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Gender differences in stroke risk factors

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Abstract

Introduction: Globally, Stroke is a growing public health concern. Women face an excessive burden of stroke mortality and disability. They have considerable differences in the strength of association of stroke risk factors.

Aim or work: The aim of this case-control study is to examine gender-specific predictors of ischemic stroke including both modifiable and non-modifiable risk factors.

Patients and methods: 118 SVD patients and 47 LVD patients were included in the study. Lipid profile, complete blood picture, liver and kidney function tests, magnetic resonance imaging (MRI), carotid duplex, electrocardiogram (ECG), and echocardiography were carried out for all patients.

Results: The age at the onset of stroke in female patients was greater than that in males in either of the groups. Significantly, more hypertensive and diabetic patients were observed in the SVD group and more hypertensive and diabetic females were observed in both the LVD and the SVD groups. Median HDL-cholesterol was higher in higher in female than male patients in both groups, while the median Total cholesterol was higher in SVD male patients.

Conclusion: Diabetes mellitus and hypertension were found to be potential stroke risk factors for both LVD and SVD female patients while ischemic heart disease was found to be a potential stroke risk factors only for SVD female patients. Total cholesterol was found to be a stroke risk factors in SVD male patients, while HDL-cholesterol was found to be a protective factor for both LVD and SVD female patients.

Keywords: Gender, ischemic stroke, risk factors

Introduction

Stroke in women is a growing public health concern. Women face an excessive burden of stroke mortality and disability. They have considerable differences in the strength of association of stroke risk factors. Moreover, there are differences in presentation, treatment response, and stroke outcomes in women. Throughout the adult life span, deaths due to stroke are greater in women than men^[1]. Worldwide, the lifetime risk of stroke (from age 25 years onward) is 25.1% in women and 24.7% in men^[2]. The social context for women who experience stroke is important as well. Age at onset of stroke is on average 4 to 6 years older in women than men. Moreover, women have a higher degree of disability in their activities of daily living than men at the time of their stroke^[3, 4]. Given that women have a higher lifetime risk for stroke and account for more than half of all stroke deaths, gender-specific stroke risk factors merit investigation and may help target public health interventions^[5].

Aim of work

The aim of this case-control study is to examine gender-specific predictors of ischemic stroke including both modifiable and non-modifiable risk factors

Patients and methods

Patients

This study was performed on 118 ischemic stroke patients. All patients were selected from neurology and psychiatry department in Ain shams university hospitals. The patients were classified into two groups:

i) Group I: (SVD patients; n= 118)

This group included 118 patients with small vessel disease. The diagnosis was based on clinical, biochemical, MRI and carotid duplex investigations according to Adams *et al.*, 1993 [6].

ii) Group II: (LVD patients; n= 47)

This group included 47 patients with large vessel disease. The diagnosis was based on clinical, biochemical, MRI and carotid duplex investigations according to Adams *et al.*, 1993 [6].

Methods

Laboratory investigations

Lipid profile (total cholesterol, triglycerides, HDL and LDL).

Complete blood picture, PT, PTT, INR and HbA1C.

Liver function tests.

Kidney function tests.

Medical and clinical investigations

Full history taking, including family history of stroke, past history of any risk factor e.g., hypertension and diabetes mellitus along with history of present illness.

Detailed neurological examination in addition to calculation of National Institutes of Health Stroke Scale (NIHSS) according to [7] and MRS according to the Modified Rankin Scale for Neurologic Disability modified by [8].

Magnetic resonance imaging (MRI)

All patients underwent MRI stroke protocol including MRA. MRA was used to detect intracranial stenosis for diagnosis of LVD in addition to evidence of significant stenosis by carotid duplex.

Carotid duplex

All patients underwent carotid duplex for evidence of extracranial stenosis. If clinically indicated CT angiography was carried out.

Electrocardiogram (ECG)

ECG was carried out for all patients. Candidates with evidence of AF (atrial fibrillation) were excluded.

