

Role of Migraine as a Risk Factor of Ischemic Stroke in Young Women

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Abstract

Background: Migraine is a chronic primary headache disorder with episodic attacks which affects the people in the most productive periods of their working lives; women are affected up to four times more often than men. **Objective:** The purpose of the present study was to identify the association of migraine and risk of ischemic stroke in young women. **Methodology:** It's a hospital based case-control study carried out in the Department of Neurology, Bangabandhu Sheikh Mujib Medical University from January 2010 to December, 2012. **Results:** The result obtained from our study shows that migraine and ischemic stroke were strongly associated; 60% (95% confidence interval 48% to 71%) of cases had migraine compared with 30% (23% to 37%) of controls ($P < 0.001$). This association persisted after we controlled for age, history of hypertension, use of oral contraceptives, and smoking. Women with migraine had a more than threefold increased risk of ischemic stroke compared with women without migraine. This increase occurred with both types of migraine, although the risk was higher with migraine with aura (odds ratio 6-2) than with migraine without aura. **Conclusion:** In conclusion, the risk of ischemic stroke was higher among young women with migraine who smoked or who took oral contraceptives. [*Journal of National Institute of Neurosciences Bangladesh, July 2022;8(2):193-197*]

Keywords: Migraine; ischemic stroke; young women

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Introduction

Migraine is a chronic primary headache disorder with episodic attacks which affects the people in the most productive periods of their working lives; women are affected up to four times more often than men¹ Migraine is a recurrent headache disorder manifesting in attacks lasting 4 to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia².

Up to one third of patients with migraine experience an aura before or during the migraine headache characterized by neurological symptoms most often involving the visual field such as seeing zigzag lines or flash spots but may also include sensory or motor symptoms³. An association between migraine and ischaemic vascular events, particularly ischaemic stroke, has been debated for many years. Over the last decades, an increasing bodies of publications have linked migraine, specifically migraine with aura, with ischaemic stroke. Several retrospective case-control,

three prospective, as well as one cross-sectional cohort study, have been published on the association between migraine and stroke risk³⁻⁵.

The precise mechanisms by which migraine may lead to ischaemic vascular events are currently unknown and likely to be complex. Several hypotheses⁶⁻⁸ can be envisioned that migraine may directly cause an ischaemic event; migraine may be an indirect cause of cerebral ischaemia as its pathophysiology may affect the endothelial function and by this alone or in combination with existing local vascular pathologies increase the risk of stroke outside of a migraine attack; migraine is associated with an increased prevalence of risk factors for ischaemic vascular events; the link is caused by migraine-specific drugs and migraine and ischaemic vascular events are linked via a genetic component⁹. The purpose of the present study was to identify the association of migraine and risk of ischemic stroke in young women.

Methodology

Study Settings and Population: This study was a hospital based case-control study. This study was carried out in the Department of Neurology at Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2010 to December, 2012. Women aged 15 to 48 years attended or admitted to the Department of Neurology with a diagnosis of ischemic stroke over the study period were included in the study provided they meet the inclusion and exclusion criteria. Ischemic stroke was defined clinically according to the World Health Organization's criteria, and was confirmed in all patients by computed tomography or MRI of the brain. Controls were age matched women without stroke, after considering exclusion criteria who attended the same hospital for benign orthopaedic conditions or routine surgical procedures. Up to three hospital based controls, matched by 5 year age bands were recruited for each case as previously described. Informed written consent was sought from the subjects voluntarily expressing their intention to participate in the study.

