Sex Differences in Stroke Severity, Symptoms, and Deficits After First-ever Ischemic Stroke

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Objective: The purpose of the study was to assess whether there were sex differences in stroke severity, infarct characteristics, symptoms, or the symptoms-deficit relationship at the time of acute stroke presentation. *Methods:* In a prospective study of 505 patients with first-ever ischemic stroke (the Ischemic Stroke Genetics Study), stroke subtype was centrally adjudicated and infarcts were characterized by imaging. Deficits were assessed by National Institutes of Health Stroke Scale (NIHSS) and stroke symptoms were assessed using a structured interview. Kappa statistics were generated to assess agreement between the NIHSS and the structured interview, and a Chi square test was used to assess agreement between the NIHSS and the structured interview by sex. *Results:* In all, 276 patients (55%) were men and 229 (45%) were women. Ages ranged from 19 to 94 years (median, 65 years). The mean (±SD) NIHSS score of 3.8 (±4.5) for men and 4.3 (±5.2) for women was similar ($P = .15$). No sex difference was observed for the symptoms of numbness, visual deficits, or language. Weakness occurred in a greater proportion of women (69%) than men (59%) ($P = .03$). Stroke subtype did not differ significantly between sexes ($P = .79$). Infarct size and location were similar for each sex. The association between symptoms and neurologic deficits did not differ by sex. *Conclusions:* We found no sex difference in stroke severity, stroke subtype, or infarct size and location in patients with incident ischemic stroke. A greater proportion of women presented with weakness; however, similar proportions of men and women presented with other traditional stroke symptoms. **Key Words:** Ischemia—stroke—sex differences—stroke severity.

Sex differences have been observed in the way patients present for medical care. Women with ischemic coronary syndromes tend to have greater delay from symptom onset,[1] report more shortness of breath and nausea,[2] and report less diaphoresis[2] than men with the same condition. One study of patients presenting to emergency departments with acute cerebrovascular events suggested that there may be sex differences in reporting of

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All participants in this part of the Ischemic Stroke Genetics Study are listed in the Appendix.

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acute stroke symptoms.[3] Women had nontraditional symptoms such as pain and change in level of consciousness more commonly than men.

The advent of effective acute stroke therapies has made rapid recognition of stroke symptoms by patients and physicians imperative. If sex differences in stroke presentation are observed consistently, awareness of these differences may facilitate recognition of stroke syndromes and delivery of therapies to larger numbers of patients.

We assessed whether there were sex differences in stroke severity, infarct characteristics, symptoms, and the symptoms-deficit relationship at the time of presentation for medical attention for acute ischemic stroke in the Ischemic Stroke Genetics Study (ISGS).

Methods

The ISGS protocol has been published.[4] Briefly, patients were enrolled prospectively at 5 US medical centers. Eligible patients were aged 18 years or older and had a first-ever ischemic stroke with onset of symptoms within 30 days of enrollment. Ischemic stroke was defined according to World Health Organization criteria in addition to appropriate findings on head computed tomography or magnetic resonance imaging. Patients were excluded if the stroke was thought to be iatrogenic or attributable to septic embolism, cardioembolism related to mechanical heart valve, or vasospasm after aneurysmal subarachnoid hemorrhage; or if the patient had a single-gene disorder that was likely causative.

Demographic information was obtained in addition to medical and lifestyle risk factors. Stroke subtype according to the Trial of Org 10172 in Acute Stroke Treatment,[5] the Oxfordshire Community Stroke Project,[6] and the Baltimore-Washington Cooperative Young Stroke Study[7] criteria was assigned to every case patient by a single neurologist (R. D. B.) after systematically reviewing all available medical records.

A study neurologist or clinical coordinator rated the severity and extent of neurologic deficits and functional impairment at enrollment with the National Institutes of Health Stroke Scale (NIHSS),[8] Barthel Index (BI),[9] Oxford Handicap Scale,[10] and Glasgow Outcome Scale.[11] All raters were certified in administering the NIHSS using recorded live patient vignettes.