Echocardiography

All patients underwent transthoracic echocardiography. Patients with evidence of cardioembolic source of stroke were excluded.

Results

The present study included 118 small vessel disease (SVD) patients (69 males and 49 females) and 47 large vessel disease (LVD) patients (37 males and 10 females) serving as controls. The median [IQR] age in the control LVD group was 58 [22] years, while in the SVD group it was 68 [14] years. 51.1% of the LVD controls were hypertensive, compared to 64.4% of the SVD patients with no significant difference between them. The frequency of smokers was significantly higher in the LVD control group (48.9%) compared to that in the SVD patients (26.3%). No significant differences could be detected comparing the frequencies of patients with ischemic heart disease or diabetes among the two groups (Table 1).

The median [IQR] age in the female LVD patients was 70 (3) years, which was significantly higher than that in the

male patients; which was 55 (20) years. The frequency of smokers was significantly higher in the LVD male patients (59.5%) compared to that in the female patients (10%) (Table 2).

The median [IQR] age in the female SVD patients was 71 (6) years, which was significantly higher than that in the male patients; which was 64 (18) years. 81.6% of female patients were hypertensive compared to only 81.6% of the male patients, with a high significant difference between them ($p < 0.001$). The frequency of smokers was significantly higher in the male patients (43.5%) compared only 2% in the female patients. Ischemic heart disease was significantly more prevalent in female the patients (32.7%) compared to that in the male patients (11.6%) (Table 3). No significant differences could be found between LVD and SVD patients concerning whether HbA1c or any of the parameters of the lipid profile (Table 4).

Serum total cholesterol levels were significantly higher in male SVD patients (201[47.25]) compared to female SVD patients (158[79.75]). The opposite was true for HDL-cholesterol levels, where mean HDL levels in female patients were significantly higher in female SVD patients 49[12.5] compared to male SVD patients (36[12.5]) (Table 5). HDL levels were significantly higher in female SVD patients 45.5[11.88] compared to male SVD patients (37.5[12.65]) (Table 6).

Discussion

Several factors can affect the risk of stroke including non-modifiable and modifiable factors. Non-modifiable factors include gender, race, age, and heredity while modifiable factors include, for example, hypertension, diabetes mellitus, obesity, cardiac disease, alcohol abuse, cigarette smoking, lifestyle and dyslipidemia. Hypercholesterolemia represents a modifiable risk factor for ischemic stroke; however, not all cholesterol increase represents a risk [9]. In the current study, we aimed to investigate the impact of gender on age at onset of the first stroke, and on some of the modifiable stroke risk factors, including hypertension, diabetes, hypercholesterolemia, smoking and ischemic heart disease, in two stroke subtypes: SVD and LVD.

Age

The present study included 118 SVD patients and 47 LVD patients, serving as controls. The median age in the LVD group was 58 [22] years which was significantly lower than that in the SVD group; which was 68 [14] years. The number of male patients in the LVD group was significantly higher than that of female patients, with frequencies of 78.7% and 21.3%, respectively. The same was true for the SVD group, with frequencies of 58.5% and 41.5%, for male and female patients, respectively.

The median age of male patients in the LVD group was 55 [20] years, which was significantly lower than that of females, which was 70 [3]. The same findings were true for the SVD group, where the median age of male patients was 64 [18], which were significantly lower than that of female patients, which was 71 [6]. The current results are in accordance with several previous studies which revealed that, generally, the incidence of stroke is 1.25 times higher in males than females and increases steadily with age for both males and females, and revealed also that women are older at the time of their first stroke [10, 11].

Another study in 2009 has found that, in 98 studies spanning 19 countries and 5 continents, the mean age of first-ever stroke is 72.9 years in women compared to 68.6 years in men [12]. Research has also shown that, due to longer life span; women have more strokes during their lifetime [13]. The lifetime risk of stroke is higher for women than men, with a 1 in 4 risk of stroke for women after age twenty-five [2]. The change in stroke risk with age varies by gender; stroke incidence is higher in women than men for those <30 years of age, while rates are higher in men than women during midlife and either equal by sex or higher among women beginning in the eighth decade [14]. However, data on female-to-male incidence rate ratios during the reproductive years conflict [15].

