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BRIEF COMMUNICATION

Sex Differences in Intracranial Atherosclerosis in Patients With Hypertension With Acute Ischemic Stroke

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BACKGROUND: Studies suggest the presence of sex differences in hypertension prevalence and its associated outcomes in atherosclerosis and stroke. We hypothesized a higher intracranial atherosclerosis burden among men with hypertension and acute ischemic stroke compared with women.

METHODS AND RESULTS: A multicenter retrospective study was performed from a prospective database identifying patients with hypertension presenting with intracranial atherosclerosis-related acute ischemic stroke and imaged with intracranial vessel wall magnetic resonance imaging. Proximal and distal plaques on vessel wall magnetic resonance imaging were scored. Negative binomial models assessed the associations between plaque-count and sex and the interaction between sex and treatment. Covariates were selected by a least absolute shrinkage and selection operator procedure. Sixty-one patients (n=42 men) were included. There were no significant differences in demographic or cardiovascular risk factors except for smoking history (P=0.002). Adjusted total and proximal plaque counts for men were 1.6 (95% CI, 1.2–2.1; P<0.01) and 1.4 (95% CI, 1.0–1.9; P=0.03) times as high as women, respectively. Female sex was more protective for proximal plaque if treated for hypertension. The risk ratio of men versus women was 1.5 (95% CI, 1.0–2.1) for treated patients. The risk ratio of men versus women was 0.7 (95% CI, 0.4–1.3) for untreated patients. The relative difference between these 2 risk ratios was 2.0 (95% CI, 1.1–3.9), which was statistically significant from the interaction test, P=0.04.

CONCLUSIONS: Men with hypertension with acute ischemic stroke have significantly higher total and proximal plaque burdens than women. Women with hypertension on anti-hypertensive medication showed a greater reduction in proximal plaque burden than men. Further confirmation with a longitudinal cohort study is needed and may help evaluate whether different treatment guidelines for managing hypertension by sex can help reduce intracranial atherosclerosis burden and ultimately acute ischemic stroke risk.

Key Words: atherosclerosis ■ hypertension ■ sex-differences ■ vessel wall MR

Hypertension affects ≈1.39 billion adults globally.[1] Hypertension is associated with the development and severity of intracranial atherosclerosis (ICAS), which in turn is one of the leading causes of acute ischemic stroke (AIS).[2,3] ICAS can progress silently for years in patients before clinical disease becomes apparent. Therefore, it is conceivable that hypertension in early-to-mid-life directly influences the prevalence and severity of ICAS in late life and the risk of AIS. As the most common modifiable cardiovascular risk factor, preventing and controlling hypertension may be an impactful treatment strategy to ultimately reduce AIS risk.

Although hypertension is more common in men at younger ages, prevalence rates in women exceed

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those in men by the seventh decade.[4] These findings may be attributable to both sex-specific survival bias and a more rapid age-related increase in blood pressure experienced by women. Whether these prevalence rate differences in hypertension between the sexes impact ICAS burden is unknown. Previous literature used lumen-based imaging techniques such as computed tomography angiography with stenosis or calcifications as a proxy for ICAS.[2,3] However, intracranial vessel wall magnetic resonance imaging (VW-MRI) enables us to directly visualize intracranial plaques and is thus more sensitive for detecting ICAS.[4,5] With this novel imaging technology, in a cohort of patients with hypertension with ICAS-related AIS and imaged with VW-MRI, we hypothesized a higher ICAS burden in men than women. As ICAS is one of the leading causes of AIS, understanding sex-differences in hypertension and ICAS burden may provide insight into personalized strategies to reduce the risk of AIS.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study was approved by each site's institutional review committee and informed consent was waived because of the retrospective nature of the study (Pro00055925). From a prospectively designed multicenter study identifying patients with AIS confirmed by diffusion weighted imaging, imaged with VW-MRI within 8 weeks of the event, without contraindications to magnetic resonance imaging and exclusion of cardiac or aortic stroke etiologies, a retrospective review was performed from October 2015 to March 2021 with the following inclusion criteria: AIS attributable to ICAS as determined by a neurologist; preadmission diagnosis of hypertension established by the treating physician; <50% cervical carotid stenosis; and age >18 years. Exclusion criteria included: history of endovascular intervention; intracranial proximal/large vessel occlusion confirmed by MR angiography or computed tomography angiography; and poor VW-MRI image quality as assessed by a neuroradiologist. Patients with a preadmission history of hypertension and on an anti-hypertensive medication were defined as being treated. Collected demographic, clinical, and laboratory data included age, sex, race, medical diagnoses and medications of hypertension, diabetes, dyslipidemia, history of stroke/transient ischemic attack and coronary artery disease prior to admission, history of smoking, body mass index, hemoglobin A1c, total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein.

