Acute Stroke Symptoms Comparing Women and Men

Lynda D. Lisabeth, PhD; Devin L. Brown, MD; Rebecca Hughes, BA; Jennifer J. Majersik, MD; Lewis B. Morgenstern, MD

Background and Purpose—In a recent meta-analysis, women with stroke had 30% lower odds of receiving tissue plasminogen activator than did men, and some studies have reported greater in-hospital delays in women with stroke. Causes of these disparities are unclear but could result from a different symptom presentation in women. Our objective was to prospectively investigate gender differences in acute stroke symptoms.

Methods—Ischemic stroke/TIA cases presenting to the University of Michigan Hospital (January 2005 to December 2007) were identified. Stroke/TIA symptoms, ascertained by patient interview, were classified as traditional or nontraditional (pain, mental status change, lightheadedness, headache, other neurological, nonneurological). Prevalence of any nontraditional symptom and of each symptom were calculated by gender. Logistic regression was used to compare nontraditional symptoms by gender adjusted for stroke vs TIA, proxy use, age, and discharge disposition (home vs other).

Results—Included were 461 cases (48.6% women; median age, 67). Among women, 51.8% reported ≥1 nontraditional stroke/TIA symptom compared to 43.9% of men (P=0.09). The most prevalent nontraditional symptom was mental status change (women, 23.2%; men, 15.2%; P=0.03). The odds of reporting at least 1 nontraditional stroke/TIA symptom were 1.42 times (95% CI, 0.97–2.06) greater in women than in men.

Conclusion—A high prevalence of nontraditional symptoms among both genders was found, with women more likely to report nontraditional symptoms and, in particular, altered mental status, compared with men. Larger-scale studies focusing on stroke in women are warranted and could confirm gender differences in symptoms in a larger, more representative stroke population and address the clinical consequences. (Stroke. 2009;40:2031-2036.)

Key Words: cerebrovascular disease ■ female ■ sex factors ■ stroke ■ women

In a recent meta-analysis, women with stroke had 30% lower odds of receiving tissue plasminogen activator than did men.1 Some but not all studies have reported greater out-of-hospital delays in women with stroke compared with men.2–6 Studies have also reported greater in-hospital delays for women with stroke, including increased time to see an emergency department physician6 and time to head imaging.7–11 compared with men. Reasons for these gender disparities in access to acute stroke care are unclear but could be the result of women having a different spectrum of stroke symptoms at presentation that contributes to both out-of-hospital and in-hospital delays.

In a study by Labiche et al,12 women with stroke were more likely to present with “nontraditional” stroke symptoms compared with men (OR, 1.6; 95% CI, 1.2–2.2). Nontraditional symptoms more frequently reported by women included pain and reduced level of consciousness. In contrast, “traditional” stroke symptoms of imbalance and hemiparesis were more frequently reported by men. A small number of studies, primarily from European and Canadian registries, have also reported a greater frequency of change in level of consciousness13–15 and headaches in women with stroke.13,16,17 Other studies have documented gender differences in some traditional stroke symptoms, but results have not been consistent or have failed to measure nontraditional symptoms.16,18 Whether women with acute stroke present differently from men and the impact of this on prehospital and posthospital delay remains unclear.

If women do present differently with stroke from men, then there are important public health implications. Recognition of potential gender differences in stroke symptoms through education aimed at both the public and health care professionals could result in decreased out-of-hospital and in-hospital delays, thus increasing access to acute stroke therapy in women. The objective of this study was to prospectively investigate gender differences in acute stroke symptoms using data collected by patient interviews to confirm or refute previous findings of an increased frequency of nontraditional stroke symptoms in women.

Materials and Methods
The study population included adult men and women presenting to the University of Michigan Hospital, Ann Arbor, Michigan, with...
ischemic stroke or TIA during the time period January 2005 through December 2007. The University of Michigan Hospital is a large academic teaching hospital. Exclusion criterion included age younger than 18 years.

Active surveillance of emergency department and admission logs for potential ischemic stroke and TIA cases was conducted prospectively on weekdays (Monday to Friday) during business hours (8:00 AM to 5:00 PM). Cases admitted overnight or during the weekend were identified on the next business day. Patients were approached for participation in the study as soon as possible after their admission or stay in the emergency department to minimize recall bias. If a subject was unable to communicate clearly based on a set of brief orientation questions, then a proxy was sought to complete the interview. In-person structured interviews with stroke/TIA patients or their proxies were then conducted by trained interviewers. Interviewers were trained by 1 study investigator (L.D.L.), and all interviewers were observed conducting an interview and provided with feedback by this same investigator. All interview questions were scripted. Eighty-six percent of interviews were conducted by 3 female interviewers. Written informed consent was obtained from all subjects, and this project was approved by the University of Michigan’s Institutional Review Board.