Hypertension

64.4% of the SVD patients were hypertensive, compared to only 51.15 of the LVD patients, with a statistically significant difference between them. These results are in agreement with a study in 2004, which suggested that hypertension may be involved in the etiology of SVD [16]. On the other hand, the frequency of female hypertensive patients in the LVD group was higher than that of hypertensive males, with frequencies of 70% and 45.9%, respectively, but with no significant difference between them. Likewise, in the SVD group, the frequency of female hypertensive patients was significantly higher than that of hypertensive males, with frequencies of 81.6% and 52.2%, respectively.

Although some previous data indicate inconsistent gender difference in the association between increasing systolic blood pressure and stroke risk [17], some published data from the US and international cohorts demonstrate a stronger association between hypertension and risk of incident total and ischemic stroke in women compared with men, adjusted for the use of antihypertensives [18]. Longitudinal data in the United States have revealed a faster rise in blood pressure for women than men starting in the third decade, supporting a sexual dimorphism in the contribution of blood pressure to cardiovascular disease and stroke later in life [19]. Several large-scale observational studies indicated that stroke risk becomes significant at a lower threshold of systolic blood pressure for women than men; (120 versus 150 mm Hg, respectively) [20]. It has been demonstrated that controlling blood pressure reduces the incidence of ischemic stroke [21]. Additionally, lower rates of recurrent stroke have been associated with lower blood pressures [22].

Diabetes

The frequency of diabetics in the LVD group (42.6%) was lower than that in the SVD group (53.4%), however; it did not reach a statistical significance. In the LVD group, the frequency of diabetic females (60%) was higher than the frequency of diabetic males (37.8%), with no significant differences between them. The same was true for the SVD group, where the frequency of diabetic females (61.2%) was higher than the frequency of diabetic males (47.8%), with no significant differences between them. These results are in accordance with Samai and Martin-Schild, (2015) [11], who revealed that women with DM are at increased risk for stroke compared with their male counterpart. In the Framingham study cohort, diabetic women had a 3.5 times higher risk for stroke compared with non-diabetic women,

whereas diabetic men had a 2.1 times higher risk for stroke compared with non-diabetic men [23].

Smoking

The frequency of smokers in the LVD group was 48.9% which was significantly higher than that in the SVD group (26.3%). The current results are in agreement with previous studies which revealed that smoking was one of the significant discriminative factors for LVD vs. SVD [16]. Another study in 2010 [24] reported smoking to be one of the significant risk factors for stroke among Saudi population, along with hypertension, diabetes mellitus and heart disease. On the other hand, in the LVD group, the frequency of male smokers (59.9%) was significantly higher than that of female smokers (10%). The same was true for the SVD group, where male smokers were significantly higher than female smokers, with frequencies of 43.5% and 20%, respectively. In both sexes, smoking is associated with an increased risk for stroke, and quitting is associated with a reduction of that risk. Furthermore, women who smoke appear to have a greater overall disease risk associated with smoking compared with men, especially in relation to disease processes that may also lead to ischemic stroke [18]. In 2018, a retrospective study was conducted on 321 Egyptian patients who were admitted to Al-Azhar University Hospitals and Nasser Institute with a main primary diagnosis of acute ischemic stroke, the authors revealed that, in spite of the high prevalence of stroke risk factors among the study patients, the power wasn't enough to show any association with stroke severity except for smoking and obesity, where smokers and obese patients were proved to be more susceptible to higher stroke severity [25].