Patients were scanned on a 3.0-Tesla MR system (MAGNETOM Prisma, Verio, Skyra, Siemens, Erlangen, Germany) with a 64-channel head-neck coil (Prisma), 32-channel head coil (Verio), or 20-channel head-neck coil (Skyra). VW-MRI was performed using a recently proposed cerebrospinal fluid-suppressed whole-brain 3-dimensional T1-weighted variable-flip-angle turbo spin-echo sequence.[6,7] Imaging parameters for the vessel wall pulse sequence include the following: voxel size, isotropic 0.53 or 0.55 mm; repetition time, 900 ms; echo time, 15 ms; field of view, 170×170 or 170×210 mm^2; 224 or 240 slices; scan time, 8 minutes. Post-contrast VW-MRI was acquired 5 minutes after the injection of a single dose (0.1 mmol/kg of body weight) of contrast agent (Magnevist from Schering or Gadavist from Bayer HealthCare Pharmaceuticals).

Plaques were defined as eccentric wall thickening on the orthogonal view with or without luminal stenosis[8] and identified by a neuroradiologist (J.X., 5 years of experience) masked to clinical data and side of stroke. Each plaque was categorized as proximal (up to A1/M1/P1 segments of the anterior/middle/posterior cerebral arteries) or distal (A2 anterior cerebral arteries, P2 posterior cerebral arteries, and M2-M3 middle cerebral arteries). The sum of proximal and distal plaque counts was considered total plaque burden. A culprit plaque was defined as the most stenotic plaque in the vessel supplying the ischemic territory and identified by consensus between a neuroradiologist (J.X.) and a vascular neurologist (K.S., >10 years of experience). Commercial software (Osirix MD; Pixmeo SARL, Bernex, Switzerland) was used for image analysis.

Data distribution was examined using histograms. Data are reported as means and SDs, medians, and interquartile ranges or frequency and percentages. Given a skewed distribution of plaque counts, we started with a Poisson regression with log link function for the model fitting. The overdispersion assumption was investigated through the goodness-of-fit test using Pearson Chi-square/degrees of freedom ratio. When this ratio was larger than 1 (1.5 was considered the threshold), a negative binomial distribution was used. Using the log link function for modeling, the reported associations were interpreted as relative risks, ie, the ratio of plaque count between men and women. The multiplicative interaction term between sex and treatment was interpreted as whether the ratio of plaque count between the sexes differed by treatment. Covariates were selected by a least absolute shrinkage and selection operator procedure to perform adjusted analyses. $P \leq 0.05$ was considered statistically significant. SAS 9.4 was used for all data analyses.

RESULTS

From 115 patients, 46 were excluded because of alternate stroke etiologies, 5 because of poor VW-MRI image quality and 3 because of a large vessel occlusion. Sixty-one (n=42, men) patients were included in the analysis. There

were no significant sex differences in age, demographic characteristics, or cardiovascular risk factors except for smoking history (*P*=0.002) (Table S1). The culprit plaque causing ischemia in men and women with hypertension was proximal in 95% and 92% of cases, respectively.

The adjusted total and proximal plaque counts for men with hypertension was 1.6 (95% CI, 1.2–2.1; *P*<0.01) and 1.4 (95% CI, 1.0–1.9; *P*=0.03) times as high as women, respectively. The adjusted distal plaque count for men was also higher than women although not statistically significant (count ratio: 1.5; 95% CI, 0.9–2.6; *P*=0.12) (Table 1).

As shown in Table 2, female sex was more protective for proximal plaque burden if treated for hypertension. The risk ratio of men versus women was 1.5 (95% CI, 1.0–2.1) for treated patients. However, if not treated, female sex was a risk for proximal plaque burden. The risk ratio of men versus women was 0.7 (95% CI, 0.4–1.3) for untreated patients. The relative difference between these 2 risk ratios was 2.0 (95% CI, 1.1–3.9), which was statistically significant from the interaction test, *P*=0.04. A similar trend emerged for total plaque burden although not statistically significant. Figure shows VW-MRI examples of ICAS.

DISCUSSION

The results show among patients with hypertension and AIS, men have significantly higher total and proximal plaque burdens compared with women. A sex-effect with anti-hypertensive treatment was also present showing a significantly greater reduction in proximal plaque burden among women with AIS treated for hypertension compared with men. Given culprit plaques were proximal in location in >90% of the cases in both sexes, understanding how to reduce proximal ICAS burden may also help reduce AIS risk.

