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Gender differences in presenting and prodromal stroke symptoms

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Gender differences in presenting and prodromal stroke symptoms

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Abstract

Background and Purpose—Prompt recognition of stroke symptoms is critical to timely treatment and women have increased delay to treatment. Women may be more likely to present with atypical symptoms, but this hypothesis has not been extensively evaluated.

Methods—We examined gender differences in the prevalence of presenting and prodromal stroke symptoms among 1,107 consecutive patients hospitalized with neurologist-confirmed acute ischemic stroke. Patient demographics, clinical variables, and stroke symptoms were abstracted from medical records by trained abstractors using standardized forms. Estimates were age standardized to the age distribution of men and women combined. Presenting symptoms occurred within 24 hrs of incident stroke admission, prodromal symptoms occurred ≥ 24 hours of admission

Results—Women were significantly older (p<.001), more likely to have cardioembolic stroke (p<.001) and less likely to receive aspirin (p=.014) or statins (p<0.001). 35% of the sample (n=389) reported prodomal symptoms. Women were more likely to have ≥ 1 somatic prodromal and presenting symptom (p=.03; p=0.008), but did not differ from men on specific somatic symptoms. Women did not differ from men in classic presenting stroke symptoms (p=.89)

Conclusion—Women did not differ significantly in the prevalence of traditional stroke symptoms, but were more likely to have somatic presenting and prodromal symptoms. We found no differences in specific prodromal symptoms, making it difficult to craft a public health message about gender differences in early warning signs of stroke. These results suggest that the focus of stroke prevention education for women should continue to emphasize traditional stroke risk factors.

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Keywords

Gender; stroke; symptoms

Stroke is a leading cause of long-term morbidity and disability in the United States and there is a growing awareness of the clinical and public health importance of stroke in women. [1, 2] Although age-specific stroke incidence and mortality rates are higher in men than women, women experience a greater number of strokes per year (60,000) [1] because they live longer and at the oldest age (≥85 years) women have higher mortality rates than men.[1] These gender differences in incidence, prevalence, and prognosis of stroke in women will become even more important as the population ages and the proportion of women, particularly older women, increases. [1, 3, 4]

In addition to concerns about the increasing prevalence of stroke, women have been shown to be more likely than men to delay seeking treatment for stroke symptoms [5] and to have poorer outcomes after a stroke including disability and poor quality of life. [1, 3, 6] Delay in seeking treatment is a major factor limiting the timely delivery of therapeutic interventions, [6] and prompt, accurate, recognition of stroke symptoms is a critical first step in seeking treatment. [7–9] In general, public awareness of stroke symptoms is increasing. [10, 11] In one study across 17 states, more people could correctly identify all five symptoms of stroke (52.3%) than could identify all five symptoms of heart attack (24.4%). [10] Despite that, delay to stroke treatment is high and women have been noted to delay three times longer than men. [5]

One hypothesis for why women delay longer in seeking treatment is that they may experience different symptoms than men. Gender differences in acute and prodromal symptoms have been reported for MI, [12] but little is known about possible gender differences in stroke symptoms. Despite this lack of evidence however, some public websites have posted information on the "unique symptoms" women experience with stroke and it has become part of the public's perception of stroke symptoms. [13] If indeed there are gender differences in the symptoms women experience prior to a stroke, this is critical information as a first step in recognizing and appraising the significance of a symptom and seeking prompt treatment. If, however, there are no gender differences, misinformation about unique symptoms may contribute to unnecessary delays in seeking life-saving treatment.

The purpose of this study, therefore, is to examine gender differences in the prevalence of acute and prodromal stroke symptoms.

Subjects and Methods

Data Collection

This study was approved by the Committee on Clinical Investigations at the Beth Israel Deaconess Medical Center. We identified all patients 21 years of age or older admitted to Beth Israel Deaconess Medical Center between April 1, 1999 and December 31, 2004 with a neurologist-confirmed diagnosis of acute ischemic stroke and residing in the Boston metropolitan region. Patient's medical records were reviewed by trained abstractors to confirm the diagnosis of acute ischemic stroke. Patients with in-hospital strokes or transient ischemic attacks were excluded from further analysis.

