Young women's stroke etiology differs from that in young men: an analysis of 511 patients

Emily Nakagawa,1 Michael Hoffmann2
1Neurology Department, University of South Florida, Tampa, FL; 2Stroke and Cognitive Neurology Division, Neurology Service, James A. Haley VA Hospital, Tampa, FL, USA

Abstract

Women are known to have particular heterogeneity in stroke etiology related to childbearing and hormonal factors. Although there are continued acute stroke treatment advances focusing on clot dissolution or extraction, effective secondary prevention of stroke, however, is dependent on an accurate etiological determination of the stroke. Otherwise, more strokes are likely to follow. Analysis of young women's stroke etiology in a large stroke registry incorporating contemporary neurovascular and parenchymal imaging and cardiac imaging. Young people (18-49 years old) with stroke were consecutively accrued over a 4 year period and an investigative protocol prospectively applied that incorporated multimodality magnetic resonance imaging, angiography, cardiac echo and stroke relevant blood investigations. All patients were classified according to an expanded Trial of Org 10172 in Acute Stroke Treatment − TOAST − classification and neurological deficit by the National Institute of Health stroke admission scores. In 511 registry derived, young stroke patients (mean age 39.8 years, 95% confidence interval: 39.1; 40.7 years), gender (women n=269, 53%) the etiological categories (women; men) included: i) small vessel disease (39/55;25/55), ii) cardioembolic (16/42;26/42), iii) large vessel cervical and intracranial disease (24/43;19/43), the other category (132/226; 91/226), which included, iv) substance abuse (15/41; 26/41, 4.6), v) prothrombotic states (22/57;15/37), vi) dissection (11/30;19/30, 7.1), vii) cerebral venous thrombosis (15/19; 4/19, 12.4), viii) vasculitis (8/12; 4/12), ix) migraine related (10/11, 1/11) and x) miscellaneous vasculopathy (38/52;14/52). The latter entities comprised of aortic arch atheroma, vessel redundancy syndrome, vertebralbasilar hypoplasia, arterial fenestrations and dolichoectasia. Some conditions occurred solely in women, such as eclampsia (5), Call Fleming syndrome (4), fibromuscular dysplasia (3) and Moya Moya syndrome (2). Categories aside from bland infarction included: ii) intracerebral hemorrhage (43/106; 63/106) and xiii) stroke of undetermined etiology (6/10; 4/10). Admission mean National Institute of Health Stroke Scale scores differed significantly between women and men (4.7; 6.0 t=1.8, P=0.03). Young women's stroke is significantly different from men in 7/12 stroke etiological categories in addition to 4 unique subtypes that require specific management.

Introduction

The etiological identification in young stroke patients, ages <49 years, has been challenging. In this population, the traditional risk factors for stroke such as high blood pressure, hyperlipidemia, or coronary vascular disease are much less frequent.1 Young patients with stroke are often misdiagnosed on initial presentation to the emergency room, especially if they have posterior circulation stroke.2 Notable advances in the past two decades included multimodality magnetic resonance imaging techniques with improved evaluation and there are now several population-based studies of stroke etiology in young adults. The average annual incidence of stroke in patients’ ages 15-49 based on studies in Sweden, Italy, United Kingdom, and in Finland is estimated to be 8.7-11.3 per 100,000.13-7 Currently there are no studies specifically comparing stroke etiologies between young men and women. Younger women are known to have unique stroke predisposing factors related to pregnancy and hormonal factors.

The aim of the present study was to identify and compare stroke etiologies unique to men and women.

Materials and Methods

Clinical and investigative data

This was a prospective study conducted from September 2002 to December 2006 with consecutive collection of clinical, radiological, sonographic and laboratory data. Only patients with first ever stroke were included in the study. Consecutive patients with stroke, aged 18-49 years were accrued through a prospectively coded dedicated stroke registry in a tertiary referral center. The registry was approved by the University Institutional Review Board and in compliance with HPIPA (Health Insurance Portability and Accountability Act) regulations. All patients signed informed consent for the evaluation and the collection of their neurological, medical and neurocognitive data. Analysis of the stroke mechanism subtypes was performed retrospectively.

Ischemic stroke was defined as acute onset of focal neurological deficits with correlating imaging evidence of stroke. Neurological deficits were classified by National Institute of Health (NIH) stroke scale. All patients were evaluated by a stroke neurologist and an investigative protocol was applied using magnetic resonance (MR) imaging brain, MR angiography, echocardiography and stroke relevant blood investigations. A modified version of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification was used that defines 5 subtypes of ischemic stroke, large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology.8 For our study the majority of the young patients fell under the subtype of other, therefore etiology of stroke was classified by expanded TOAST classification to include: large vessel cerebrovascular disease, small vessel cerebrovascular disease, cardiogenic, dissection, prothrombotic states, migraine induced (type 3a and 3b Welch), cerebral venous thrombosis, vasculitides, vasculopathy other miscellaneous and unknown.9

Statistical analysis

Descriptive analysis, including means, 95% confidence intervals and standard deviations for continuous variables and frequency distributions for categorical variables, were obtained for all study parameters. T-tests were
used to compare means and a P value of ≤0.05 was regarded as significant. Associations between continuous variables were analyzed using Pearson’s product moment correlation. All analyses were run in SAS version 9.1. The etiological classifications included in the models were cardioembolic, hemorrhage, large vessel disease, small vessel disease, other and unknown. These independent variables were also coded as binary (yes/no). Stepwise multivariate logistic regression analyses were used to determine the significant etiological and topographical associations.

Results

Demographics

Of the 511 young patients (mean age 39.8 y, 95% CI: 39.1;40.7 y) with women (n=269, 53%), mean age 39.8 y, 95% CI: 39.1;40.7 y) and men (40.0 y, 95% CI: 38.7, 41.3 y) with gender distribution of young women stroke patients representing n=269 or 53% and first time stroke patients numbered 363.