Estrogen is thought to play a protective role in cardiovascular health in women.[9] Although aging is characterized by increases in blood pressure in both sexes, the incidence of hypertension in women increases and rises steeply after menopause. Estrogen may help explain this trend in women.[10] Given the positive association between hypertension and ICAS, we expected to see similar sex differences in ICAS burden as seen in hypertensive prevalence rates. Indeed, in our hypertensive cohort with mean ages of 56.6 (men) and 59.2 (women) years, men had significantly higher total and proximal ICAS burdens than women, presumably related to the protective effect of estrogen in women in early mid-life.[9]

Our results are also in keeping with Li et al who used transcranial Doppler exams in a Chinese cohort of 551 patients with AIS and showed men (odds ratio, 2.3; 95% CI, 1.48–3.26) had a significantly higher prevalence of ICAS than women.[11] By contrast, among 2864 Chinese patients with AIS (mean age, 61.9 years), Pu et al showed no significant sex difference in the percentage of patients with ICAS using ≥50% luminal stenosis on time-of-flight magnetic resonance angiogram as a proxy for ICAS. However, for patients aged >63 years, the percentage of women with ICAS was significantly higher than men suggesting indeed there may be a sex difference that emerges with age.[12] Both studies used lumen-based imaging techniques, which are suboptimal to VW-MRI. In fact, a concordance study comparing intracranial VW-MRI with 3-dimensional time-of-flight magnetic resonance angiogram showed 3-dimensional time-of-flight magnetic resonance angiogram has lower sensitivity for plaque detection.[5] Thus some of the conflicting results in the literature may be because of differences in imaging technique and how plaque is detected on imaging.[8] With the increasing adoption of VW-MRI, future studies should consider using VW-MRI for accurate ICAS detection.

Interestingly, our results also showed significant sex differences in the magnitude of ICAS reduction with anti-hypertensive treatment. This finding raises several interesting questions. Do men versus women respond to anti-hypertensive treatment differently? Should there be different hypertensive treatment guidelines for women given a steep increase in incidence of hypertension in postmenopausal women in late life? Some studies suggest achieving blood pressure control in elderly women may be more challenging compared

Table 1. Unadjusted and Adjusted Associations of Plaque Burden With Sex and Interaction of Treatment With Sex

Plaque burden	Men (n=42)	Women (n=19)	Relative risk	Pearson Chisq*	Model
Total	10.7 (95% CI, 9.0–12.7)	8.0 (95% CI, 6.1–10.4)	1.3 (95% CI, 1.0–1.9), *P*=0.07	0.9	0
	9.9 (95% CI, 7.3–13.3)	6.3 (95% CI, 4.2–9.4)	1.6 (95% CI, 1.2–2.1), *P*<0.01	1.4	1
Proximal	7.1 (95% CI, 6.2–8.3)	5.2 (95% CI, 4.0–6.6)	1.4 (95% CI, 1.0–1.8), *P*=0.03	1.0	0
	8.7 (95% CI, 6.4–12.0)	6.2 (95% CI, 3.9–9.8)	1.4 (95% CI, 1.0–1.9), *P*=0.03	1.1	2
Distal	3.5 (95% CI, 2.7–4.7)	2.8 (95% CI, 1.8–4.3)	1.3 (95% CI, 0.8–2.1), *P*=0.37	1.0	0
	2.8 (95% CI, 1.5–5.1)	1.8 (95% CI, 0.8–4.2)	1.5 (95% CI, 0.9–2.6), *P*=0.12	1.2	3

Model 0: unadjusted model. Model 1: adjusted model with covariates race, age, history of stroke, or transient ischemic attack. Model 2: adjusted model with covariates race, age, smoking, history of stroke or transient ischemic attack, high-density lipoprotein, statin. Model 3: adjusted model with covariates race, age, high- and low-density lipoprotein, statin, antiplatelet medication. Chisq indicates Chi-square.

*Index for overdispersion, needs to be <1.5.