For each case, trained abstractors using standardized forms recorded data on patient demographics, past medical history, admission medications, and acute and prodromal symptoms from patient charts or electronic medical records. Race was categorized as White, African American, Asian, other or unknown. Presumed stroke etiology was determined

according to an abbreviated TOAST classification system [14] after review of the diagnostic work-up. Acute symptoms were defined as self-reported or witness-reported symptoms occurring within 24 hours of admission to hospital. Prodromal symptoms were defined as self-reported symptoms that preceded the 24 hours of admission to hospital. A neurology nurse practitioner abstracted information on presenting and prodromal symptoms from the admission or discharge note written by the stroke service neurologists. If the patient was aphasic or had a reduced level of consciousness, the family or other witnesses often provided information on prodromal and presenting symptom; or if the patient's condition improved and they could provide a more complete history, the information was abstracted from the discharge summary. There were not a sufficient number of these patients to assess if the characteristics differed in frequency between men and women.

Statistical Analysis

Descriptive statistics were calculated separately for men and women. We tested the null hypothesis of no difference by gender using a two-sample t-test for continuous variables and Pearson's Chi-square test of association for categorical variables. Because the age distribution differed between men and women, variables were age-standardized using as the standard the overall age distribution among men and women combined. All hypothesis tests are 2-sided and $p<0.05$ was considered statistically significant. Analyses were carried out using SAS v9.1.3 (SAS Institute Inc., Cary, NC).

Results

We obtained data on 1107 consecutive patients hospitalized with neurologist-confirmed diagnosis of acute ischemic stroke. Patients were predominantly non-Hispanic white (62.7%) and female (54.9%) with a mean age of 73.0±14.5 years (mean ± SD). Women hospitalized with acute ischemic stroke tended to be older than men, and this difference was statistically significant (women: 75.8±14.5 years; men: 69.7±13.8 years; $p<0.0001$). No statistically significant between group differences were noted for race or ethnicity ($p=0.34$). Presumed stroke etiology differed by gender (Table 1). Women were more likely to have cardioembolic stroke or for the mechanism to be undetermined and men were more likely to have large or small vessel stroke. On admission to hospital there were no gender differences in blood pressure for either systolic (women: 159 mmHg±31.7: men 158 mmHg±29.1; $p=0.64$) or diastolic (women: 79 mmHg±19.5: men: 79 mmHg±15.8; $p=0.69$) blood pressure.

Table 2 compares the prevalence of co-morbid conditions and admission medications by gender. Women were statistically significantly less likely to have a history of dyslipidemia, diabetes, coronary artery disease, myocardial infarction or to be current smokers. However, after adjusting for age, differences in the prevalence of dyslipidemia and current smoking were only marginally statistically significant. Women were more like than men to have a history of atrial fibrillation, but this difference was not statistically significantly different after age adjustment. Women and men were equally likely have two or more co-morbidities noted on admission (68.7% vs 73.7% respectively, $p=0.18$).

On admission, women were statistically significantly less likely than men to be on aspirin or statins, and this difference remained statistically significant after adjusting for age. No statistially significant differences were observed by gender for use of Coumadin, ACE inhibitors, beta blockers, or calcium channel blockers.

The prevalence of specific presenting symptoms did not differ by gender (Table 3). After age-standardization women were as likely as men to report symptoms of: weakness, clumsiness, numbness, seizure, difficulty speaking, difficulty walking, headache, change in behavior, difficulty understanding, nausea, change in vision, feeling "funny", fatigue, malaise or a variety

of non-specific complaints (other). Women and men were also equally likely to report at least one of the classic symptoms that are included in public education about stroke (numbness, weakness, difficulty speaking, change in vision, difficulty walking, headache, clumsiness, or difficulty understanding). However, women were more likely to report at least one non-specific or somatic symptom (p=0.008).

Prodromal symptoms were identified in 35.1% of patients and the prevalence of reported prodromal symptoms did not differ significantly by gender (p=0.64). Women were less likely to report prodromal symptoms of weakness and clumsiness as compared to men, even after age-standardization (Table 1). Numbness was also noted more frequently in men than women, but this difference was not statistically significant in age-standardized estimates. Headache was more commonly reported by women as a prodromal symptom, but this difference was only marginally statistically significant (p=0.051) when age-standardized estimates were considered. When clustered into a single variable, women were more likely to report at least one somatic prodromal symptom.