Stroke/TIA Symptom Collection and Definitions

Stroke symptom information was collected by asking patients to describe the symptoms that caused them to go to the hospital and by recording appropriate boxes on a stroke symptom checklist. If the patient described symptoms that were not part of the checklist, then they were recorded as “other.” In addition to stroke symptom information, the survey included demographics and self-reported stroke risk factors.

The main end point was the dichotomous variable of any nontraditional stroke/TIA symptom vs none. Definitions for traditional and nontraditional symptoms were based on the American Stroke Association’s published stroke warning signs19 (considered traditional) and the Labiche et al12 study’s classification of nontraditional symptoms with some modification. Nontraditional symptoms included pain (face or hemi-body pain), mental status change (disorientation, confusion, or loss of consciousness), lightheadedness, headache, general neurological symptoms (nausea, hiccups, nonfocal weakness), and nonneurological symptoms (chest pain, palpitations, shortness of breath). Headache is included on the American Stroke Association’s list of stroke warning signs because it is a symptom of subarachnoid hemorrhage. Given that the focus of the current study was on ischemic stroke/TIA and that headache is common in many medical disorders20 and not a focal neurological symptom, headache was included as a nontraditional symptom. Unlike in the Labiche et al12 study, headache was not included as its own symptom rather than being included in the pain category. Definitions for traditional symptoms included hemi-body numbness, diplopia, other visual disturbances, aphasia, dysarthria, discoordination/ataxia, hemiparesis, facial weakness, and vertigo.19 The number of traditional and nontraditional symptoms was calculated for each patient. The number of nontraditional symptoms was categorized as 0, 1, or ≥2 symptoms and the number of traditional symptoms was categorized as 0, 1, 2, 3, or ≥4 symptoms as the sample sizes for the upper tails of the distributions were small.

Date and time of symptom onset were recorded during the interview. Using previously published methods, patients who woke with symptoms were assigned an onset time of 11:00 PM the previous evening or the time that they went to bed if after 11:00 PM.5 In patients who did not have a clear time of onset, a time of 12:00 AM on the day of onset was used. The frequency of missing symptom onset date and time was small (1.9%) and did not differ by gender (P=0.32). Date and time of hospital arrival were collected from the medical record or from the patient. Time from symptom onset to hospital arrival was then calculated.

Stroke/TIA Validation and Discharge Disposition

Potential cases were validated as ischemic stroke, TIA, or other using discharge summaries. In instances in which the validation could not be determined from the discharge summary, fellowship-trained stroke neurologists validated the potential case as stroke/TIA using source documentation collected from the medical record including the discharge summary and any reports from brain imaging performed as part of the acute stroke workup. Neurologists were blinded to gender. At the time of validation, cases were classified as stroke or TIA. Ischemic stroke was defined as the acute onset (minutes to hours) of a focal neurological deficit specifically attributable to a cerebrovascular distribution that persisted for >24 hours and not attributable to another disease.21 The definition of TIA differed only in that symptoms ceased within 24 hours of onset. Information on discharge disposition (home, assisted living, nursing home/long-term care or skilled nursing facility, inpatient rehabilitation, other) was also recorded from the discharge summary.

Statistical Analysis

Statistical analyses were restricted to 1 event per person. For those with multiple events, the first event in the study time period was used. Demographic variables (gender, race/ethnicity), and admission source (emergency department, transfers, direct admits, in-hospital) were summarized using frequencies and percents. Age was summarized using a median and interquartile range (IQR) and compared by gender using a Wilcoxon rank sum test. Stroke risk factors, stroke vs TIA, proxy use (yes/no), and discharge disposition (other vs home) were summarized by gender using frequencies and percents and compared using χ² tests.

