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Intracranial Atherosclerotic Burden on 7T MRI is Associated with Markers of Extracranial Atherosclerosis— the SMART-MR study

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Abstract

Background and Purpose—Intracranial atherosclerosis (ICAS), a major risk factor for ischemic stroke, is thought to have different atherogenic mechanisms than extracranial atherosclerosis. Studies investigating their relationship *in vivo* are sparse and report inconsistent results. We studied the relationship between ICAS and extracranial atherosclerosis in a cohort of patients with a history of vascular disease.

Materials and Methods—Within the SMART-MR study cross-sectional analyses were performed in 130 patients (68±9 years) with a history of vascular disease and with assessable 7T intracranial vessel wall–MRI data. ICAS burden was defined as the number of intracranial vessel wall lesions in the Circle of Willis and its major branches. Age- and sex-adjusted unstandardized regression coefficients (*b*) were calculated with ICAS burden as the dependent variable, and ECAS markers as independent variables.

Results—Ninety-six percent of patients had one or more vessel wall lesions, with a mean ICAS burden of 8.5±5.7 lesions. Significant associations were observed between higher ICAS burden and carotid intima-media thickness (*b*=0.53 lesions per +0.1 mm; 95% CI 0.1 to 1.0), 50–100% carotid stenosis vs. no stenosis (*b*=6.6 lesions; 95% CI 2.3 to 10.9), ankle-brachial index < 0.9 vs. >0.9 (*b*=4.9 lesions; 95% CI 1.7 to 8.0) and estimated glomerular filtration rate (*b*=−0.77 lesions per +10 ml/min; 95% CI −1.50 to −0.03). No significant differences in ICAS burden were found between different categories of vascular disease.

Conclusion—ICAS was associated with various extracranial markers of atherosclerosis, not supporting a different etiology.

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Introduction

Intracranial atherosclerosis (ICAS) is a major cause of adverse cerebrovascular events such as ischemic stroke.¹ Furthermore, it is associated with an increased risk of cognitive decline and dementia.² A wide range of prevalence estimates for ICAS have been reported, ranging from 4-51% in asymptomatic populations to 43-70% in ischemic stroke patients.^{3,4}

ICAS is currently seen as the intracranial phenotype of atherosclerosis, a generalized disease that can affect all large arteries. Nonetheless, correlations between intracranial and extracranial atherosclerotic disease in post-mortem studies are modest.⁵ Furthermore, ICAS has a later time of onset, slower rate of progression and different plaque morphology compared to other arterial territories.⁶⁻⁸ As a result, it has been suggested that ICAS might have a different etiology than extracranial disease. Studies investigating the relationship between intracranial and extracranial disease *in vivo* are sparse and often limited to one extracranial vessel bed. Furthermore, all of these studies have used lumenographic imaging methods, which can only assess atherosclerotic stenosis.^{9,10} Therefore, intracranial plaques without stenosis, i.e. due to arterial remodeling, will not be detected, leading to an underestimation of the actual ICAS burden.¹¹

Vessel wall lesions are a novel neuroimaging marker of ICAS which can be assessed using intracranial vessel wall-MRI.¹² Vessel wall-MRI enables visualization of the intracranial arterial walls, allowing a more direct evaluation of ICAS.¹³ Currently, 7 Tesla (7T) is the highest field strength at which vessel wall-MRI has been performed in humans *in vivo*, and has been shown to be superior to lower field strengths in the detection of vessel wall anomalies.¹⁴

In the current study, we investigated in patients with atherosclerotic disease to what extent markers of extracranial atherosclerosis (ECAS) were associated with the burden of ICAS measured by 7T vessel wall-MRI, thereby providing insight into the etiology of ICAS and its relationship with ECAS.

Materials and Methods

Study sample

Data were used from the Second Manifestations of ARterial disease-Magnetic Resonance (SMART-MR) study, a prospective cohort study at our institution with the aim to investigate risk factors and clinical outcomes of MRI neuroimaging markers in patients with arterial disease.¹⁵ In brief, from 2001 through 2005, 1309 patients newly referred to our institution with cerebrovascular disease, peripheral arterial disease, coronary artery disease, or abdominal aortic aneurysm, and without MRI contraindications were enrolled in the SMART-MR study. On a one-day visit to our institution's hospital the participants received a 1.5T MRI of the brain, a physical examination, ankle-brachial index (ABI) assessment, ultrasonography of the carotid arteries, blood and urine sampling, and questionnaires to assess risk factors, medical history, and daily functioning. Follow-up exams of the SMART-MR cohort were performed in 2006-2009, and 2013-2017.