Lipid profile

Total cholesterol and HDL-cholesterol

Serum lipid levels have established effects on short-term stroke mortality. To reduce the incidence of stroke and stroke-related mortality, it is important to assess lipid levels in subtypes of strokes [26]. In many studies, both hemorrhagic and ischemic stroke were evaluated in tandem, thereby clouding the association. Overall, it appears that total cholesterol may have a cooperative effect with other factors that may contribute to the atherosclerotic process and, by extension, contribute to rates of ischemic stroke [27].

In the present study, when the plasma lipid profile was compared between the SVD and LVD subtypes, only HDL-C was discriminating, with a significantly lower level in patients with LVD than in those with SVD (37.4 ± 10.6 vs. 41.7 ± 13.4 mg/dl; $p = 0.047$).

On the other hand, comparing lipid profile markers between male and female SVD patients revealed significantly higher Serum total cholesterol in male patients compared to female patients, with median levels of 201 [47.25] and 158 [79.75], respectively. In contrast, HDL levels were significantly higher in female SVD patients compared to male SVD patients, with levels of 49 [12.5] and 36 [12.5], respectively. When the same comparison was made for LVD patients, only HDL levels were significantly higher in female SVD patients compared to male LVD patients, with levels of 45.5 [11.88] and 37.5 [12.65], respectively.

Our results are in agreement with several previous studies which revealed that high-density lipoprotein (HDL) appears to have a direct association with ischemic stroke. Men and

women have comparable HDL levels until puberty, but the level of HDL decreases significantly in men during adolescence to a normal adult level [28]. In women, there is a steady increase in HDL levels over time, possibly contributing to the later presentation of carotid disease [29]. Several studies have demonstrated increased rates of ischemic stroke among men with low levels of HDL [27]. In both men and women, every 1 mmol/L increase in HDL is associated with a 47% reduction in ischemic stroke. Moreover, the authors couldn't find any significant differences in any of the lipid profile markers between SVD and LVD patients. In fact, studies concerning the different stroke risk factors and the correlation between hyperlipidemia and ischemic stroke or some of its specific subtypes have long been controversial [16]. Plasma lipid levels are generally thought to be regulated by sex hormones leading to sexual dimorphism in the lipid profile [30].

Low-density lipoprotein and triglycerides

Comparing LVD to SVD patients, no significant differences could be observed concerning either LDL-cholesterol or triglycerides. The same was true comparing male and female patients in either of the studied groups.

Evidence regarding the association between low-density lipoprotein (LDL) and ischemic stroke is limited. Overall, high LDL levels appear to correlate with thrombosis, particularly large vessel atherothrombosis [31]. In both men and women, it appears that elevated LDL confers a marginal increase in risk for ischemic stroke [32].

On the other hand, the relationship between triglycerides and ischemic stroke remains a subject of debate. Some studies have suggested that high triglycerides are not related to an increased risk for ischemic stroke [33]. More recent research appears to contradict that theory. In 2008, the Copenhagen Heart Study found high triglyceride levels to be associated with increased risk for ischemic stroke in both men and women. However, in both the, 55 and. 55 age groups, the 10-year risk was greater in men than in women (2.6% and 16.7% vs 1.9% and 12.2%) [34]. In 2011, Varbo *et al.*, [35] corroborated these findings with their study results that suggested a stepwise relationship between triglyceride level and ischemic stroke risk.

A meta-analysis of 13 Chinese and Japanese cohorts, comprising 125,000 subjects and 1,800 strokes, showed a tendency toward a decreased risk for ischemic stroke as cholesterol levels decreased [36]. Another meta-analysis of 45 prospective cohorts, including 450,000 subjects and 13,000 strokes, found no association between total cholesterol and stroke (Prospective Studies Collaboration, 1995). The conflicting results of these studies may be due to several reasons. In some studies, there might be a masking effect due to the inclusion of patients with cerebral hemorrhage for which an inverse correlation with hyperlipidemia has been reported [36, 37]. In others, the lipid fractions exerted a different influence on stroke risk [38], and their effect varied

according to whether fatal or non-fatal stroke was [39]. Another possible reason is that the impact of hyperlipidemia may be different according to ischemic stroke subtype [40].