Stroke scores and etiology

Admission mean NIHSS scores differed significantly between women (4.7) and men (6.0) (t=1.8, P=0.03). Both men and women had similar stroke subtypes of small vessel disease (women 30/55; men 25/55, 0.09, P=NS), and large vessel cervical and intracranial disease (women 24/43; men 19/43, 0.19, P=NS). Men however had a greater number of the subtype due to cardioembolism (26/42 3.9 P=0.05) compared to women. In the remaining 29 (5.7%) patients, multiple etiological possibilities were found and these were accordingly labeled indeterminate etiologies. Women on the other hand, had greater numbers of the subtype other (132/226, 6.8 P=0.01) (Figure 1). These subtypes added together translated into a total of 396 instances in 363 patients as in 33 (9.1%) patients more than one etiology (range 2-5) was determined it was not possible to state with certainty which was causative.

Overall a significant number of the young stroke patients (226/511; 44%) had non-traditional etiologies for stroke. This concurs with a recently published study of 87 young stroke patients <45 years old, revealing that

Figure 1. Stroke etiology (TOAST categories) in men and women (X axis: stroke subtype and Y axis: number of strokes).

Figure 2. Stroke Etiology in the expanded other category (Y axis: etiology, X axis: number of strokes).

Discussion

Our study focuses on comparing and contrasting stroke etiologies of women and men. Just under half (n=226/511; 44%) had non-traditional etiologies for stroke. This concurs with a recently published study of 87 young stroke patients <45 years old, revealing that categories aside from ischemic infarction, included (women:men) intracerebral hemorrhage (43/106; 63/106, P=0.01) and stroke of undetermined etiology (6/10; 4/10, 0.2, P=NS).
the most frequent stroke etiology found was also the other entity, as well other studies with 34%, and one with 1008 patients with 26% of other etiology. In our study where 44% had stroke due to other etiology and more women than men had a stroke etiology within the other category. The other category also included a group of miscellaneous entities and a generic vasculopathy was the most common stroke etiology for women. The four unique conditions that were only found in women stroke patients under this category were: eclampsia, fibromuscular dysplasia, Call Fleming syndrome and moyamoya syndrome. Using the expanded TOAST classification to include more rare etiologies for stroke helps guide stroke management, prevention of future strokes and tailor the treatment approach for young patients with stroke.

Women (ages 15-44) with preeclampsia have an increased risk of ischemic stroke, postpartum and peripartum due to disrupted cerebral autoregulation. As preeclampsia is postpartum and peripartum due to disrupted cerebral autoregulation. Women with migraine with aura is estimated to be 17-19 per 100,000; while the risk of stroke of non-aura migraine remains unknown. Our study estimated that of the young women with a history of migraine who had strokes, between 20-40% had strokes that developed directly from their migraine attack.

Our study did however differ in some respects from other young stroke studies. Many studies evaluating stroke in young patients, also often list cardioembolism as a frequent etiology hence, this may be consistent finding. In fact cardioembolism may be the most frequent or one of the most common causes however in our study this accounted for 11.6% but even the most recent large studies showed a wide variation (19.6-47%). There was also variation in the entity of multiple etiologies which were very common (26%) in the largest study of young stroke (Putaala et al.) whereas in our study this was 5.7%. Methodological variability is purported to be the most likely factor in this regard with geographic, race ethnicity other possibilities. Cardioembolism was also more frequent in men than women in one study (Ji et al.) although significance was in the marginal category. The present study also found that men had more strokes with etiologies related to cardioembolism and substance abuse.

Men and women showed no etiological difference in prothrombotic states and dissection as well as SVD and LVD. In northern Sweden 21% of their young adult ischemic strokes had unknown etiology according to the modified TOAST criteria with spontaneous cervical arterial dissection as the leading probable etiology. Overall women had lower mean NIH stroke scores (women 4.7; men 6; and more rare/non-specific etiology). In our study this was 5.7%. There was also variation in the entity of multiple etiologies which were very common (26%) in the largest study of young stroke (Putaala et al.) whereas in our study this was 5.7%. Methodological variability is purported to be the most likely factor in this regard with geographic, race ethnicity other possibilities. Cardioembolism was also more frequent in men than women in one study (Ji et al.) although significance was in the marginal category. The present study also found that men had more strokes with etiologies related to cardioembolism and substance abuse.

Men and women showed no etiological difference in prothrombotic states and dissection as well as SVD and LVD. In northern Sweden 21% of their young adult ischemic strokes had unknown etiology according to the modified TOAST criteria with spontaneous cervical arterial dissection as the leading probable etiology. Overall women had lower mean NIH stroke scores (women 4.7; men 6; and more rare/non-specific etiology). In our study this was 5.7%. Methodological variability is purported to be the most likely factor in this regard with geographic, race ethnicity other possibilities. Cardioembolism was also more frequent in men than women in one study (Ji et al.) although significance was in the marginal category. The present study also found that men had more strokes with etiologies related to cardioembolism and substance abuse.

Conclusions

Although acute stroke treatment advances focus on clot dissolution or extraction, prevention is more effective in terms of the population at large. Effective secondary prevention of stroke, is however, dependent on an accurate etiological determination of the stroke, otherwise, more strokes are likely to follow. In this study, young women’s stroke was significantly different from men in 7/12 stroke etiological categories (cardioembolism, cerebral venous thrombosis, vasculitis, migraine, vasculopathy, substance abuse, intracerebral hemorrhage) in addition to 4 unique subtypes that require specific management. Hence, due attention to the expanded diagnostic classification and gender specificity may assist in identification of the diverse etiology of stroke in young people.

References