Discussion

Prior research seeking to understand gender differences in stroke has centered on incidence rates, knowledge of stroke risk factors, clinical presentation, delay to treatment, medical care and outcomes. [2, 5, 6, 15] Although recognition of symptoms is critical to timely treatment, [1, 6, 10, 12,16] and gender-related differences in women's symptoms with acute myocardial infarction has been observed, [12] little is known about potential differences in stroke symptoms experienced by women. We are aware of only one published study on the prevalence of symptoms among incidence strokes stratified by gender [15] and none that reported on prodromal symptoms.

In this analysis of 1,107 consecutive patients hospitalized for confirmed acute ischemic strokes we found some differences in somatic stroke symptoms for women, but the importance is unclear. Over one third of patients experienced prodromal symptoms, and women were more likely to report having at least one somatic prodromal symptom compared to men. There were no differences between men and women in the prevalence of specific somatic prodromal symptoms, so it is difficult to identify specific symptoms that women should be educated about. Similarly, women were more likely to self-report somatic presenting symptoms, but again there were no statistically significant differences in the specific symptoms reported. Thus, we are not able to identify unique early warning signs of stroke in women. However, it is reassuring to note that more than 97% of both men and women report at least one classic symptom in the twenty-four hours prior to hospital admission.

We did observe that men were more likely to experience the prodrome of weakness, clumsiness and numbness, but after adjusting for age, numbness was not statistically significant. These data are similar to the gender differences noted in the ARIC study where they found that for the most part women did not significantly differ from men in the prevalence of classic symptoms although men were more likely than women to experience gait disturbance (6.7% vs 14.4%; p=0.007). [15] Since these symptoms are included in the classic symptoms disseminated in public health information, the data fit with current practice and do not necessitate any tailoring of the message.

Recommendations from the NIH National Institute of Neurological Disorders and Stroke (NINDS) multidisciplinary working group on Advancing the Study of Stroke in Women, state that research is needed that is focused on gender differences in the perception of risk and prevention for stroke compared with, and independent of, heart disease. [2] They also conclude that there is a need for better education regarding stroke symptoms for women and their care

providers. Our data suggest that we should continue to focus on classic or traditional signs and symptoms of stroke for women and perhaps introduce, but not emphasize, less specific, somatic symptoms.

Age standardization added an important dimension to the understanding of presenting and prodromal symptoms. Women who experience stroke tend to be older and some of the co-morbidities and symptoms observed are likely influenced by age. For example, when we adjusted for age, the gender differences noted for the prevalence of atrial fibrillation were attenuated as might be expected since atrial fibrillation is more prevalent in older populations. Other than one symptom (clumsiness) and one prodromal symptom (prodromal numbness) we did not observe material differences in the crude and age-standardized analyses, leading to the conclusion that the gender differences we observed for symptoms were not materially confounded by age; an important consideration as women hospitalized with ischemic strokes tend to be older.

Similar to prior studies [17–19] we found that women were less likely than men to be on aspirin or statins at the time of admission even after adjusting for age, This finding is concerning given existing evidence that these treatments might be helpful in preventing stroke in women and the finding in our study that women were more likely to experience cardiembolic stroke.. Several recent studies have demonstrated that aspirin reduced the risk of ischemic stroke in women, but not men, even for those at low risk for cardiovascular disease. [20, 21] Also of interest, inflammation has been associated with the risk of incident and recurrent cardiac events, and probably stroke. [22–24] The NINDS working group to advance the study of stroke in women identified the role of various therapies (ie, statins) that have been shown to lower inflammatory markers in women at risk as a priority research area. [2] Thus the finding in the present study that women were less likely to be on Aspirin or statins, could have implications for adequate prevention of stroke in women.

This study has some potentially important limitations. First, the data were obtained through medical record review which presents the potential for misclassification or missing data particularly in regard to presenting and prodromal symptoms. During the time period of the study however, there were a limited number of attending neurologists who reviewed all admission and discharge notes. This increased the consistency and completeness of the notes. Second, early warning or prodromal symptoms were abstracted without knowledge of whether these symptoms appeared or changed in intensity or frequency before the incident stroke and disappeared or returned to previous levels of intensity or frequency afterward. Some have suggested that individuals need time after an incident event to reflect on and accurately identify prodromal symptoms. [12] Finally, our sample was largely white, precluding subanalysis by race or ethnicity and potentially limiting the generalizability of these findings.