The frequency and percent of reporting any nontraditional stroke/TIA symptom, of an isolated nontraditional stroke/TIA symptom(s), and of each individual stroke/TIA symptom collected were calculated by gender and compared using χ² or Fisher exact tests. The numbers of nontraditional and traditional symptoms reported were also compared by gender using χ² tests. Logistic regression models were used to compare the odds of nontraditional symptoms in women and men. Models were run unadjusted and adjusted for ischemic stroke vs TIA, use of a proxy (yes/no), age (modeled continuously), and discharge disposition (other vs home). Stratified logistic regression models were run to determine whether the association between gender and nontraditional symptoms was modified by use of a proxy (yes/no). In the stratified model including only those cases that required a proxy, stroke vs TIA was not included because 91% (86 of 95) of these cases were ischemic strokes.

Time from symptom onset to hospital arrival was summarized using a median and IQR and compared by gender using a Wilcoxon rank-sum test. Time to hospital arrival was also compared by the presence or absence of a nontraditional symptom using a Wilcoxon rank-sum test.

Results

Six hundred forty-two patients were approached for participation; of which 573 agreed (participation rate=89.3%), and 568 completed/partially completed the interview (response rate=88.5%). Those who completed an interview did not differ from those who did not participate by gender (P=0.24) or age (P=0.18). Before analysis, 88 interviews were excluded because the cases were validated as not stroke/TIA (n=82), the interview was incomplete/missing (n=3), or the patient did not have symptoms or recalled the wrong event (n=3). After these exclusions, there were 480 stroke/TIA cases. Limiting to 1 event per individual, there were 461 individual cases. Of the 461 cases, 364 (79.0%) were seen in the emergency department, 68 (14.8%) were transfers from outside hospitals, 15 (3.3%) were directly admitted to the hospital, and 14 (3.0%) were in-hospital strokes/TIAs.

Among the 461 individuals, 49% (n=224) were women. Eight-seven percent (n=401) were white, 10% (n=44) were black, 2% (n=9) were Asian/Pacific Islander, and 2% (n=7)
Table 1. Prevalence of Stroke Risk Factors by Gender (n=461)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Women (n=224)</th>
<th>Men (n=237)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>149 (66.5)</td>
<td>142 (59.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes</td>
<td>58 (25.9)</td>
<td>50 (21.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>114 (50.9)</td>
<td>130 (54.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>69 (30.8)</td>
<td>78 (32.9)</td>
<td>0.63</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>49 (21.9)</td>
<td>37 (15.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Current smoking</td>
<td>40 (17.9)</td>
<td>49 (20.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>Previous stroke/TIA cases</td>
<td>66 (29.5)</td>
<td>60 (25.3)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Among women, 51.8% (n=116) reported at least 1 nontraditional stroke/TIA symptom in comparison to 43.9% (n=104) of men (P=0.09). The unadjusted odds of reporting a nontraditional stroke/TIA symptom were 1.37 (95% CI, 0.95–1.98) times greater in women compared with men. After adjusting for stroke vs TIA, age, proxy use, and discharge disposition (Table 2), the association between gender and nontraditional symptoms was relatively unchanged (OR, 1.42; 95% CI, 0.97–2.06) and of borderline significance (P=0.07). Proxy use was associated with nontraditional symptoms, with those patients requiring a proxy being more likely to report nontraditional symptoms (OR, 1.72; 95% CI, 1.05–2.84). Age was associated with nontraditional symptoms in that older individuals were less likely to report nontraditional symptoms (OR, 0.99; 95% CI, 0.97–1.00). Stroke type (ischemic vs TIA) and discharge disposition (other vs home) were not associated with nontraditional symptoms in the multivariable model.

Table 2. Results of Multivariable Logistic Regression Model of Gender and ≥1 Nontraditional Stroke/TIA Symptom (n=461)

<table>
<thead>
<tr>
<th>Risk</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>1.00</td>
</tr>
<tr>
<td>Men</td>
<td>1.00</td>
</tr>
<tr>
<td>Women</td>
<td>1.42 (0.97, 2.06)</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.98, 1.00)</td>
</tr>
<tr>
<td>Stroke type</td>
<td>1.00</td>
</tr>
<tr>
<td>TIA</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.72 (1.05, 2.84)</td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Discharge disposition</td>
<td>1.00</td>
</tr>
<tr>
<td>Home</td>
<td>1.00</td>
</tr>
<tr>
<td>Other</td>
<td>1.04 (0.65, 1.67)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.

*Three cases were missing stroke type information and were excluded from the model.