Study Procedure: Both cases and controls was interviewed about their history of headaches and their vascular risk factors. The questionnaire covered the patients' history of hypertension, diabetes, cigarette smoking, use of oral contraceptives, hypercholesterolaemia, weight, height, and educational background, details of medical and reproductive history, use of drugs, family history of premature stroke and heart attack, or both and report of all investigations

to determine the cause of stroke will be recorded. All interviews was conducted by using a structured questionnaire, including different questions on headache based on the International Headache Society's criteria and from which the diagnosis of migraine could be easily derived. Prior to the commencement of this study, the research protocol was approved by the Ethical review committee of BSMMU, Dhaka. To conduct this study ethical clearance and permission were taken from the concerned department and the authorities. A pre-tested questionnaire and a data collection sheet, which included all relevant information from history, physical examination and investigations addressing all the variable of interest. Following demographic and clinical variables were studied like age, body mass index, sedentary life style, smoking or tobacco consumption, alcohol, oral contraceptives, hypertension, diabetes, cardiac disease, dyslipidaemia, family history of migraine, family history of stroke at early age.

Statistical Analysis: Statistical Packages for Social Sciences (SPSS-15) was used for statistical analyses of the results. A 'p' value < 0.05 was considered as significant. Multiple logistic regression analysis to evaluate the risk factors. Odd ratios for stroke associated with a history of migraine compared with women who had not had migraine will be computed by conditional logistic regression and adjusted for confounding variables. Ischaemic stroke was fitted as dependent variable and known risk factors and migraine status were independent variable.

Results

About 3.9% cases were 15 to 20 years of age, 17.0% cases were in 21 to 30 years of age, and 43.1% cases were 31 to 40 years of age and 35.3% cases were 41 to 48 years. Most 22(42.1%) of the patients were in 4th decade in cases. However, in control group majority 55(37.4%) of the patients were in 5th decade. The mean age in cases were 37.57± 7.56 years and in control were 34.77± 11.08 years. The mean age difference was not statistically significant (p>0.05) (Table 1).

Table 3 showed relation between risk of ischemic stroke and migraine, using oral contraceptives, and smoker/tobacco leaf. The risk of stroke in migrainous women using oral contraceptives was 2.71 compared with those without migraine not using oral contraceptives (P<0.001). Of the women who used oral contraceptives, those who had migraine still had a threefold increased risk of ischemic stroke.

Table 1: Baseline Characteristics of Women in Case and Control groups

Baseline Characteristics	Case Group	Control Group	P value
Age Group (Years)			
• Mean ± SD	37.57±7.56	34.77±11.08	^a 0.096
Body mass index (kg/m ²)			
• Mean±SD	23.5±4.3	24.7±4.9	^a 0.122
Hypertension	16(31.4%)	32(21.8%)	^b 0.167
Sedentary life style	4(7.8%)	2(1.2%)	^b 0.065

Case group: Women with ischemic stroke; Control group: Women without ischemic stroke; ^aP value reached from unpaired t-test

Table 2: Occurrence of Migraine of the Study Patients (n=198)

Occurrence of Migraine	Case Group	Control Group	P value
Without migraine	32(6.27%)	115(78.2%)	
With migraine*	19(37.3%)	32(21.8%)	0.029
• Migraine with Aura**	12(23.5%)	17(11.6%)	0.037
• Migraine without Aura***	7(13.7%)	15(10.2%)	0.491

P value reached from Chi-square test; *With Migraine; Odd ratio (95% confidence interval)= 2.13(1.01-4.5); ** Migraine with Aura; Odd ratio (95% confidence interval)= 2.51(1.03-6.18); *** Migraine without Aura; Odd ratio (95% confidence interval)= 1.4(0.48-3.97)

Table 3: Risk of ischemic stroke in women by having migraine, using oral contraceptives and smoking. Values are odds ratios (95% confidence intervals)

Variables	Case Group OR (95% CI)	Control Group OR (95% CI)
Use of oral contraceptive		
• Yes	2.71(0.96 – 7.71)	0.37 (0.13 – 1.04)
• No	1.12 (0.33 – 3.71)	1
Smoker/tobacco consumer		
• Yes	2.23 (0.62 – 8.22)	1.22(0.39 – 3.67)
• No	0.45(0.12 -1.62)	1

Patients having family history (stroke in early age) 5.25 times more increase risk to developed ischemic stroke (95% CI 1.23% to 22.45%). Patients received oral contraceptives 3.97 times more increase risk to developed ischemic stroke (95% CI 1.79% to 8.81%). Smoker having 3.23 times more increase risk to developed ischemic stroke (95% CI 1.34% to 7.82%). Patients having migraine (any type) before stroke 2.98 times more increase risk to developed ischemic stroke (95% CI 0.61% to 14.56%) (Table 4).