From June 2016 to October 2017, we included 147 patients participating in the second follow-up examination of the SMART-MR study who had intracranial vessel wall-MRI performed as part of a 7T MRI of the brain.¹² A flowchart of the study sample is provided in Supplemental Figure 1. Seventeen patients were excluded from the current study because of artifacts hampering vessel wall-MRI assessment of 1 major segment of the Circle of Willis (CoW; major segments included the distal internal carotid artery and primary branches (M1, A1, P1) of the anterior, middle and posterior cerebral artery), leaving 130 patients for final analysis. For the current study, measurements of extracranial atherosclerosis, and risk factor assessment, including questionnaire data and blood and urine sampling, was performed median 2.3 (range, 0.6 to 8.6) years prior to the 7T MRI.

Comparison of ECAS markers between the excluded patients and the patients for final analysis showed a higher prevalence of 50-100% carotid stenosis in the excluded patients (7.0% vs. 23.5%; $p = 0.04$, χ^2 -test). Also, the excluded patients were older, although this was not statistically significant (70 ± 7 vs. 68 ± 9 years; $p = 0.11$, Student's t-test). Sex distribution did not differ between included and excluded patients (88% vs. 88% male; $p = 0.95$, χ^2 -test).

Vascular risk factors

Information on general vascular risk factors was obtained by questionnaires, physical examination and blood sampling. Height and weight were used to calculate the body mass index (BMI; kg/m²). Systolic blood pressure (SBP; mmHg) and diastolic blood pressure (DBP; mmHg) were measured by averaging three separate measurements with a sphygmomanometer. Hypertension was defined as a SBP of >140 mmHg, a mean DBP of >90 mmHg, or self-reported use of antihypertensive drugs. Diabetes mellitus was defined as fasting serum glucose levels of ≥ 7.0 mmol/L, and/or use of glucose-lowering medication, and/or a known history of diabetes. Patients who did not meet these criteria, but with a fasting plasma glucose level ≥ 7.0 mmol/L at baseline, were considered to have diabetes at baseline if they received treatment with glucose-lowering medication within 1 year after baseline. Hyperlipidemia was defined as a total cholesterol of >5.0 mmol/L, a low-density lipoprotein cholesterol of >3.2 mmol/L, or use of lipid-lowering medication. Metabolic syndrome was determined by the National Cholesterol Education Program Adult Treatment Panel III criteria.¹⁶

Markers of extracranial atherosclerosis

An experienced technician performed carotid ultrasonography with a 10MHz linear-array transducer. Mean carotid intima-media thickness (cIMT) was calculated from six measurements (anterolateral, posterolateral and mediolateral in both common carotid arteries). Extracranial carotid stenosis was ultrasonographically assessed and defined according to standard criteria based on the peak systolic velocity.¹⁷ ABI measurements were conducted by experienced technicians, and were calculated from the highest systolic blood pressure measured at the posterior tibial and dorsal pedal arteries by Doppler and at both brachial arteries by a semiautomatic oscillometric device in supine position. Renal function was assessed using the estimated glomerular filtration rate (eGFR) calculated by the Cockcroft-Gault equation adjusted for body weight and body mass index.¹⁸

Coronary artery disease was defined as a history of myocardial infarction, a history of coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty at inclusion or in the past. Cerebrovascular disease was defined as transient ischemic attack or stroke at inclusion or in the past. Peripheral artery disease was defined as intermittent claudication or rest pain at inclusion, or a history of surgery or angioplasty of the arteries supplying the lower extremities. Abdominal aortic aneurysm (AAA) was defined as presence of an AAA (distal aortic anteroposterior diameter ≥ 3 cm) or previous AAA surgery. Multivascular disease was defined as presence of ≥ 2 of the above defined vascular diseases.