The Questionnaire for Verifying Stroke-free Status (QVSS) was administered to all patients at enrollment. The 6-item QVSS inquires about cardinal symptoms of stroke.[12]

Statistical Analysis

Chi square tests were used to assess differences in categorical variables (e.g., race, smoking status, alcohol use) between men and women, and Wilcoxon rank sum tests were used to assess differences in continuous measures (e.g., age at stroke, NIHSS, BI). A total of 4 nonmutually exclusive categories were developed according to presence of weakness, numbness, visual deficits, and language deficits on the NIHSS and QVSS. For the NIHSS, "weakness" included facial or limb weakness, "numbness" included diminished pinprick or loss of cortical sensation (neglect or extinction), "visual deficits" included partial or complete homonymous visual field defect on confrontation, and "language deficits" included aphasia or dysarthria. Agreement for a specific symptom was calculated as the number of observations for which the NIHSS and QVSS matched (both no or both yes) divided by the total number of cases having both measures. Kappa statistics were generated to quantitate the chance-corrected agreement between the NIHSS and QVSS, and a Chi square test was used to determine whether the agreement between the NIHSS and QVSS symptoms varied by patient sex.

Informed consent was obtained from the patient (or surrogate). Institutional review boards at all sites approved the ISGS protocol.

Results

A total of 505 patients with first-ever ischemic stroke were prospectively enrolled. Approximately equal numbers were accrued at each of the 5 study sites. In all, 276 were male and 229 were female. Patients ranged in age from 19 to 94 years (median, 65 years); 40% were aged 70 years or older. On average, women were approximately 5 years older than men at presentation ($P = .001$). The race distributions were similar for men and women; overall, 68% were white, 29% were black, and 3% were other races. Men were more likely to be current or former smokers (76% *v* 59%; $P < .001$) and to have one or more drinks a week (46% *v* 25%; $P < .001$). Men were also more likely to exercise vigorously at least once a week (58% *v* 36%; $P < .001$).

Hypertension occurred in 71% of patients. Hyperlipidemia was present in 45%, diabetes mellitus in 27%, and migraine headaches in 25%. Myocardial infarction was more common among men (20% *v* 10%; $P = .002$) and hypertension was less common among men (66% *v* 78%; $P = .002$).

Table 1 shows stroke subtypes by sex. There was no significant difference between the sexes for the Trial of Org 10172 in Acute Stroke Treatment, Oxfordshire Community Stroke Project, or Baltimore-Washington classifications.

Table 2 shows stroke severity, infarct characteristics, and symptoms by sex. Stroke severity as quantified by the NIHSS, Oxford Handicap Scale, and Glasgow Outcome Scale did not differ significantly between men and women. The BI, however, did differ significantly between men and women, with men having higher scores (better

Table 1. *Classification of ischemic stroke subtypes by sex of study patient*

Classification	Male		Female		
	No.	%	No.	%	*P* value*
Total (N = 505)	276		229		
TOAST					.79
Large-artery atherosclerosis	55	20	40	17	
Small-vessel occlusion	47	17	46	20	
Cardioembolism	64	23	59	26	
Other cause	11	4	8	3	
Undetermined cause	99	36	76	33	
OCSP					.39
Lacunar infarct	74	27	67	29	
Total anterior circulation infarct	25	9	25	11	
Partial anterior circulation infarct	119	43	102	45	
Posterior circulation infarct	58	21	35	15	
Baltimore-Washington					
Atherosclerotic vasculopathy	109	39	94	41	.72
Nonatherosclerotic vasculopathy	11	4	4	2	.14
Lacunar	50	18	45	20	.66
Cardiac/transcardiac	90	33	69	30	.55
Hematologic other	3	1	4	2	.71†
Migrainous stroke	1	0	1	0	>.99†
Oral contraceptives	0	0	1	0	.45†
Drug related	1	0	1	0	>.99†
Indeterminate	57	21	48	21	.93

OCSP, Oxfordshire Community Stroke Project; *TOAST*, Trial of Org 10172 in Acute Stroke Treatment.
*Chi square tests unless specified otherwise.
†Fisher exact test.

function). Infarct size and location were similar for men and women. Physical signs of numbness, visual deficits, and communication problems were found equally between sexes. Physical signs of weakness were more common in women. Similar proportions of men and women reported symptoms in each of the 4 categorical domains.

