it has been hypothesized that carotid atherosclerosis may represent a proxy marker for cerebrovascular risk factors that result in both carotid atheroma formation and progression of brain atrophy [9]. Third, CAS may lead to reduced cerebral blood flow that, if not adequately compensated for by collateral circulation, may result in greater

brain atrophy [11]. Until now, however, no previous studies to our knowledge reported on the association of CAS with progression of ipsilateral and contralateral brain atrophy. The findings of the present study suggest that severe CAS could represent a risk factor for greater tissue loss of the ipsilateral cerebral hemisphere. Our observation that this relationship was largely independent of brain infarcts and WMH on MRI suggests that mechanisms other than ischemic cerebrovascular disease may underlie the relation between CAS and brain atrophy. Given the novelty of our findings, however, further longitudinal studies in other cohorts are needed to the replicate the present association and to further investigate the exact underlying mechanisms.

As noted previously, a limited number of cross-sectional studies examined the association between CAS and hemispheric brain volumes [12–15]. A study in patients with ≥70% unilateral CAS reported smaller hemispheric brain volumes ipsilateral to the side of CAS but only in patients with moderate or severe WMH [13]. In our study, however, we observed that the association between severe right-sided CAS and right hemispheric atrophy was independent of WMH volume on baseline and follow-up MRI. In two studies comparing regional brain volumes between patients with ≥70% unilateral CAS and healthy controls, it was found that patients with ≥70% CAS showed smaller cortical gray matter volumes ipsilateral to the side of stenosis [14, 15]. Similarly, a study comparing cortical thickness in patients with ≥80% unilateral CAS reported smaller cortical gray matter volumes on the side of stenosis [12].

Our study has several limitations. First, we observed that some estimates, in particular those reflecting change between mild and moderate left-sided CAS, were positive (i.e., suggesting an increase in brain volume over time). Although none of these estimates were statistically significant, an underlying technical measurement error cannot be excluded. Second, the present study had a relatively short follow-up period and a relatively small number of patients with a severe CAS, which may have led to reduced statistical power to detect small differences in brain volume change. Third, we did not adjust the analyses for multiple comparisons. Fourth, the volumetric technique that we used did not allow us to measure region-specific brain volume changes. We therefore could not determine whether brain atrophy was due to volume loss of the gray matter, white matter or both.

Strengths of our study are the longitudinal design, the use of a large cohort of patients with varying degrees of CAS, and volumetric assessment of total and hemispheric brain volumes. In addition, the data on cardiovascular risk factors and cerebrovascular lesions allowed us to determine whether the association between CAS and ipsilateral hemispheric brain atrophy was independent of potential confounders.

In conclusion, our findings indicate that severe (≥70%) CAS could represent a risk factor for greater ipsilateral brain volume loss in patients with manifest arterial disease, independent of cerebrovascular risk factors, brain infarcts or WMH on MRI. Further longitudinal studies in other cohorts are needed to confirm this novel finding.

Acknowledgments

We gratefully acknowledge the contribution of the research nurses: R. van Petersen (data manager); B. van Dinther (study manager) and the members of the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease-study group: F.W. Asselbergs and H.M. Nathoe, Department of Cardiology; G.J. de Borst, Department of Vascular Surgery; M.L. Bots and M.I. Geerlings, Julius Center for Health Sciences and Primary Care; M.H. Emmelot, Department of Geriatrics; P.A. de Jong and T. Leiner, Department of Radiology; A.T. Lely, Department of Obstetrics/Gynaecology; N.P. van der Kaaij, Department of Cardiothoracic Surgery; L.J. Kappelle and Y. Ruigrok, Department of Neurology; M.C. Verhaar, Department of Nephrology: F.L.J. Visseren (chair) and J. Westerink, Department of Vascular Medicine, University Medical Center Utrecht and Utrecht University.

Statement of Ethics

The SMART-MR study was approved by the Medical Ethics Committee of the University Medical Center Utrecht, approval number 96/048. Written informed consent was obtained from all patients according to the guidelines of the Declaration of Helsinki of 1975.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

Funding Sources

Funding for this paper was received as part of a grant from the Netherlands Organization for Scientific Research-Medical Sciences (NWO-MW: project No. 904-65-095). This funding source had no role in the design; data collection, data analysis, and data interpretation of the study; or writing of the report. We also gratefully acknowledge the funding from the European Research Council under the European Union's Horizon 2020 Programme (H2020)/ERC grant agreement No. 637024 and No. 66681 (SVDs@target).

Author Contributions

Rashid Ghaznawi, MD, MSc: literature search, figures, tables, data collection, data analysis, data interpretation, and writing. Ina Rissanen, MD, PhD and Jeroen de Bresser, MD, PhD: data interpretation and critical review of the manuscript. Hugo J. Kuijf, PhD: MR image processing and analysis, critically reviewed the manuscript. Nicolaas P.A. Zuithoff, PhD: data analysis and critical review the manuscript. Jeroen Hendrikse, MD, PhD: critically reviewed the manuscript. Mirjam I. Geerlings, PhD: study design, data interpretation, and critical review of the manuscript

Data Availability Statement

For use of anonymized data, a reasonable request has to be made in writing to the UCC-SMART study group, and the third party has to sign a confidentiality agreement.

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