7T MR imaging protocol

A 7T whole-body system (Philips Healthcare, USA) was used with a volume/transmit coil for transmission and a 32-channel receive head coil (Nova Medical, Wilmington, MA, USA). Vessel wall-MRI was performed using a T_1 -weighted Magnetization-Prepared Inversion Recovery Turbo Spin Echo (T_1 -MPIR-TSE) sequence, with the following parameters: FOV 250x250x190 mm³, acquired resolution 0.8x0.8x0.8 mm³ (reconstructed to 0.49x0.49x0.4 mm³), repetition time / inversion time / echo time 3952/1375/37 ms, acquisition time 10:40 minutes (min).¹⁹ In addition, an SWI sequence was performed, with the following parameters: FOV 200x200x120 mm³, acquired resolution 0.5x0.5x0.7mm³ (reconstructed to 0.4x0.4x0.35 mm³), repetition time / echo time 1/ echo time 2, 20/6.9/15.8 ms, flip angle 12 degrees, acquisition time 09:17 min.

Assessment of intracranial atherosclerosis

For the assessment of vessel wall lesions, axial multiplanar reconstructions were calculated from the T_1 -MPIR-TSE sequence (slice thickness 0.8 mm; no slice gap); angulated to the nasion-foramen magnum line. One observer (MHTZ, over 5 years of experience in neuroradiology) assessed all images, blinded to patient characteristics. MHTZ was trained by a senior observer with 8 years of experience in interpreting vessel wall-MRI images (AK), using a practice set of 15 patients from the IVI study²⁰; and a consensus set of 20 patients from the current study. An interobserver agreement of 0.75 (dice similarity coefficient) was obtained, which was regarded as good.

Vessel wall lesions were rated according to the methodology previously published by Lindenholz et al.²¹ A lesion was defined as either a focal or more diffuse thickening of the arterial wall greater than 50%, assessed visually, using the normal contralateral or neighboring arterial wall as reference. Uncertain lesions were verified in multiple planes. After a lesion was identified, it was subsequently classified as eccentric ($\geq 50\%$ wall circumference) or concentric ($>50\%$ wall circumference) and by arterial segment location: internal carotid arteries (C6, C7), middle cerebral arteries (M1, M2), anterior cerebral arteries (A1, A2), posterior communicating arteries, posterior cerebral arteries (P1, P2 and P1-P2 bifurcation), basilar artery and vertebral arteries (V4). One single segment could contain multiple lesions, making the total lesion count theoretically unlimited. Lesions that extended into multiple segments were counted as separate lesions for each involved segment. Furthermore, lesions with eccentric and concentric components, were regarded as separate lesions.

A maximum intensity projection of the SWI was used to assess the course of smaller arteries (M2, A1, P2, PCom). We did not assess luminal stenosis because the SWI quality in our study did not permit accurate measurement, especially of small lesions. Of note, we did not perform a refined MRA because it was logistically not feasible, and at the time of study design, the diagnostic accuracy of MRA in the detection and grading of intracranial stenosis was still relatively low.²²

Statistical analysis

First, characteristics of the study sample were described. Next, the association of ECAS markers with ICAS burden was estimated using linear regression analyses, with the ECAS measure as the independent variable and ICAS burden as the dependent variable. ICAS burden was defined as the total number of intracranial vessel wall lesions. All analyses were adjusted for age and sex. ECAS measures were entered into the model as continuous and/or dichotomous variables. ABI was dichotomized by the clinical cut-off for peripheral artery disease (< 0.9).²³ For eGFR, the clinical threshold for chronic kidney disease (< 60 ml/min) was used. cIMT was categorized into quartiles. Categorization of carotid stenosis was based on the most severe lesion in the bilateral extracranial common or internal carotid arteries. In the analyses of vascular disease, patients with ≥ 2 vascular diseases were categorized as multivascular, making categories mutually exclusive. Patient with only coronary artery disease were used as the reference category. A sensitivity analysis was performed to control for the time interval (in days) between the date of ECAS measurements and date of the 7T MRI.

Statistical analyses were performed using SPSS v. 25.0 for Windows (IBM Corporation, USA).