Nontraditional Stroke/TIA Symptoms by Gender

Among women, 51.8% (n=116) reported at least 1 nontraditional stroke/TIA symptom in comparison to 43.9% (n=104) of men (P=0.09). The unadjusted odds of reporting a nontraditional stroke/TIA symptom were 1.37 (95% CI, 0.95–1.98) times greater in women compared with men. After adjusting for stroke vs TIA, age, proxy use, and discharge disposition (Table 2), the association between gender and nontraditional symptoms was relatively unchanged (OR, 1.42; 95% CI, 0.97–2.06) and of borderline significance (P=0.07). Proxy use was associated with nontraditional symptoms, with those patients requiring a proxy being more likely to report nontraditional symptoms (OR, 1.72; 95% CI, 1.05–2.84). Age was associated with nontraditional symptoms in that older individuals were less likely to report nontraditional symptoms (OR, 0.99; 95% CI, 0.97–1.00). Stroke type (ischemic vs TIA) and discharge disposition (other vs home) were not associated with nontraditional symptoms in the multivariable model.

Among women, isolated nontraditional symptoms were reported in 4.0% (n=9) of cases compared with 3.0% (n=7) of cases among men (P=0.53). Among women, 48.2%, 33.0%, and 18.8% reported 0, 1, or ≥2 nontraditional symptoms, respectively. Among men, the parallel figures were 56.1%, 28.3%, and 15.6%. The numbers of nontraditional and traditional symptoms reported were not associated with gender (P=0.24 and P=0.27).

Individual Stroke/TIA Symptoms by Gender

The frequency and percent of each stroke/TIA symptom by gender are presented in Table 3. The most prevalent nontraditional symptom was mental status change, reported by 23.2% of women and 15.2% of men (P=0.03). There was a trend toward women reporting more nonneurological symptoms (P=0.10), although the prevalence of nonneurological symptoms was low in both genders. There was a borderline association between gender and diplopia (P=0.08), with women being more likely to report this symptom compared with men. Other symptoms did not differ largely by gender.
change among women (23% compared with 15% in men; P = 0.03). Other studies have described similar findings.12,14,15 Glader et al13 reported 78% of women with stroke to be fully conscious on admission compared to 84% of men. Labiche et al12 reported that 17% of women with stroke/TIA had a change in level of consciousness compared with 12% of men.

In our study, other nontraditional symptoms, including pain, lightheadedness, headache, other neurological or nonneurological symptoms, were less prevalent (<16%) and did not differ largely by gender. The prevalence of traditional symptoms was similar among the genders with the exception of diplopia, which was more commonly reported in women. Consistent gender differences in traditional symptoms have not been clearly demonstrated in the literature.12,16,18,22

The public health and clinical importance of the high frequency of nontraditional symptoms across the genders and the observation that women report nontraditional stroke symptoms more frequently than men, including the impact on timely diagnosis of stroke, delays in seeking care, prompt triage, and access to acute stroke therapy, deserves further attention. In our population, isolated nontraditional stroke symptoms were rare (3%–4%), suggesting that the majority of cases present with at least 1 traditional symptom or with a combination of traditional and nontraditional symptoms. Still, 52% of women reported at least 1 nontraditional symptom and 4% of women reported only a nontraditional symptom. Given mounting evidence pointing to less favorable stroke outcomes in women compared with men,13,16,23–25 nontraditional symptoms could be critical if they lead to a delay in recognition of stroke by women, bystanders, or health care professionals and missed treatment opportunities. Although women had longer times to hospital arrival, we did not find an association between nontraditional symptoms and time to arrival. Additional research is needed to understand the impact of specific nontraditional stroke/TIA symptoms or combinations of these symptoms on access to acute stroke care.

Current public stroke education messages, including the “Give me 5” message endorsed by the American Heart Association, American Academy of Neurology, and American College of Emergency Medicine Physicians,26 and the more abbreviated FAST message,27 target traditional stroke symptoms only, as have recent trials and intervention studies aimed at increasing the public’s stroke knowledge.28,29 The question is whether stroke education messages and intervention efforts should be tailored to address the possibility that women with stroke may also experience less typical symptoms. Given growing evidence of gender differences in symptoms among cardiac patients,30–39 the American Heart Association warning signs for MI include a cautionary statement that “women are somewhat more likely than men to experience some of the other common symptoms, particularly shortness of breath, nausea/vomiting, and back or jaw pain.”40 The utility of a parallel statement in stroke is unclear, but given that 780,000 strokes occur each year, with more women than men having a stroke, even if a tailored message reached the minority of women who have isolated nontraditional symptoms, the public health impact could be large. However, adding more information to the current public stroke messages could also add complexity and confusion.