Table 2. Sex Effect on Anti-Hypertensive Medication Treatment

Outcome	Men (n=42)	Women (n=19)	Relative risk	Ratio of RR treatment/ no treatment	Pearson Chisq*	Model
Total, treatment	10.0 (95% CI, 8.1–12.4)	6.5 (95% CI, 4.8–8.9)	1.5 (95% CI, 1.1–2.3)	2.0 (95% CI, 0.9–4.4), *P*=0.1	1.2	1
Total, no treatment	10.9 (95% CI, 8.5–14.1)	13.9 (95% CI, 7.1–27.2)	0.80 (95% CI, 0.4–1.6)			
Proximal, treatment	6.6 (95% CI, 5.5–7.9)	4.5 (95% CI, 3.3–6.1)	1.5 (95% CI, 1.0–2.1)	2.0 (95% CI, 1.1–3.9), *P*=0.04	1.4	2
Proximal, no treatment	7.2 (95% CI, 5.9–8.9)	10.0 (95% CI, 6.0–16.7)	0.7 (95% CI, 0.4–1.3)			
Distal, treatment	2.6 (95% CI, 1.8–3.8)	2.4 (95% CI, 1.4–4.1)	1.1 (95% CI, 0.5–2.2)	1.1 (95% CI, 0.3–4.2), *P*=0.89	1.1	3
Distal, no treatment	3.4 (95% CI, 2.2–5.1)	3.4 (95% CI, 1.2–9.9)	1.0 (95% CI, 0.3–3.1)			

Model 0: unadjusted model. Model 1: adjusted model with covariates race, age, history of stroke or transient ischemic attack. Model 2: adjusted model with covariates race, age, smoking, history of stroke or transient ischemic attack, high-density lipoprotein, statin. Model 3: adjusted model with covariates race, age, high- and low-density lipoprotein, statin, antiplatelet medication. Chisq indicates Chi-square; and RR, relative risk.

*Index for overdispersion, needs to be <1.5.

with men.[13] Such differences in treatment effectiveness may relate back to differences in sex-hormones. Estrogen is a growth factor and have receptors expressed in vascular endothelial and smooth muscle cells. Estrogen via estrogen receptor β-signaling and α-signaling regulates arterial tone and protects against vascular injury and atherosclerosis, respectively. Studies report higher estrogen receptor expression in arteries of women than men.[14] This differential expression of estrogen receptors could explain the observed interaction between sex and anti-hypertensive treatment with ICAS burden in this study. Another explanation might be differences in education and medication compliance. Pan et al showed that among 488 Chinese patients with hypertension, women showed greater adherence to anti-hypertensives than men.[15] Although medication compliance was not measured in this retrospective study, detailing medication type and medication adherence may provide additional insights into sex differences in ICAS burden.

There are several limitations to this study. First, the retrospective design could lead to a higher number of excluded patients because of poor or incomplete imaging. Second, the inclusion criterion of 8 weeks between symptom onset and VW-MRI could change plaque burden. However, analyses showed an interval of only 8.5 to 9 days (median) mitigating this possibility. Third, the sample size was relatively small to stratify by age and confirm an age-effect. Fourth, the cohort is predominantly comprised of patients of Asian race