Results

Table 1 shows the characteristics of the 130 patients. Eighty-eight percent were men and the mean age was 68 ± 9 years. Twenty-five percent had multivascular disease. Although 19% of the population had cerebrovascular disease, in just 9% it was the only disease. A large majority of 65% had a sole history of coronary artery disease. An overview of vascular risk factors can be found in Supplemental Table 1. Of the 130 patients, 96% had ≥ 1 intracranial vessel wall lesion, and a mean ICAS burden of 8.5 ± 5.7 lesions (median 7, range 0-32). Furthermore, in the anterior circulation a mean ICAS burden of 5.3 ± 3.2 lesions (median 4, range 0-14) was found, which was 3.8 ± 3.0 (median 3; range 0-18) for the posterior circulation. More details regarding arterial or segmental distribution can be found in our prior publication.¹² Examples of vessel wall lesions in a 76-year-old male patient are shown in Figure 1.

Age and sex-adjusted linear regression analyses showed that cIMT was significantly associated with a higher ICAS burden ($b = 0.53$ lesions per $+0.1$ mm; 95% CI 0.06 to 0.98). Analysis of cIMT in quartiles indicated a threshold effect, with only Q4 suggesting an association with ICAS burden. However, since the 95% confidence interval contained 0.00, it was not statistically significant (Table 2).

Carotid stenosis of 1-49% was found to be associated with a higher ICAS burden, when compared to no carotid stenosis ($b = 2.5$ lesions for presence of 1-49% carotid stenosis; 95% CI 0.08 to 4.89). Carotid stenosis of 50-100% was also associated with a higher ICAS burden ($b = 6.6$ lesions for presence of 50-100% carotid stenosis; 95% CI 2.34 to 10.93) (Table 2).

ABI did not show a significant association with ICAS burden when analyzed as a continuous variable. However, when dichotomized by 0.9, the clinical threshold for peripheral artery disease, a significant association with a higher ICAS burden was found, when compared to $ABI > 0.9$ ($b = 4.9$ lesions for presence of $ABI > 0.9$; 95% CI 1.74 to 7.99) (Table 3).

eGFR was significantly associated with ICAS burden when analyzed as a continuous variable ($b = -0.77$ lesions per +10ml/min; 95% CI -1.50 to -0.03). Furthermore, renal dysfunction ($eGFR < 60$ ml/min) was also associated with a higher ICAS burden, when compared to $eGFR \geq 60$ ml/min ($b = 3.2$ lesions; 95% CI 0.45 to 5.91) (Table 4).

No significant differences in ICAS burden were observed between cerebrovascular, peripheral artery or multivascular disease groups, when compared to only coronary heart disease (Table 5).

As a sensitivity analysis, all models were additionally adjusted for the time interval between the date of ECAS measurement and date of 7T MRI. Supplemental Table 2 to 5 show the results of these analyses. Although the estimates slightly differed compared with the estimates without time interval adjustment, this did not lead to a change in statistical significance.

Discussion

This study examined the association between the ICAS measured with intracranial vessel wall-MRI at 7T and several markers of ECAS, in a cohort of patients with a history of vascular disease. Our results show that increasing cIMT, presence of extracranial carotid stenosis, $ABI < 0.9$, and decreasing eGFR were all associated with a higher ICAS burden, defined as the number of intracranial vessel wall lesions. No differences in ICAS burden were observed between presence of peripheral, cerebrovascular or multivascular disease when compared to coronary heart disease, the main disease in our population.

Cerebral arteries are thought to have a different response to vascular risk factors than extracranial arteries, and the relationship between ECAS and ICAS may therefore be relatively weak or absent.^{8,24,25} However, studies investigating this hypothesis *in vivo* have been based on the detection of arterial calcification or hemodynamically-significant stenosis, both related to a more advanced stage of atherosclerotic disease. Furthermore, the heterogeneous etiology of arterial calcification and localization restricted to the proximal cerebral arteries might obscure detection of an association. Vessel wall-MRI directly visualizes the pathological vessel wall, enabling more accurate measurement of the ICAS burden.^{11,12,26}

A very high frequency of ICAS was found in the current population¹², especially when compared to other neuroimaging studies. This is in line with early post-mortem studies, which reported frequencies approaching 100% in older age.^{27,28} Furthermore, the distribution of vessel wall lesions, which we recently reported on¹², was also in line with the distribution of plaques in those post-mortem studies: particularly the increased involvement of the larger cerebral arteries compared to the smaller ones. These findings suggest that vessel wall-MRI at 7T allows for a more accurate approximation of the ICAS burden, compared to other neuroimaging methods. However, more studies in different populations, in regard to age, sex and disease status are needed to confirm this.

