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Sex Differences in Stroke Evaluations in the Ischemic Stroke Genetics Study

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Abstract

Background—Epidemiologic studies suggest sex differences in evaluation of patients presenting with ischemic stroke. Sex differences in stroke evaluation could lead to sex differences in the validity of diagnosing ischemic stroke subtypes. This study assessed sex differences in the Ischemic Stroke Genetics Study (ISGS).

Methods—The ISGS is a prospective case-control genetic association study of patients with first-ever ischemic stroke at 5 US tertiary stroke centers. The diagnostic tests performed as part of medical care were recorded for each enrolled patient.

Results—A total of 505 patients were enrolled; 45% (229 of 505) were women and 55% (276 of 505) were men. Mean age at time of stroke was greater for women (66.6 v 61.9 years; $P = .001$). Frequency of brain computed tomography was 92% (254 of 276) for men and 90% (206 of 229) for women ($P = .42$). Magnetic resonance imaging was completed in 84% (232 of 276) of men and 83% (191 of 229) of women ($P = .91$). Frequency of electrocardiography was 91% (252 of 276) for men and 90% (206 of 229) for women ($P = .60$). Echocardiography was done in 74% (203 of 276) of men and 79% (180 of 229) of women ($P = .19$). Cervical arterial imaging occurred in 91% (208 of 229) of women and 86% (237 of 276) of men ($P = .09$). Intracranial vascular imaging was performed in 75% (207 of 276) of men and 79% (181 of 229) of women ($P = .28$).

Conclusions—Our findings suggest no significant sex differences in the extent to which major diagnostic tests were performed in patients in ISGS. Dedicated tertiary stroke centers may reduce the sex bias in stroke evaluation that has been identified by previous studies.

Keywords

Diagnostic evaluation; Ischemic stroke; sex differences; tertiary stroke centers

Strokes account for 5% to 10% of all deaths in the Western world, with ischemic stroke accounting for 70% to 80% of stroke cases.¹ Women have been reported to differ from men in stroke outcomes,² ischemic stroke subtypes,³ and responses to tissue plasminogen activator (tPA) treatment.⁴ There exists little literature regarding stroke evaluation in women. Smith et al,⁵ in a population-based study from Texas, found that women were less likely to have carotid ultrasonography and echocardiography than men when presenting with stroke. A study of stroke care in Europe found discrepancies between men and women, with women less likely to receive basic investigative tests for stroke, including brain imaging, carotid ultrasonography, echocardiography, and angiography.⁶ Rapid and accurate evaluation of stroke subtypes is crucial for optimal treatment and outcomes.⁷

We hypothesized that dedicated stroke centers, expected and encouraged to adhere to evidence-based protocols and clinical care guidelines, would not demonstrate significant sex differences in evaluating patients presenting with ischemic stroke.

Methods

We used data from the Ischemic Stroke Genetics Study (ISGS). All participants provided written informed consent to participate in ISGS, and data collection was approved by each site's institutional review board. ISGS is a case-control genetic association study of patients with first-ever ischemic stroke. The protocol has been previously published.⁸

All available medical records pertaining to the stroke evaluation were compiled in standardized fashion, deidentified, and centrally reviewed by a single neurologist (R. D. B.) for the purpose of assessing stroke subtype diagnoses using multiple standardized criteria. The medical records reviewer completed a stroke workup checklist, recording whether certain diagnostic testing was performed.

Because an overall measure of the level of diagnostic evaluation for acute ischemic stroke did not exist, we devised the Ischemic Stroke Assessment Index (ISAI). To develop the index, we reviewed a convenience sample of recent clinical practice guidelines in the English-language peer-reviewed medical literature to determine a consensus regarding evaluation of acute stroke. The sample included the following: the 2005 American Heart Association/American Stroke Association Guidelines for Early Management of Patients with Ischemic Stroke,⁹ the 2003 European Stroke Initiative Recommendations for Stroke Management,¹⁰ and the 2004 National Clinical Guidelines for Stroke.¹¹