Ischemic heart disease

17% of the LVD patients had ischemic heart disease, compared to 20.3% in the SVD patients with no significant differences between them. On the other hand, the frequency of ischemic heart disease in female patients with SVD was 32.7% which was significantly higher than that in the male patients in the same group (11.6%). In contrast, no significant differences could be found comparing males and females in the LVD group. Diseases of the cardiovascular system (myocardial infarction, stroke, heart failure, hypertensive heart disease, cardiomyopathy) account for 40% of all deaths in men and up to 49% of all deaths in women [41]. For a long time it was thought that the clinical picture of ischemic heart disease in men and women was similar. However, there are more reports suggesting that diverse manifestations of the symptoms of ischemic disease may be related to differences between sexes [42]. Women and men share the same traditional risk factors for ischemic heart disease. However, women have other non-traditional risk factors such as those caused by premature menopause, pre-eclampsia, depression, social and vocational disparity, and higher prevalence of autoimmune diseases. Additionally, ischemic heart disease symptoms in women are usually atypical and different from men which leads to delayed presentation, delayed diagnosis or misdiagnosis thus putting women at an increased risk. Women usually present more complications and worse functional outcomes compared to men [43].

Summary

- Though the number of males was significantly greater than that of females in both LVD and SVD patients, but, the age at the onset of stroke in female patients was greater than that in males in either of the groups.
- Significantly, more hypertensive patients were observed in the SVD group than the LVD group, and more hypertensive females were observed in both the LVD and the SVD groups.
- Significantly, more diabetic patients were observed in the SVD group than the LVD group, and more diabetic females were observed in both the LVD and the SVD groups.
- More smokers were observed in the LVD group, and male smokers were more prevalent in both the studied groups
- Median HDL-cholesterol was higher in the SVD than in LVD, and higher in female than male patients in both groups.
- Median Total cholesterol was higher in SVD male patients

Table 1: Demographic characteristics of the LVD and SVD groups.

Groups Variable	Control (LVD) No.= 47	SVD No.= 118	p-value
Gender, No. (%)			
Male	37 (78.7%)	69 (58.5%)	0.014*
Female	10 (21.3%)	49 (41.5%)	
p-value	<0.05*	<0.05*	
Age (Years) Range (Median [IQR])	58 [22]	68 [14]	0.002**
Hypertension, No. (%)			
			0.05 *

Yes	24 (51.1%)	76 (64.4%)	
No	23 (48.9%)	42 (35.6%)	
Smoking, No. (%)			
Yes	23 (48.9%)	31 (26.3%)	0.005**
No	24 (51.1%)	87 (73.7%)	
Ischemic heart disease No. (%)			
Yes	8 (17%)	24 (20.3%)	0.627
No	39 (83%)	94 (79.7%)	
Diabetes, No. (%)			
Yes	20 (42.6%)	63 (53.4)	0.209
No	27 (57.4%)	55 (46.6%)	

Age was represented as median [IQR], while gender, hypertension, smoking, ischemic heart disease and diabetes were represented as No. (%). *P* value < 0.05 was considered significant (*), while *P* value < 0.001 was considered highly significant (**)

Table 2: Demographic characteristics of male and female patients in the LVD group.

Gender Variable	Male No = 37	Female No = 10	<i>p</i> -value
Age (Years) Range (Median [IQR])	55 (20)	70 (3)	0.001**
Hypertension, No. (%)			
Yes	17 (45.9%)	7 (70%)	0.177
No	20 (54.1%)	3 (30%)	
Smoking, No. (%)			
Yes	22 (59.5%)	1 (10%)	0.006**
No	15 (40.5%)	9 (90%)	
Diabetes, No. (%)			
Yes	14 (37.8%)	6 (60%)	0.209
No	23 (62.2%)	4 (40%)	
Ischemic heart disease No. (%)			
Yes	7 (18.9%)	1 (10%)	0.505
No	30 (81.1%)	9 (90%)	

Data were represented as median [IQR]. *P* value < 0.05 was considered significant (*), while *P* value < 0.001 was considered highly significant (**).