cIMT is an established marker of generalized atherosclerosis²⁹, although studies on its association with ICAS are limited. Our results are in line with a post-mortem study, which reported an association of cIMT with the intima-media ratio of the cerebral vasculature.³⁰ Furthermore, a longitudinal study in patients with intracranial stenosis found that patients with progressive stenosis on MRA had a larger cIMT compared to those without progression, although this difference was not statistically significant.³¹

Extracranial carotid disease and ICAS are often assessed separately, likely because their prevalence varies between different ethnic populations.³² Notably, ICAS is thought to be most prevalent in populations of African and Asian descent, where it is a major cause of ischemic stroke, whereas in whites it was thought to be less prevalent, and a minor cause of ischemic stroke. However, recent studies have shown that the prevalence and importance of ICAS in whites may have been underestimated.^{12,33,34} Our results show a strong association between extracranial carotid stenosis and ICAS, a finding which in concordance with a recent Asian study.³⁵ Hence, our findings question the current segregation, and suggest that they should not be assessed separately.

Low ABI has been associated with hemodynamically significant intracranial stenosis in community-based and ischemic stroke cohorts.³⁶⁻³⁸ Our results are in line with these findings, and also show that low ABI is associated with the more continuous spectrum of disease measured by ICAS burden, and not just hemodynamic stenosis.

Renal dysfunction is an independent risk factor for cardiovascular disease³⁹, and has been linked to ischemic stroke, cerebral small vessel disease, and medial arterial calcification.^{40,41} A recent scientific abstract reported an association between renal dysfunction and intracranial arterial wall thickening, which is in concordance with our results.⁴²

No significant differences in ICAS burden were observed in patients with a history of cerebrovascular, peripheral artery, or multivascular disease when compared to coronary heart disease. An association with cerebrovascular disease might have been expected, since ICAS is a major cause of ischemic stroke.¹ In our prior study, we did find an association between ICAS burden and presence of ischemic infarcts.¹² However, in the current analyses the outcome was clinical stroke and/or TIA, which is an overlapping but different entity. Furthermore, small sample sizes of all categories, except for coronary heart disease, may also have prevented observation of significant relationships. Notably, earlier studies from our

group in acute ischemic stroke patients and controls also did not find an association between the number of vessel wall lesions and ischemic stroke.⁴³

A main strength is the use of vessel wall–MRI at 7T, one of the most accurate methods to assess intracranial atherosclerosis *in vivo*, which enabled visualization of atherosclerosis beyond stenosis. Furthermore, it provided a large coverage area which allowed assessment of CoW branches over a great length. Moreover, the increased contrast-to-noise ratio facilitated a more reliable identification of lesions than is possible at lower field strengths. A last strength is the various measures of ECAS which allowed for an integrated assessment of multiple arterial beds within the same patient.

Several limitations also need to be addressed. First, there is a paucity of radio-pathologic studies on vessel wall lesions, making it possible that not all lesions are atherosclerotic. Second, our sample size, although large compared to previous 7T studies, is still relatively small compared to other epidemiologic studies. Third, our cohort consisted of patients with a history of vascular disease with the majority being male, which may limit generalization of our results to other populations. Fourth, we used a basic uniparametric score to quantify ICAS burden, which does not account for other quantitative features, such as wall thickness. However, accurate quantitative assessment of lesions, especially the very small lesions visible at 7T, is limited at current spatial resolutions.⁴⁴ As a result, grading lesions is a qualitative process, and inherently less objective than quantitative grading. Nonetheless, increased objectiveness can be obtained by training, experience and attaining good reproducibility compared with senior observers, as was done in the current study. Furthermore, we did not assess luminal stenosis, because we did not include a refined MRA in the protocol. As advancements to current vessel wall sequences are starting to enable more accurate measurements, development of multiparametric scoring systems (e.g. the Gensini score for coronary artery disease), taking into account lesion location, stenosis grade, different geometric characteristics (e.g. remodeling index), signal intensity on various weightings, and contrast-enhanced MRI, may enable a more versatile way to study the relation between ICAS, ECAS and clinical outcomes. Lastly, due to logistic reasons the ECAS assessment and the 7T MRI were not performed on the same day and in a number of participants the time interval was quite large. As ECAS markers could have changed during this interval this may have influenced the observed associations. However, most estimates differed only slightly, and did not lead to different conclusions.