General agreement existed among these authorities regarding the importance of initial head imaging by computed tomography (CT) or magnetic resonance (MR) imaging (MRI) to define the event as a stroke and to distinguish between ischemic and hemorrhagic events (grade A recommendation by American Heart Association), as clinical findings often overlap.¹² Serial neuroimaging has been shown not to alter stroke classification, except in circumstances where the event was initially classified as of unknown cause¹³ and, hence, the status of serial imaging was not included in the index. The therapeutic implications of atrial fibrillation—whether to use anticoagulant or antiplatelet therapy—mandate that cardiac rhythm be assessed.¹⁴ Chest radiography no longer constitutes part of stroke evaluation since it was found to rarely influence management.¹⁵ Questions remain about the precise timing of certain tests, including cardiac structural evaluation and assessment of cervical vasculature. However, vascular imaging is seen as a key component of the evaluation.¹⁶ Lovett et al¹⁷ found that, although only 14% of strokes in their series were associated with large artery atherosclerosis, this subtype accounted for 37% of recurrences within 7 days, supporting the need for urgent cervical vascular imaging in patients with acute ischemic stroke. Cardioembolic stroke accounts for a high percentage of ischemic stroke. Guidelines about the use of transthoracic echocardiography (TTE) versus

transesophageal echocardiography (TEE) are currently poorly formulated. Echocardiography is necessary to exclude embolic sources, and TTE should be considered in all patients with ischemic stroke.¹⁸

The ISAI is a sum score based on points assigned for whether the following were done: (1) head imaging; (2) evaluation of intracranial arterial vasculature; (3) evaluation of cervical arterial vasculature; (4) evaluation of cardiac rhythm beyond physical examination (i.e., electrocardiography [ECG]); and (5) evaluation of cardiac structure (i.e., echocardiography). The ISAI is an ordinal scale. For each category, a single point is assigned if a relevant diagnostic test is performed. The total score ranges from 0 to 5, with a score of 5 indicating that testing was performed in all the diagnostic categories.

We used Chi square tests to assess unadjusted differences in categorical variables (e.g., race, Trial of Org 10172 in Acute Stroke Treatment [TOAST] classifications, test use) between men and women. Wilcoxon rank sum tests were used to assess unadjusted differences in ordinal and continuous variables (e.g., ISAI, age). Logistic regression was used to determine whether the sexes differed in individual test use after adjusting for site, race, age, TOAST classification, and Oxfordshire classification. Rank analysis of covariance was used to assess the sex difference in ISAI after adjustment for covariates.

Results

The study included 505 patients. Of these, 229 (45%) were women. Mean age at the time of stroke was greater for women (66.6 v 61.9 years; $P = .001$). The demographics for this population showed that race did not differ statistically between men and women (29% and 35% were nonwhite, respectively). Men were more likely to have smoked previously (76% [211 of 276] of men v 59% [136 of 229] of women; $P < .001$) and to consume alcohol (46% [128 of 276] of men v 25% [57 of 229] of women; $P < .001$). Men were also more likely than women to exercise ($P < .001$) and somewhat less likely to be overweight or obese ($P = .06$).

Data concerning medical comorbid conditions by sex are contained in Table 1. Men were found to have a higher rate of myocardial infarction (20% v 10%; $P = .002$). Hypertension was more likely in women (78% v 66%; $P = .002$). Diabetes was present in 26% of men and 28% of women ($P = .71$), and atrial fibrillation was present in 12% of men and 17% of women ($P = .09$).

The subtype and location of stroke did not differ significantly between the sexes. By the TOAST classification, 23% (64 of 276) of men and 26% (59 of 229) of women had cardioembolic stroke. Small-vessel occlusion accounted for 20% (46/229) of stroke in women and 17% (47/276) of stroke in men. Stroke that was of undetermined cause was found in 33% (76 of 229) of women and 36% (99 of 276) of men. By Oxfordshire criteria, 52% (144 of 276) of men and 55% (127 of 229) of women had total or partial anterior circulation events. Lacunar stroke occurred in 29% (67 of 229) of women and 27% (74 of 276) of men, with the difference constituting posterior circulation infarcts.

Assessment of differences between sexes was conducted individually for each category of the ISAI (Table 2), following current policy on stroke evaluation. No significant differences were noted in the testing performed on men and women for any of the evaluated modalities except for TEE and carotid ultrasonography: women were more likely to receive both (adjusted odds ratios, 1.75 and 1.78, respectively).

