Structural Integrity of Normal Appearing White Matter and Sex-Specific Outcomes After Acute Ischemic Stroke

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Background and Purpose—Women have worse poststroke outcomes than men. We evaluated sex-specific clinical and neuroimaging characteristics of white matter in association with functional recovery after acute ischemic stroke.

Methods—We performed a retrospective analysis of acute ischemic stroke patients with admission brain MRI and 3- to 6-month modified Rankin Scale score. White matter hyperintensity and acute infarct volume were quantified on fluid-attenuated inversion recovery and diffusion tensor imaging MRI, respectively. Diffusivity anisotropy metrics were calculated in normal appearing white matter contralateral to the acute ischemia.

Results—Among 319 patients with acute ischemic stroke, women were older (68.0 versus 62.7 years; *P*=0.004), had increased incidence of atrial fibrillation (21.4% versus 12.2%; *P*=0.04), and lower rate of tobacco use (21.1% versus 35.9%; *P*=0.03). There was no sex-specific difference in white matter hyperintensity volume, acute infarct volume, National Institutes of Health Stroke Scale, prestroke modified Rankin Scale score, or normal appearing white matter diffusivity anisotropy metrics. However, women were less likely to have an excellent outcome (modified Rankin Scale score <2: 49.6% versus 67.0%; *P*=0.005). In logistic regression analysis, female sex and the interaction of sex with fractional anisotropy, radial diffusivity, and axial diffusivity were independent predictors of functional outcome.

Conclusions—Female sex is associated with decreased likelihood of excellent outcome after acute ischemic stroke. The correlation between markers of white matter integrity and functional outcomes in women, but not men, suggests a potential sex-specific mechanism. **(*Stroke*. 2017;48:3387-3389. DOI: 10.1161/STROKEAHA.117.019258.)**

Key Words: brain ischemia ■ diffusion-weighted imaging ■ leukoaraiosis ■ stroke ■ white matter

After acute ischemic stroke (AIS), women have worse functional outcomes and increased likelihood of death compared with men.[1,2] Identifying and understanding the factors that mediate the disparity in sex-specific outcomes after AIS therefore offer a critical opportunity to improve patient care. White matter hyperintensity (WMH) burden represents one factor that has been associated with poor poststroke functional outcomes.[3–6] Moreover, in patients with AIS, normal appearing white matter (NAWM) structural integrity has also been shown to influence poststroke functional outcomes.[7] In this analysis, we characterized sex-specific differences in clinical and neuroimaging variables of poststroke functional recovery.

Methods

The details of the study design have been described previously by Etherton et al.[7] For additional details of the methods, please refer to the online-only Data Supplement.

Patients >18 years old presenting to our hospital with signs and symptoms of AIS and a brain MRI with a confirmed acute lesion on diffusion-weighted imaging (DWI) and available fluid-attenuated inversion recovery and diffusion tensor imaging sequences were eligible for this study. Clinical variables were obtained on admission. Modified Rankin Scale (mRS) scores were obtained at 3- to 6-month poststroke. Excellent functional outcome was defined as mRS <2.

Total WMH volume and DWI volume were determined using a semiautomated approach and normalized for differences in head size (normalized WMH volume and normalized DWI volume).[8,9] Using the constructed contralesional NAWM mask, median voxel values

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were calculated for fractional anisotropy (FA), axial diffusivity, mean diffusivity, and radial diffusivity.[7,10]

Logistic regression was performed with a model of age, sex, WMH volume, diffusivity metrics, and excellent functional outcome. Paired *t* test, Wilcoxon rank-sum, and correlation analysis using Spearman or Pearson correlation were performed when appropriate (R version 3.3.2). Statistical significance was set at $P<0.05$ in all analyses. The authors agree to make available to any researcher the data, methods used in the analysis, and materials used to conduct the research for the express purposes of reproducing the results and with the explicit permission for data sharing by the local institutional review board.

Results

Of an initial 480 participants, 319 participants met criteria for this analysis. Men comprised 58.9% (n=188 subjects) of the cohort. Women were older (68.0 versus 62.7 years; $P=0.004$), reported lower rates of tobacco use (21.1% versus 37.0%; $P=0.03$), had lower admission diastolic blood pressure (78.6 versus 83.2 mm Hg; $P=0.02$), and had increased rates of antecedent atrial fibrillation (21.4% versus 12.2%; $P=0.04$; Table I in the online-only Data Supplement). There was no significant difference between sexes in prestroke mRS, admission National Institutes of Health Stroke Scale, DWI volume, WMH burden, or rates of administration of intravenous tPA (tissue-type plasminogen activator; Table I in the online-only Data Supplement). At 3 to 6 months after AIS, there were significantly fewer women with an excellent outcome compared with men (49.6% versus 67.0%; $P=0.005$; Figure).