Conclusion

In summary, in patients with a history of various manifestations of vascular disease, ICAS burden, defined as the number of intracranial vessel wall lesions, was associated with atherosclerotic disease in all extracranial arterial beds, not supporting a different etiology. Our results may be used to further elucidate the etiology of ICAS, and may be of interest to clinical studies looking for effective ways to select patients at risk of ICAS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ICAS	intracranial atherosclerosis
7T	7 Tesla
ECAS	extracranial atherosclerosis
SMART-MR	Second Manifestations of ARterial disease-Magnetic Resonance
ABI	ankle-brachial index
BMI	body mass index
SBP	systolic blood pressure
DBP	diastolic blood pressure
cIMT	carotid intima-media thickness
eGFR	estimated glomerular filtration rate
AAA	abdominal aortic aneurysm

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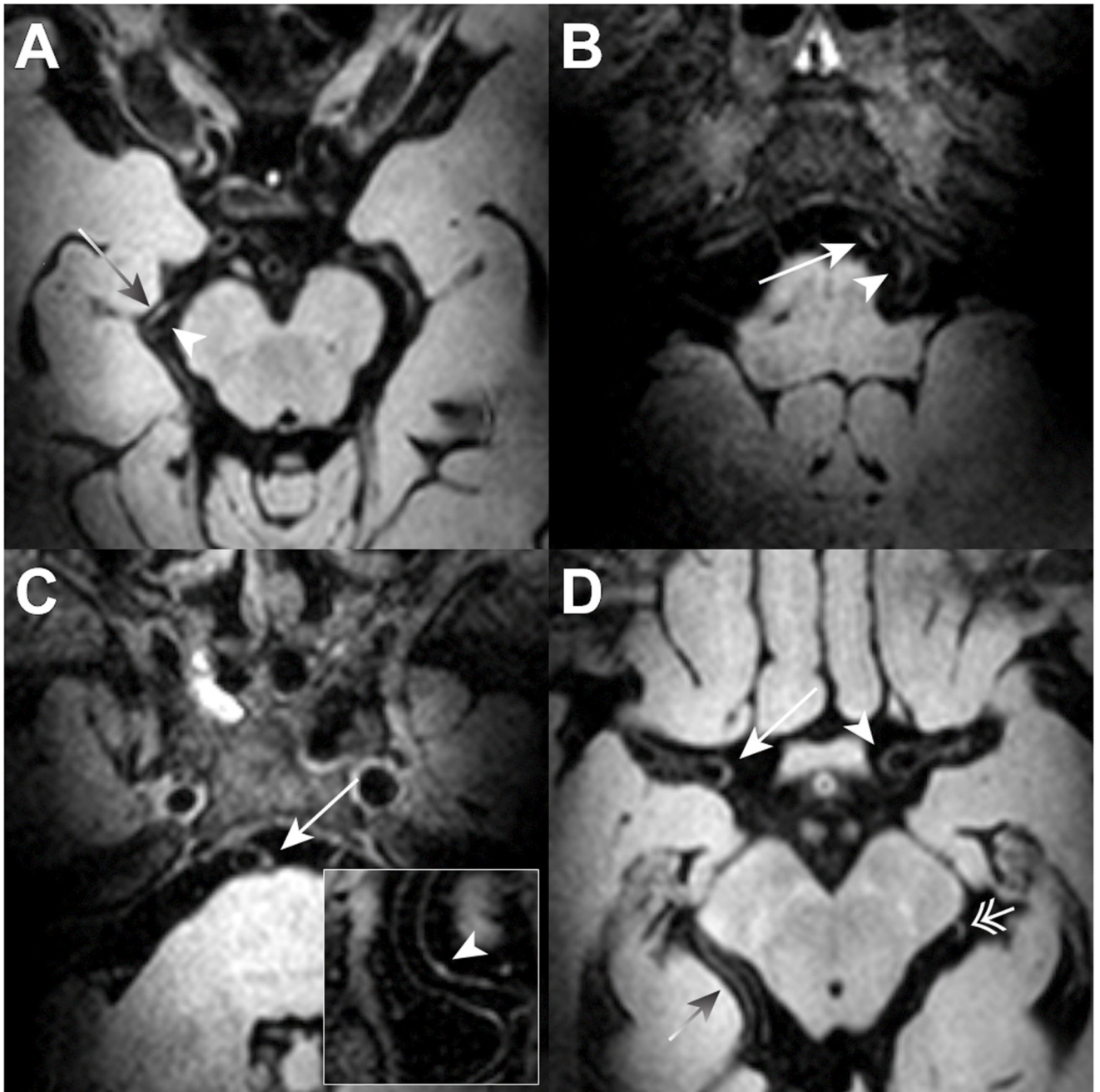


Figure 1.