All patients had head imaging performed (100% in both sexes). Similarly, comparable percentages of men and women—97% (269 of 276) and 96% (219 of 229), respectively—had cardiac evaluation, with 91% (252 of 276) of men and 90% (206 of 229) of women undergoing

ECG ($P = .60$) and 74% (203 of 276) of men and 79% (180 of 229) of women undergoing echocardiography (TEE or TTE) ($P = .19$). Cervical arterial imaging was performed in 91% (208 of 229) of women and 86% (237 of 276) of men ($P = .09$), with prominent use of MR angiography (MRA) (163 of 276 for men and 136 of 229 for women, 59% for both sexes). Frequency of brain CT was 92% (254 of 276) for men and 90% (206 of 229) for women ($P = .42$). MRI was completed in 84% (232 of 276) of men and 83% (191 of 229) of women ($P = .91$). Intracranial vascular imaging was undertaken in 75% (207 of 276) of men and 79% (181 of 229) of women ($P = .28$).

As described above, the ISAI score denotes the number of major categories represented by the various tests. Overall, women were somewhat more likely to have more of the major categories covered ($P = .03$). For men, 5%, 12%, 34%, and 49% had ISAI values of 2, 3, 4, and 5, respectively. For women, the respective percentages were 4%, 8%, 31%, and 56%. One man and one woman had a score of 1, each having only head imaging. Table 3 summarizes the odds of scoring 3 or more on the ISAI for women relative to men. As can be seen, the odds of scoring 5 (i.e., having all major categories covered) were approximately 50% higher for women than for men (adjusted odds ratio, 1.48; 95% confidence interval, 1.02-2.15).

Discussion

Women in this study were older than men by an average of almost 6 years, consistent with other studies.¹⁹ Significant demographic differences were found between men and women in relation to risk factors. Men were more likely to have smoked and were more likely to consume alcohol. Women were more likely to be sedentary and overweight. Medical history showed significant differences as well, with myocardial infarction occurring more commonly in men and hypertension occurring more commonly in women. Other medical conditions, including diabetes, atrial fibrillation, peripheral vascular disease, hyperlipidemia, migraine, and a history of transient ischemic attack, did not differ significantly between the sexes.

Stroke severity tended to be low overall but was comparable between the sexes. Stroke severity in our study may have tended to be lower than that seen in some patient series and typical acute ischemic stroke trials for several reasons—there was no lower limit cutoff in the National Institutes of Health Stroke Scale in the eligibility criteria, cases were enrolled in the subacute phase of stroke recovery, and participation in the ISGS was contingent on patients' or surrogates' providing written informed consent. No significant difference was noted in TOAST stroke subtypes. Just over 30% of patients of both sexes had stroke of undetermined origin. Stroke subtype does not influence response to treatment with recombinant tPA and, hence, is not a necessary prerequisite to recombinant tPA administration.²⁰ However, stroke subtype does have prognostic implications and impacts management and recurrence risk.⁹

In contrast to prior studies,^{5,6} we found similar use of tests in the medical evaluation of stroke in men and women. Indeed, women had a slightly greater use of tests than men in our study. Brain imaging is widely recognized as a mandatory part of the initial medical evaluation of acute stroke.⁹ Use of CT and MRI was not significantly different between men and women. There was relatively high use of MRI, with more than 4 of 5 cases undergoing MRI, without significant differences between men and women. This rate of MRI use is notably higher than that observed in other studies. For instance, Smith et al⁵ detected use of MRI in only 41% of men and 43% of women.

Noncontrast head CT remains the standard brain imaging study for initial evaluation of acute stroke. Studies have debated the benefit of initial MRI as opposed to CT. CT and diffusion-weighted imaging performed with the same delay after onset of ischemic stroke resulted in significant differences in diagnostic accuracy, with diffusion-weighted imaging showing

substantially better sensitivity and accuracy than CT.²¹ In addition, MRI may be as accurate as CT for detecting acute hemorrhage.²² Identifying patients with previous microhemorrhages that could affect the use of thrombolysis is another advantage of MRI use at stroke presentation. These factors may lead to increased MRI use in place of CT after acute stroke to prevent duplication of tests and to better control expenses. Our study did not assess whether the specific sequences used in MRI differed between men and women, but it is likely that the sequences were comparable because the studies were being done for the same indication in both men and women.