Other studies have found a similar distribution of age, co-morbidity and presumed stroke etiology to what we found in the present study. It has been previously noted that women who suffer a stroke tend to be older, and more likely to have atrial fibrillation and hypertension whereas men were more likely to have a history of diabetes, dyslipidemia, tobacco use, cardiovascular disease and myocardial infarction. [3, 25–30] In several studies, women have been found to be at increased risk of cardioembolic stroke, likely related to the increased prevalence of atrial fibrillation in older women. [3, 27, 31] Thus, given that the characteristics of our sample are comparable to other published reports, the results of the present study are plausibly generalizable beyond the Boston metropolitan area to other parts of the United States.

In conclusion, after adjusting for age, we did not find evidence that women were less likely then men to experience classic stroke symptoms in the twenty-four hours preceding hospital admission. They were however, more likely to report non-specific or somatic symptoms,

although the specific somatic symptoms remain unclear. Some have hypothesized that failure to experience classic stroke symptoms may be one reason that women delay three times longer than men in seeking treatment for acute stroke, but in the present study we did not find this difference in classic symptoms. Others have hypothesized that women were more likely to experience somatic prodromal symptoms and this could lead to confusion and delay in seeking treatment. Although we found that they were more likely to experience at least one somatic symptom, we were not able to identify specific symptoms and the mechanism is unclear and warrants further study. Also of note, we found that women were less likely to receive Aspirin and statins.

Given the retrospective nature of this study, our findings are primarily intended for hypothesis generation. However, until more information is available about the importance of gender differences in somatic symptoms, we suggest that the focus of stroke prevention education for women should continue to emphasize traditional risk factors. Somatic symptoms should be introduced and discussed in conjunction with traditional risk factors, but the message has to be carefully balanced so that women do not fail to recognize traditional stroke symptoms. In addition, providers should be encouraged to adhere to established guidelines for secondary prevention of cardiovascular disease, which recommend Aspirin for women with identified risk factors. [32]

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Table 1

Characteristics of 1107 patients hospitalized for neurologist-confirmed acute ischemic stroke, stratified by Gender.

	Female		Male		
	n	**%**	**n**	**%**	**p-value**
Total	608	54.9	499	45.1	
Race					0.34
White	370	60.9	324	64.9	
Black	72	11.8	38	7.6	
Asian	12	2.0	10	2.0	
Other	9	1.5	8	1.4	
Unknown	145	23.9	119	23.9	
Hispanic	15	3.2	15	4.0	0.58
Presumed Etiology					0.011
Large Vessel	123	20.2	124	24.9	
Small Vessel	155	25.5	158	31.7	
Cardioembolic	146	24.0	95	19.0	
Other	27	4.4	21	4.2	
Undetermined	157	25.8	101	20.2	
Etiology Determined	451	74.2	398	79.8	0.029

Values may not sum to 100 because of rounding.

Table 2

Past medical history and medications on admission among 608 female and 499 male patients hospitalized for acute ischemic stroke, stratified by gender.

	Female			Male				
		Crude	Age Standardized		Crude	Age Standardized	Crude	Age Standardized
	n	%	%	n	%	%	*P*-Value	*P*-Value
Past Medical History								
Hypertension	429	70.6	70.4	341	68.3	67.3	0.42	0.27
Dyslipidemia	202	33.2	34.4	205	41.1	39.2	0.007	0.10
Diabetes	150	24.7	25.9	176	35.3	33.9	<0.001	0.004
Coronary artery disease	133	21.9	21.4	161	32.3	34.8	<0.001	<0.001
Myocardial infarction	66	10.9	10.4	77	15.4	15.4	0.024	0.013
Stroke	145	23.8	23.5	134	26.9	28.5	0.25	0.061
Atrial fibrillation	160	26.3	23.8	102	20.4	22.7	0.022	0.66
Current Smoker	68	11.2	12.6	94	18.8	16.2	<0.001	0.083
Admission Medications								
Aspirin	236	38.8	38.8	230	46.1	46.2	0.015	0.014
Diuretic	104	17.1	16.5	57	11.4	11.4	0.008	0.015
Statins	138	22.7	23.9	190	38.1	38.0	<0.001	<0.001
Coumadin	59	9.7	9.5	12	11.6	11.9	0.30	0.19

Table 3

Prevalence of presenting symptoms among 608 female and 499 male patients hospitalized for acute ischemic stroke, stratified by gender.