Table 3 depicts the cross-tabulation between patient-reported symptoms and neurologic deficits by sex. Although the association between symptoms and deficits was statistically significant for all domains, the agreement was not particularly high with Kappa statistics ranging from 0.13 to 0.32. Agreement between symptoms and deficits was best for the category of vision, followed by communication, weakness, and numbness. Numbness is self-reported about twice as often as it is identified by NIHSS. Overall, no significant sex differences were observed in the ability to appreciate and report stroke symptoms, despite the overall poor agreement between symptoms and deficits.

Discussion

Generally, we did not find significant sex differences in ischemic stroke subtype, stroke severity, infarct characteristics (size and location), or stroke symptoms. A prior report of sex differences in acute stroke presentation included patients with cerebrovascular events defined as transient ischemia, completed ischemic stroke, and hemorrhagic stroke.[3] The greater proportion of women with subarachnoid hemorrhage and intraparenchymal hemorrhage in the aforementioned study may explain the increased frequency of nontraditional symptoms such as pain, change in level of consciousness, disorientation, and nonneurologic symptoms. Headache and decreased level of consciousness are more common in hemorrhagic stroke than in ischemic stroke.[13,14] Vomiting on admission has also been observed more frequently in patients with intracerebral hemorrhage.[13,15] Our study population comprised cases of first-ever ischemic stroke, and this difference may account for the disparity between our results and those previously reported. Incident ischemic stroke cases also minimize the likelihood of confounding by residual signs or symptoms in patients with prior stroke. Although the instrument we used to assess stroke symptoms does not capture nontraditional symptoms, recognition of sex differences in symptoms most commonly observed on presentation should be of considerable practical clinical value. Nontraditional symptoms, when present, are likely to co-

Table 2. *Stroke severity, cerebral infarct characteristics, and symptoms by patient sex*

Characteristic	Male		Female		*P* value*
	No.	%	No.	%	
Total (N = 505)	276		229		
Stroke severity scores, mean (SD)					
NIHSS	3.8 (4.5)		4.3 (5.2)		.15†
BI	80.6 (27.2)		75.3 (28.6)		.01†
OHS	1.9 (1.3)		2.0 (1.3)		.27†
GOS	1.7 (0.8)		1.7 (0.8)		.94†
Cerebral infarct					
Diameter, cm					.56
Not seen	19	7	23	10	
<1.5	88	32	65	28	
1.5-3.0	75	27	64	28	
>3.0	94	34	77	34	
Location					.57
Not seen	19	7	23	10	
Supratentorial left	104	38	86	38	
Supratentorial right	104	38	86	38	
Infratentorial	47	17	31	14	
Multiple locations	2	1	3	1	
Symptoms/deficits					
Weakness					
QVSS	180/272	66	157/226	69	.43
NIHSS	164/276	59	158/229	69	.03
Numbness					
QVSS	157/272	58	123/226	54	.46
NIHSS	81/276	29	72/229	31	.61
Visual deficits					
QVSS	51/273	19	44/225	20	.80
NIHSS	53/276	19	46/229	20	.80
Communication					
QVSS	103/273	38	102/226	45	.09
NIHSS	107/276	39	92/229	40	.75
No. of symptoms by QVSS, mean (SD)	2.0 (1.3)		2.1 (1.3)		.47†

Data were incomplete for some characteristics.

BI, Barthel index; *GOS,* Glasgow Outcome Scale; *NIHSS,* National Institutes of Health Stroke Scale; *OHS,* Oxford Handicap Scale; *QVSS,* Questionnaire for Verifying Stroke-free Status.

*Chi square tests unless specified otherwise.

†Wilcoxon rank sum test.

exist in the context of symptoms such as weakness, language disturbance, or visual impairment seen in traditional stroke syndromes.

Table 3. *Agreement between self-reported and physician-ascertained symptoms*

Symptom	Men	Women	*P* value
Weakness	0.13 (0.01-0.25)	0.19 (0.06-0.33)	.51
Numbness	0.12 (0.03-0.22)	0.17 (0.06-0.28)	.55
Vision	0.31 (0.17-0.45)	0.30 (0.15-0.45)	.96
Communication	0.32 (0.21-0.44)	0.21 (0.09-0.34)	.21

Values are Kappa statistics (95% confidence intervals).