Comorbid cardiac conditions are relevant for defining stroke mechanism,^{23,24} prognosticating recurrence,^{25,26} and influencing the course of management.²⁷ Tests of cardiac rhythm and cardiac structure were similar for men and women. ECG was performed in 90% of patients. However, ambulatory ECG monitoring was used very little. This may have been because of the wide availability of cardiac telemetry at participating study hospitals. Similar rates of application were found for TTE. However, women were more likely to receive TEE. On analysis of the means and degree of investigation for each study site independently, no significant differences between sites were found, except for the use of TEE. We speculate that this might reflect relative controversy regarding the use of TTE versus TEE to evaluate the heart structurally. The Significance of TEE in the Prevention of Recurrent Stroke investigators found cardiac abnormalities using TEE in patients with unexplained cerebral ischemia.²⁸ There are no firm guidelines for TEE versus TTE application, but it has been suggested that TEE use can be better refined by applying clinical characteristics, ECG results, and TTE findings to the selection of patients for TEE.²⁹ TEE findings were diagnostic of potential embolic sources in 61% of patients, changed treatment plans in 32% of patients, and precipitated anticoagulation use in 11% of patients with cerebrovascular accident in a recent series by Dawn et al.³⁰ Elderly patients have higher rates of abnormalities implicated as sources of thromboembolism, including impaired left ventricular ejection fraction³¹ and intramural thrombus,³² but specific therapies to address these abnormalities are still poorly defined. Lack of directed therapies may explain some of the variability in practice patterns related to the use of TEE in elderly patients with suspected embolic events.³³ In addition to the ongoing uncertainties about TEE use, differences in individual resources or logistics at the various centers may have played a part.

Excluding potentially remediable carotid stenosis is a standard component of stroke evaluation. Exceptions include posterior circulation strokes, massive disabling stroke, and unacceptable operative risk. Although differences of opinion exist regarding optimal timing of carotid revascularization after an acute nondisabling stroke, there is growing appreciation for the safety, feasibility, and tolerability of urgent (within 2 days of admission) surgical revascularization.³⁴ The potential to promptly revascularize mandates screening for carotid stenosis in all patients with nondisabling anterior circulation stroke of appropriately low surgical risk. A high proportion of patients in ISGS underwent cervical arterial testing in the acute or subacute poststroke period. Contrary to the findings in a European sample,⁶ women were actually more likely to receive carotid ultrasonography than men. MRA accounted for a high proportion of cervical imaging, 59% in both sexes, reflecting relatively high MRI use in this study population. Overall, cervical arterial imaging did not differ significantly between the two sexes at the stroke centers in our study. This lack of sex difference is in keeping with indications for endarterectomy in symptomatic patients.³⁵

Our study captured data on 4 modalities for assessing the intracranial vasculature. Overall, 72% had MRA, 1% had digital subtraction angiography, and 10% had CT angiography. (These percentages are of all patients, not just those with MRI.) No patient underwent transcranial Doppler ultrasonography. The predominance of MRA use might be attributed to its noninvasive nature and the frequency of MRI use, making MRA readily available. CT angiography was the

next most frequent modality to evaluate intracranial vasculature at these stroke centers. The Warfarin Versus Aspirin for Symptomatic Intracranial Disease study recently demonstrated increased adverse effects from use of warfarin for intracranial stenosis and suggested aspirin use instead for intracranial stenosis.³⁶ In the future, increased aspirin use may reduce the push for intracranial vascular imaging because of reduced impact on management decisions.

We wish to mention the following potential limitations in this analysis. This is a nested substudy of a parent study focusing on genetics, which may introduce bias at the point of inclusion by patient consent. In addition, we are unable to comment on sex differences regarding care provided at facilities that are not stroke centers. Further work is needed in this field to fully explore potential sex and treating physician differences and to guide future policy decisions.

Epidemiologic observational studies that have wide access to appropriate diagnostic technologies and apply standardized causal classifications provide a much better understanding of underlying risk factors for initial stroke, recurrence, and mortality.³⁷ In this study, it appears that hospital-based, protocol-driven studies limit bias. Hospital admission with acute stroke is justified because the emergency department evaluation cannot reliably identify patients whose condition will worsen.³⁸ Dedicated stroke centers are desirable for these protocols. With findings similar to these, Kapral et al³⁹ detected no difference between sexes regarding stroke evaluation at dedicated stroke centers in Canada. Variations have been detected in the extent to which diagnostic procedures are performed in acute stroke among medical disciplines (neurology, internal medicine, and geriatrics).⁴⁰ Whether this variation has therapeutic implications remains to be clarified. In addition, creating and adhering to clinical practice guidelines in stroke patients has an economic implication, with lowered costs and shorter hospitalizations.⁴¹ It is possible that the ISAI could provide a frame-work within which the investigation of acute stroke can be facilitated.