Including the current study, there are now 2 studies to our knowledge conducted in different populations, settings, and geographic regions that support a moderate association between gender and nontraditional symptoms, specifically altered mental status. The enthusiasm for a larger confirmatory

<p>| Table 3. Prevalence of Stroke/TIA Symptoms by Gender (n=461) |
|---------------------------------|-----------------|--------|--------|--------|--------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Women (n=224)</th>
<th>Men (n=237)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemibody numbness</td>
<td>67</td>
<td>80</td>
<td>33.8</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>86</td>
<td>93</td>
<td>39.2</td>
</tr>
<tr>
<td>Aphasia</td>
<td>58</td>
<td>25.9</td>
<td>62</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>52</td>
<td>23.2</td>
<td>70</td>
</tr>
<tr>
<td>Visual disturbance excluding diplopia</td>
<td>35</td>
<td>15.6</td>
<td>4</td>
</tr>
<tr>
<td>Diplopia</td>
<td>12</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Facial weakness</td>
<td>30</td>
<td>13.4</td>
<td>35</td>
</tr>
<tr>
<td>Discordination/ataxia</td>
<td>103</td>
<td>46.0</td>
<td>106</td>
</tr>
<tr>
<td>Vertigo</td>
<td>18</td>
<td>8.0</td>
<td>12</td>
</tr>
<tr>
<td>Nontraditional symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face or hemibody pain</td>
<td>9</td>
<td>4.0</td>
<td>8</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>29</td>
<td>13.0</td>
<td>36</td>
</tr>
<tr>
<td>Mental status change</td>
<td>52</td>
<td>23.2</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>31</td>
<td>13.8</td>
<td>28</td>
</tr>
<tr>
<td>Other neurologic symptoms</td>
<td>33</td>
<td>14.7</td>
<td>35</td>
</tr>
<tr>
<td>Nonneurologic symptoms</td>
<td>11</td>
<td>4.9</td>
<td>5</td>
</tr>
</tbody>
</table>
study may be somewhat dampened by the low prevalence of isolated nontraditional symptoms. However, recent evidence of gender disparities in stroke, including tissue plasminogen activator use and poststroke outcomes, suggest that further investigation of stroke in women is necessary. A large, multicenter study could address a variety of questions to broaden our overall understanding of stroke in women including: (1) whether there are gender differences in nontraditional symptoms among a representative population of stroke cases and (2) whether symptom presentation may have clinical consequences, including explaining some existing gender disparities. In addition, such a study could also serve as the infrastructure to begin to unravel other gender disparities in stroke, including differences in poststroke functional outcomes and quality of life.

Some limitations warrant discussion. The study was conducted in 1 academic medical center; therefore, results may not be generalizable to the broader stroke population. Several statistical tests were conducted; therefore, it is possible that observed differences may be attributable to chance. Our sample size was based on the results of Labiche et al12 study and the number of cases seen at University of Michigan Hospital. Therefore, our power was limited to detect the smaller observed OR for the gender–nontraditional symptom association. Given the nature of the study, patients interacted with clinicians and nurses before interview, which may have biased their reporting of symptoms. In certain cases, proxies were required. These interviews were conducted with the patient present whenever possible. Nonetheless, the accuracy of the proxy reports is unknown and the proxies may report symptoms differently from the patient. Proxy use did not differ by gender, suggesting that this factor did not confound our observed association. Although use of proxies may be viewed as a limitation, it allows for a broader stroke population to be studied, including more severe cases. Proxy use was associated with reporting of nontraditional symptoms, suggesting that proxy use should be noted and controlled for in future studies of this nature. We did not have data on all confounders, including ischemic stroke subtype or objectively measured stroke severity. However, gender differences in subtype and severity have not been consistently demonstrated.13,14,16,18,22,24

Summary
In this prospective, observational study of ischemic stroke and TIA patients, we found a high prevalence of nontraditional symptoms among women and men, with women being more likely to report nontraditional symptoms and, in particular, altered mental status, compared with men. Additional larger-scale studies focusing on stroke in women are warranted and could confirm gender differences in stroke symptoms in a larger, more representative stroke population, as well as address their potential clinical consequences.

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Disclosures
None.

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