Among the cases recruited into ISGS, a greater proportion of women had objective weakness on neurologic examination compared with men. Given the similarity of stroke subtype and location between men and women, this observation is difficult to explain. If not caused by chance, a female preponderance of weakness would be unlikely to alter recognition of acute stroke syndromes because hemiparesis is a well-recognized symptom of focal cerebral ischemia. The frequency of weakness in women likely explains the sex difference observed for the BI. Motor disability impacts functional independence in basic activities of daily living as measured by the BI. Greater disability because of stroke in women has been observed previously,[16] and our results suggest the same. The mean scores for both men and women (80.6 *v* 75.3)

were above generally accepted thresholds for poor neurologic outcome[17] and are in keeping with the relatively minor stroke severity as measured by the NIHSS.

The association between stroke symptoms and neurologic deficits was significant for each of the 4 categories of deficit. There was no sex difference between categories. There are several reasons why the symptom-deficit agreements were marginal. Patients reported numbness about twice as frequently as it was observed by NIHSS. This difference may reflect the fact that NIHSS only assesses crude pain sensation. Further, patients with paresthesia, but not hypoesthesia, may report numbness. Patients with severe aphasia or dysarthria are unable to report symptoms of impaired communication, although NIHSS does capture these deficits.

Our study has limitations. Strokes tended to be minor. This likely relates to the consecutive nature of recruitment, the informed consent process, and the facts that recruitment was not as restricted as in many stroke clinical trials and only first-ever stroke cases were enrolled. Our findings may not generalize to populations of more severe stroke. Furthermore, infarct size was characterized in categorical terms based on maximum diameter and lesion location in 3 territories. A study of sex differences is warranted in more severely affected patients and where lesion size is characterized continuously by volume of infarction using standardized imaging.

Our observations may be of relevance for ongoing or future clinical studies of stroke therapies by minimizing concerns of significant sex differences in stroke severity or location, which may confound interpretation of study results. Sex may influence outcome and recovery after stroke, and warrants further study. However, sex does not appear to impact the presentation of acute stroke in a group of patients with ischemic stroke.

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Appendix. ISGS Centers (as of October 6, 2005)

Study Centers

Mayo Clinic, Jacksonville, Florida (patients enrolled, 188): Principal investigator (PI): James F. Meschia, MD; coordinators: Alexa N. Richie, Dale M. Gamble, Sothear Luke; subinvestigators (SI): Thomas G. Brott, MD, Benjamin H. Eidelman, MD, Pablo R. Castillo, MD, Frank A. Rubino, MD.

University of Florida/Shands Hospital, Jacksonville, Florida (216): PI: Scott Silliman, MD; coordinators: Barbara Quinn, RN, Yvonne Douglas, Marc Lojacono, CCRC; SI: Nader Antonios, MD.

Emory University School of Medicine, Atlanta, Georgia (228): PI: Michael R. Frankel, MD; coordinator: Sharion Smith, RN.

University of Virginia Charlottesville, Virginia (212): PI: Bradford B. Worrall, MD, MSc; coordinators: Martha Davis, RN, Helen Roehl, RN.

Mayo Clinic, Rochester, Minnesota (228): PI: Robert D. Brown, Jr, MD; coordinators: Colleen S. Albers, RN, Debra E. Herzig, RN.

Statistical Center

Wake Forest University School of Medicine, Winston-Salem, North Carolina: Stephen S. Rich, PhD, L. Douglas Case, PhD, Wesley Roberson, Laurie Russell, Darrin Harris, Carolyn Bell.

Genetics Laboratory

Laboratory of Neurogenetics, Bethesda, Maryland: John Hardy, PhD, Andrew Singleton, PhD.

DNA Repository

Coriell Institute for Medical Research, Camden, New Jersey: Jeanne Beck, PhD, Judy Keen, PhD.

National Institute of Neurological Disorders and Stroke

Project Officer for ISGS: Scott Janis, PhD.

Human Genetics Resource Center Project Officer: Katrina Gwinn-Hardy, MD.