Our findings suggest that there are not major sex differences in the extent to which major diagnostic tests are performed in patients enrolled in ISGS. Therefore, ischemic stroke subtype diagnoses are likely to be of comparable validity among men and women.

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Table 1**Medical history of cases by sex**

Characteristic	Male	Female	<i>P</i> [*]
No.	276	229	
TIA	44 (16)	31 (14)	.46
CHF	29 (11)	24 (10)	.97
Angina	53 (12)	18 (8)	.13
Myocardial infarction	55 (20)	23 (10)	.002
Atrial fibrillation			
Chronic	15 (5)	16 (7)	.45
Intermittent	18 (7)	23 (10)	.14
Any	33 (12)	39 (17)	.10
Hypertension	181 (66)	178 (78)	.002
Deep vein thrombosis	17 (6)	15 (7)	.87
Pulmonary embolus	4 (1)	5 (2)	.74 [†]
Peripheral vascular disease	10 (4)	13 (6)	.28
Migraine headaches			
With aura	17 (6)	20 (9)	.26
Without aura	52 (19)	38 (17)	.53
Any	69 (25)	58 (25)	.91
Hyperlipidemia	127 (47)	101 (44)	.59
Diabetes mellitus			
On insulin	24 (9)	28 (12)	.19
Not on insulin	49 (18)	36 (16)	.54
Any	73 (26)	64 (28)	.71

CHF, Congestive heart failure; *TIA*, transient ischemic attack.

Values are number (percentage) unless indicated otherwise. Data were incomplete for some characteristics.

* Chi square tests unless specified otherwise.

[†] Fisher exact test.

Table 2

Odds that a diagnostic test would be performed on a woman with ischemic stroke relative to the odds that the same test would be performed on a man with ischemic stroke

Diagnostic test	Unadjusted		Adjusted*	
	OR	95% CI	OR	95% CI
Head imaging				
CT	0.78	0.42-1.43	0.62	0.33-1.18
MRI	0.95	0.59-1.53	1.08	0.65-1.80
Cardiac rhythm by ECG				
12-lead	0.85	0.47-1.56	0.82	0.42-1.60
Holter	0.30	0.03-2.69	0.31	0.03-2.84
Any ECG	0.85	0.47-1.56	0.82	0.42-1.60
Cardiac structure by echocardiography				
TTE	0.96	0.67-1.38	0.90	0.58-1.40
TEE	1.28	0.90-1.82	1.75	1.12-2.72
Any echocardiography	1.32	0.87-2.00	1.45	0.94-2.26
Cervical arterial imaging				
Carotid ultrasonography	1.47	1.03-2.10	1.78	1.09-2.90
MRA of neck	1.01	0.71-1.45	1.09	0.73-1.64
Digital subtraction angiography	0.34	0.07-1.65	0.36	0.07-1.79
CT angiography	0.66	0.33-1.34	0.75	0.37-1.54
Any cervical arterial imaging	1.63	0.93-2.86	1.75	0.94-3.22
Intracranial vascular imaging				
MRA of head	1.13	0.76-1.67	1.32	0.86-2.02
Digital subtraction angiography	0.80	0.13-4.84	0.92	0.15-5.64
CT angiography	0.70	0.39-1.26	0.67	0.35-1.29
Any intracranial vascular imaging	1.26	0.83-1.91	1.55	0.97-2.47

CI, Confidence interval; CT, computed tomography; ECG, electrocardiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; OR, odds ratio; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

* Adjusted for age at time of stroke, race/ethnicity, and site of enrollment in the study.

Table 3
Odds ratio of female-to-male study patients with regard to having high or low ISAI with varying cut points

ISAI score	Unadjusted		Adjusted [*]	
	OR	95% CI	OR	95% CI
≥3 v 0-2	1.26	0.55-2.86	1.34	0.57-3.16
≥4 v 0-3	1.45	0.88-2.39	1.60	0.94-2.72
5 v 0-4 [†]	1.32	0.93-1.88	1.48	1.02-2.15

CI, Confidence interval; ISAI, Ischemic Stroke Assessment Index; OR, odds ratio.

^{*} Adjusted for age at time of stroke, race/ethnicity, and site of enrollment in the study.

[†] Unadjusted $P = .08$ (Wilcoxon rank sum test); adjusted $P = .03$ (rank analysis of covariance).