Examples of intracranial vessel wall lesions on vessel wall-MRI in a 76-year-old male patient with a history of coronary artery disease. A detailed description of rating criteria can be found in the methods section. A) Lesion in lateral wall of right P2 segment (arrow) versus non-discernable normal neighboring medial wall (arrowhead). B) Lesion in right vertebral (arrow) and left vertebral (arrowhead) artery. C) Lesion in proximal basilar artery (arrow), with coronal orientation shown in enclosed panel (arrowhead). D) Lesion in C7 segment of the right ICA (arrow), when compared to normal-appearing contralateral C7 segment

(arrowhead) and proximal right M1 segment. Furthermore, note the long lesion in the distal half of the right P2 segment (grey arrow), and focal lesion in the left P2 segment (dual arrow).

Table 1
Markers of extracranial atherosclerosis (N=130).

Age (years)	68±9
Male	88%
Carotid IMT (mm)	0.84±0.22
Carotid stenosis ^a	
No stenosis	23%
1-49 stenosis%	70%
50-100% stenosis ^b	7%
Ankle-brachial index	
ABI	1.09±0.18
ABI 0.9	11%
Renal function	
eGFR (ml/min)	72.8±17.3
eGFR < 60 ml/min	21%
History of vascular disease ^c	
Cerebrovascular disease	9%
Coronary artery disease	65%
Peripheral artery disease	9%
Multivascular disease	17%

Values are presented as mean±SD for continuous variables and percentages for dichotomous variable.

^aCategories are mutually exclusive. Patients were categorized according to most severe stenosis grade.

^bIncludes 4 patients with 1 carotid artery occlusion(s).

^cCategories are mutually exclusive. Multivascular category consisted of 22 patients with a history of 2 vascular diseases: 95% had coronary artery disease, 60% cerebrovascular disease, 60% peripheral artery disease, and 14% abdominal aortic aneurysm.

Table 2
Association between carotid atherosclerosis and ICAS burden.

	ICAS burden, <i>b</i> (95% CI)
cIMT, per +0.1 mm	0.53 (0.06 to 0.98)
cIMT quartiles	
Quartile 1	0 (reference)
Quartile 2	0.62 (-2.31 to 3.55)
Quartile 3	0.40 (-2.61 to 3.41)
Quartile 4	2.89 (-0.01 to 5.80)
Carotid stenosis	
No stenosis	0 (reference)
1-49% stenosis	2.48 (0.08 to 4.89)
50-100% stenosis	6.62 (2.34 to 10.93)

b values are unstandardized linear regression coefficients adjusted for age and sex.

Table 3
Association between ABI and ICAS burden.

	ICAS burden, <i>b</i> (95% CI)
ABI, per +0.1 in ratio	-0.36 (-0.91 to 0.19)
ABI > 0.9	0 (reference)
ABI 0.9	4.86 (1.74 to 7.99)

b values are unstandardized linear regression coefficients adjusted for age and sex.

Table 4
Association between renal function and ICAS burden.

	ICAS burden, <i>b</i> (95% CI)
eGFR, per +10 ml/min	-0.77 (-1.50 to -0.03)
eGFR ≥ 60 ml/min	0 (reference)
eGFR < 60 ml/min	3.18 (0.45 to 5.91)

b values are unstandardized linear regression coefficients adjusted for age and sex.

Table 5
Association between history of vascular disease and ICAS burden.

	ICAS burden, <i>b</i> (95% CI)
Coronary artery disease	0 (reference)
Peripheral artery disease	-0.22 (-3.99 to 3.55)
Cerebrovascular disease	0.01 (-3.46 to 3.48)
Multivascular disease	2.08 (-0.60 to 4.76)

b values are unstandardized linear regression coefficients adjusted for age and sex.
Categories are mutually exclusive.