We observed no difference between men and women in contralesional NAWM diffusivity anisotropy metrics (Table II in the online-only Data Supplement). Mean diffusivity, axial diffusivity, and radial diffusivity correlated with follow-up mRS in both sexes; however, FA was inversely correlated with mRS in women but not men ($\rho=-0.182$, $P=0.048$ versus $\rho=-0.096$, $P=0.201$; Table III in the online-only Data Supplement). We observed a statistically significant negative correlation between FA and age in women but not men (women: $\rho=-0.259$, $P=0.003$; men: $\rho=-0.087$, $P=0.25$). normalized WMH volume was positively correlated with mRS in both sexes (women: $\rho=0.221$, $P=0.015$; men: $\rho=0.160$, $P=0.030$). In a logistic regression model of excellent functional outcome (mRS <2), sex and the interaction of sex with FA, axial diffusivity, and radial diffusivity were independently associated with excellent functional outcome (Table).

Discussion

In this retrospective analysis of patients with AIS, we found that despite no observed differences in stroke severity, WMH burden, or treatment with intravenous tPA, fewer women achieved an excellent functional outcome (mRS <2) after stroke than men. Whereas the underlying explanation for this observation is unclear, several findings from our study suggest potential associated factors.

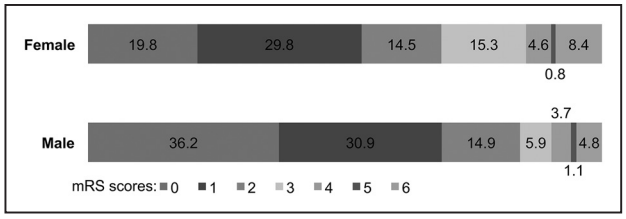

Figure. Follow-up modified Rankin Scale (mRS) at 3 to 6 months postacute ischemic stroke according to sex. Horizontal bar chart depicts follow-up mRS as a percentage of total patients per sex.

Table. Determinants of Excellent Functional Outcome (mRS<2)

Variable	Estimate	*P* Value
Age	−0.02	0.217
Female sex	−39.07	0.002*
nWMHv	0.02	0.151
FA	−22.07	0.166
MD	−9.11	0.584
AD	12.34	0.230
RD	−22.08	0.265
Age×sex	−0.01	0.616
nWMHv×sex	0.02	0.440
FA×sex	97.39	0.002*
MD×sex	−2.72	0.884
AD×sex	−52.23	0.003*
RD×sex	101.82	0.003*

AD indicates axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; mRS, modified Rankin Scale; nWMHv, normalized WMH volume; and RD, radial diffusivity.

*Significant values which were pre-set at $P<0.05$.

In our population, women were older and more likely to have premorbid atrial fibrillation. The advanced age, as compared with men, could contribute to the disparity in functional outcomes and agrees with prior studies demonstrating worse outcomes in women after AIS.,[1,2,11,12] We also demonstrated that, despite similar WMH burden and contralesional NAWM diffusivity anisotropy metrics, contralesional FA correlated with functional outcomes in women but not men. This observed inverse relationship between FA and mRS suggests that reduced FA may be associated with worse functional outcomes after stroke. These findings are further supported by our logistic regression model demonstrating that female sex was an independent determinant of worse functional outcomes and that the interaction between sex and multiple diffusivity metrics was independently associated with functional outcomes. We previously demonstrated that the median FA values of contralesional NAWM are predictive of functional outcomes after AIS.[7] Moreover, an inverse correlation between FA and age in women, but not men, suggests that there may be sex-specific differences in the loss of white matter microstructural integrity with age. Although the tissue integrity of NAWM is negatively impacted by age and hypertension, no sex-specific differences have been reported to date.[13] Thus, our data suggest that white matter structural integrity may be a contributing variable on AIS functional outcomes in women.

There are several limitations of the current study that merit consideration in the overall interpretation and applicability of our findings, including exclusion of patients with infratentorial or bilateral strokes, the relatively low stroke severity of our population (median National Institutes of Health Stroke Scale score 3), lack of data on discharge destination and intensity of rehabilitation, and a potential bias from partial volume

averaging occurring because of nonisotropic voxel sizes for diffusion tensor imaging analysis. Going forward, a large-scale study looking at clinical and neuroimaging variables in relation to sex-specific functional outcomes is warranted.

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Disclosures

L. Cloonan is employed by Decision Resources Group. The other authors report no conflicts.

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