	Female			Male				
		Crude	Age Standardized		Crude	Age Standardized	Crude	Age Standardized
	n	%	%	n	%	%	*P*-Value	*P*-Value
Weakness	500	82.2	81.1	402	80.6	81.7	0.48	0.79
Clumsiness	201	33.1	34.4	197	39.5	38.6	0.027	0.15
Numbness	158	26	27.2	137	27.5	26.0	0.58	0.64
Seizure	24	3.9	3.8	14	2.8	2.4	0.30	0.20
Difficulty speaking	315	51.8	50.4	274	54.9	55.8	0.30	0.074
Difficulty walking	182	29.9	30.3	169	33.9	33.8	0.16	0.21
Headache	64	10.5	12.2	56	11.2	9.3	0.71	0.12
Change in behavior	80	13.2	11.8	62	12.4	13.6	0.72	0.36
Difficulty understanding	194	31.9	30.6	138	27.7	29.8	0.12	0.78
Nausea	21	3.5	3.6	25	5.0	5.1	0.20	0.23
Change in vision	160	26.3	26.0	121	24.2	23.9	0.43	0.43
Feels *“funny”*	10	1.6	1.9	12	2.4	2.2	0.37	0.77
Fatigue	16	2.6	2.5	12	2.4	2.2	0.81	0.74
Malaise	42	6.9	6.7	32	6.4	6.1	0.74	0.71
Other	230	37.8	37.5	163	32.7	33.0	0.074	0.12
Classic Cluster[†]	596	98.0	97.7	489	98.0	97.8	0.97	0.89
Somatic Cluster[‡]	446	73.4	72.6	324	64.9	65.2	0.002	0.008

[†]Defined as the presence of ≥1 of the following: numbness, weakness, difficulty speaking, change in vision, difficulty walking, headache, clumsiness, or difficulty understanding.

[‡]Defined as the presence of ≥1 of the following: headache, change in behavior, difficulty understanding, nausea, change in vision, feels “funny”, fatigue, malaise, or “other” presenting symptom.

Table 4

Prevalence of prodromal symptoms among 210 female and 179 male patients with ≥1 prodromal symptom.

	Female			Male				
		Crude	Age Standardized		Crude	Age Standardized	Crude	Age Standardized
	n	%	%	n	%	%	*P*-Value	*P*-Value
Any symptom	210	34.5		179	35.9		0.64	0.84
Weakness	81	38.6	36.8	89	49.7	50.1	0.027	0.008
Clumsiness	20	9.6	11.1	35	19.6	19.9	0.005	0.016
Numbness	34	16.2	19.9	43	24	22.8	0.053	0.24
Seizure	7	3.3	2.9	7	3.9	3.4	0.76	0.78
Difficulty speaking	69	32.9	31.1	62	34.6	34.1	0.71	0.52
Difficulty walking	50	23.8	23.1	51	28.5	29.9	0.29	0.12
Headache	45	21.4	23.4	32	17.9	15.5	0.38	0.051
Change in behavior	26	12.4	11.6	17	9.5	10.6	0.37	0.76
Difficulty understanding	36	17.1	16.8	26	14.5	14.6	0.48	0.56
Nausea	14	6.7	7.2	17	9.5	10	0.30	0.32
Change in vision	33	15.7	16.6	21	11.7	10.9	0.26	0.10
Feels *“funny”*	21	10	9.6	10	5.6	5.8	0.11	0.16
Fatigue	12	5.7	5.5	13	7.3	7.4	0.53	0.46
Malaise	23	11	9.8	14	7.8	7.6	0.29	0.45
Other	90	42.9	42.3	67	37.4	38.3	0.28	0.42
Classic Cluster[†]	186	88.6	89.0	168	93.9	92.1	0.070	0.29
Somatic Cluster[‡]	159	75.7	75.3	116	64.8	65.2	0.019	0.030

[†]Defined as the presence of ≥1 of the following prodromal symptoms: numbness, weakness, difficulty speaking, change in vision, difficulty walking, headache, clumsiness, or difficulty understanding.

[‡]Defined as the presence of ≥1 of the following: headache, change in behavior, difficulty understanding, nausea, change in vision, feels “funny”, fatigue, malaise, or “other” prodromal symptom.