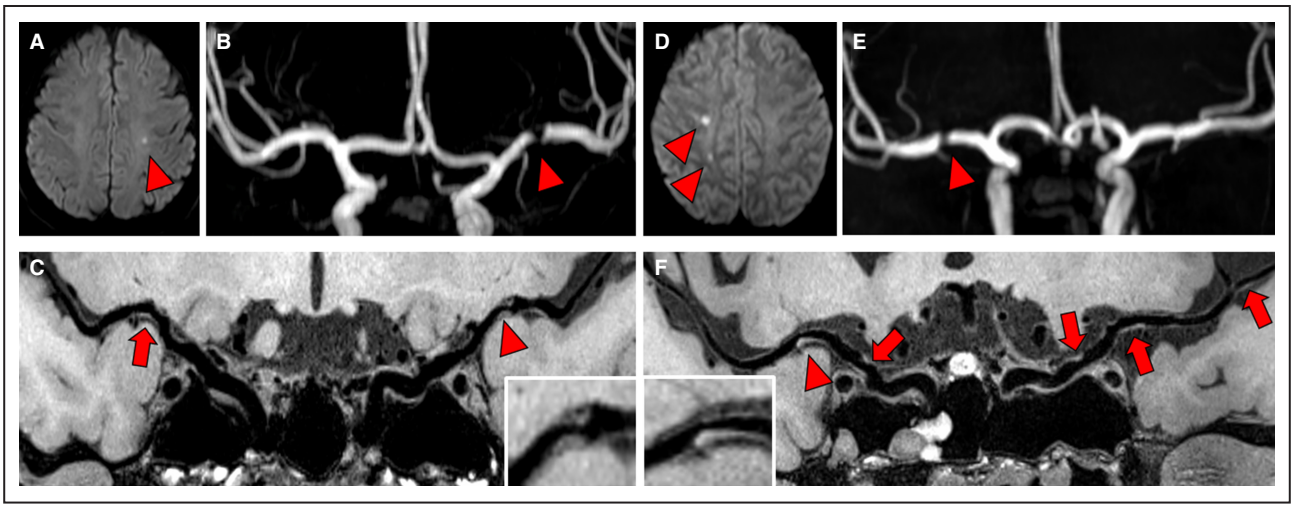

Figure 1. Vessel wall magnetic resonance imaging of intracranial atherosclerosis.
A, Forty-two-year-old woman with hypertension with a left frontal acute infarct on diffusion-weighted imaging (**A**, arrowhead) showed (**B**) a severe left middle cerebral artery stenosis (arrowhead) on a 3-dimensional time-of-flight magnetic resonance angiogram. (**C**) A culprit plaque (arrowhead; inset) was detected on vessel wall magnetic resonance imaging. A nonstenotic right middle cerebral artery plaque (**C**, arrow) was also detected. **D**, Fifty-one-year-old man with hypertension with right frontoparietal acute infarcts on diffusion-weighted imaging (**A**, arrowheads) showed (**E**) a severe right middle cerebral artery stenosis (arrowhead) on 3-dimensional time-of-flight magnetic resonance angiogram. (**F**) A culprit plaque (arrowhead, inset) on vessel wall magnetic resonance imaging was detected. Four additional bilateral middle cerebral artery plaques (arrows) on vessel wall magnetic resonance imaging were present, illustrating a high plaque burden in this man with hypertension.

limiting generalizability to other patient populations. Fifth, the cross-sectional design limits the conclusion of a causal relationship. Future directions include a prospective, longitudinal study with larger sample size and details of hypertension medications and compliance, menopausal state, and hormone levels to gain better insight into sex differences.

CONCLUSIONS

Among patients with hypertension and AIS, men have significantly higher total and proximal plaque burdens than women. Women treated for hypertension and AIS showed a greater reduction in total proximal plaque burden than men. Further confirmation of these preliminary results with a longitudinal cohort study is needed and may help evaluate whether different treatment guidelines for managing hypertension by sex can help reduce ICAS burden and ultimately AIS risk.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Demographics.

	Males (N=42)	Females (N=19)	P
Imaging Data			
Days between Ischemic Stroke and MR-VWI, median (IQR)	8.5 (5, 14)	9 (3, 12)	0.7
Demographic Data			
Age (years), mean (SD)	56.6 (11.6)	59.2 (9.9)	0.4 (95% CI 8.7, 3.6)
Race, n (%)			
White	4 (10)	0 (0)	0.44
Black	1 (2)	0 (0)	
Asian	36 (86)	18 (95)	
Hispanic	1 (2)	1 (5)	
Medical History			
Diabetes Mellitus	17 (40)	5 (26)	0.3
Dyslipidemia	16 (38)	5 (26)	0.4
Smoking	22 (52)	2 (11)	0.002*
History of Stroke/TIA	9 (24)	3 (19)	1.00
History of MI or CAD	4 (11)	1 (6)	1.00
Clinical & Laboratory Data			
SBP, mean (SD)	157 (19.3)	152 (17.2)	0.4 (95% CI 5.8, 14.9)
DBP, mean (SD)	91 (12.5)	85 (8.5)	0.6 (95% CI 0.2, 12.4)
Body Mass Index, median (IQR)	25 (23.5, 28) (N=37)	24 (23, 27) (N=15)	0.5
Hemoglobin A1c (%), median (IQR)	5.9 (5.4, 8.4) (N=28)	5.7 (5.4, 7.2) (N=13)	0.6
LDL (mg/dL), median (IQR)	2.4 (1.7, 3.7) (N=38)	2.43 (0.91, 4.0) (N=14)	0.8
HDL (mg/dL), median (IQR)	1.1 (0.9, 1.7) (N=38)	1.2 (1, 1.8) (N=14)	0.3
Total Cholesterol (mg/dL), median (IQR)	4.3 (3.1, 5.8) (N=38)	4.5 (3.2, 6.3) (N=15)	0.9
Triglycerides, median (IQR)	1.6 (0.94, 3.5) (N=38)	1.8 (1.3, 3.3) (N=15)	0.5
Total Cholesterol, median (IQR)	1.6 (0.94, 3.5) (N=38)	1.8 (1.3, 3.3) (N=15)	0.9
Medications			
Anti-diabetic, n (%)	8 (22)	3 (20)	0.9
Statin, n (%)	6 (16)	2 (13)	0.8
Antiplatelet, n (%)	6 (16)	5 (33)	0.2

IQR, interquartile range; CI, confidence interval; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; MI, myocardial infarction; CAD, coronary artery disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MR-VWI, vessel wall MR imaging; *p<0.01