Table 3: Demographic characteristics of male and female patients in the SVD group.

Gender Variable	Male No = 69	Female No = 49	<i>p</i> -value
Age (Years) Range (Median [IQR])	64(18)	71(6)	0.00**
Hypertension, No. (%)			
Yes	36(52.2%)	40(81.6%)	0.001**
No	33(47.8%)	9(18.4%)	
Smoking, No. (%)			
Yes	30(43.5%)	1(2%)	0.00**
No	39(56.5%)	48(98%)	
Diabetes, No. (%)			
Yes	33(47.8%)	30(61.2%)	0.151
No	36(52.2%)	19(38.8%)	
Ischemic heart disease No. (%)			
Yes	8(11.6%)	16(32.7%)	0.005**
No	61(88.4%)	33(67.3%)	

Data were represented as median [IQR]. *P* value < 0.05 was considered significant (*), while *P* value < 0.001 was considered highly significant (**).

Table 4: Comparison between Serum levels of HbA1c and lipid profile in LVD and SVD patients.

Variable Median [IQR]	(LVD) N=47	SVD No.=118	- value <i>p</i>
HbA1c (%)	6.2 [2.8]	6.35 [2.72]	0.406
Triglycerides (mg /dl)	113 [59]	110 [72.5]	0.334
Total cholesterol (mg /dl)	195 [97]	186.5 [69.18]	0.78
LDL-cholesterol (mg /dl)	124 [90.5]	118.5 [66.63]	0.365
HDL-cholesterol (mg /dl)	40 [13.7]	41.25 [16.5]	0.444

Data were represented as median [IQR]. *P* value < 0.05 was considered significant (*), while *P* value < 0.001 was considered highly significant (**).

Table 5: Comparison between Serum levels of HbA1c and lipid profile in male and female patients in the SVD group.

Variable Median [IQR]	HbA1c (%)	Total cholesterol (mg /dl)	LDL (mg /dl)	HDL (mg /dl)	TGs (mg /dl)
Gender	males	201 [47.25]	123 [67.25]	36 [12.5]	122 [62]

	females	6.5 [3.45]	158 [79.75]	108 [66.45]	49 [12.5]	102 [78]
	<i>p</i> -value	0.473	0.001**	0.109	0.00**	0.173

Data were represented as median [IQR]. *P* value < 0.05 was considered significant (*), while *P* value < 0.001 was considered highly significant (**)

Table 6: Comparison between Serum levels of HbA1c and lipid profile in male and female patients in the LVD group.

Variable	Median [IQR]	HbA1c (%)	Total cholesterol (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	TGs (mg/dl)
Gender	males	6.09 [2.5]	211 [96.4]	149.25 [97.1]	37.5 [12.65]	122 [61]
	females	8.15 [7.26]	185 [86.65]	124 [74.85]	45.5 [11.88]	111.48 [45.5]
	<i>p</i> -value	0.061	0.835	0.765	0.01*	0.275

Data were represented as median [IQR]. *P* value < 0.05 was considered significant (*), while *P* value < 0.001 was considered highly significant (**)

Conclusion

Despite substantial progress in examining gender differences in stroke, as well as specific factors influencing risk and outcomes in women, significant research gaps remain. The current study revealed that men and women differ in their risk with respect to various predictors of ischemic stroke:

Diabetes mellitus and hypertension were found to be potential stroke risk factors for both LVD and SVD female patients while ischemic heart disease was found to be a potential stroke risk factors only for SVD female patients. Total cholesterol was found to be a stroke risk factors in SVD male patients, while HDL-cholesterol was found to be a protective factor for both LVD and SVD female patients.

Further research is warranted in each of these areas to better understand the complexities of the effect of gender on ischemic stroke risk, etiology, and progression.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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