Table 4: Multivariate logistic regression analysis for prediction of ischaemic stroke with different factors (n=198).

Variables	Adjusted OR	95% CI		P value
		Lower	Upper	
Family history (stroke in early age)	5.25	1.23	22.45	0.025s
Oral contraceptives	3.97	1.79	8.81	0.001s
Smoker	3.23	1.34	7.82	0.009s
H/O Migraine (any type) before stroke	2.98	0.61	14.56	0.021s
Vasculitic disorder	2.08	0.73	5.99	0.171ns
Diabetes	2.23	0.89	5.64	0.088ns
Hypertension	1.37	0.58	3.30	0.472ns
Cardiac diseases	1.04	0.92	17.78	0.065ns
Constant	0.05			0.001s

Discussion

This was a hospital based case-control study of young women of Bangladesh aged 15-48 year's stroke. We found that migraine to be strongly associated with ischemic stroke in young women independently of the main vascular risk factors (adjusted odds ratio 2.98). The risk of ischemic stroke was particularly increased for migrainous women who were currently using oral contraceptives, and were current heavy smokers. Age distribution among the cases shows that 3.9% were 15-20 years of age, 17% were in 21 to 30 years of age, and 43.1% were 31-40 years of age. And 35.3% were 41-48 years. Most 22(42.1%) of the patients were in 4th decade in cases. However, in control group majority 55(37.4%) of the patients were in 5th decade. The mean age in cases were 37.57± 7.56 and in control were 34.77± 11.08. The mean age difference was not statistically significant (p>0.05) in unpaired t-test. These findings are consistent with another study¹⁰ conducted in a tertiary hospital who also found majority (45.0%) the stroke case of young women aging in their forth decade. This findings are also consistent with another study¹¹ who also found their majority cases whose age was in the fourth decades. Second majorities was women of 3rd decade of age. This study investigate the association between migraine and ischemic or haemorrhagic stroke in young women. Results shows that Adjusted odds ratios associated with a personal history of migraine were 1.78 (95% confidence intervals, 1.14 to 2.77), 3.54 (1.30 to 9.61), and 1.10 (0.63 to 1.94) for all stroke, ischemic stroke, and haemorrhagic stroke respectively. Odds ratios for ischemic stroke were similar for classical migraine

(with aura) (3.81, 1.26 to 11.5) and simple migraine (without aura) (2.97, 0.66 to 13.5). This findings are also consistent with the case control study¹². This study investigate the association between migraine and ischaemic or haemorrhagic stroke in young women. Results shows that adjusted odds ratios associated with a personal history of migraine were 1.78 (95% confidence intervals, 1.14 to 2.77), 3.54 (1.30 to 9.61), and 1.10 (0.63 to 1.94) for all stroke, ischaemic stroke, and haemorrhagic stroke respectively. Odds ratios for ischaemic stroke were similar for classical migraine (with aura) (3.81, 1.26 to 11.5) and simple migraine (without aura) (2.97, 0.66 to 13.5). This findings are different from the another study¹⁵ who did the first prospective cohort study by using data from the Women's Health Study, which included over 39000 apparently healthy women 45 years of age or older who were followed for an average of 9 years. This study found a 1.7-fold increased risk for ischaemic stroke (relative risk, 1.71; 95% CI, 1.11–2.66) for women who reported migraine with aura when compared with women without migraine but no increased risk of stroke among women with migraine without aura, compared with women with no migraine history.

However, few studies¹³⁻¹⁵ have specifically addressed this issue. The association between migraine and ischaemic stroke in young women in particular was evaluated only by the Collaborative Group for the Study of Stroke in Young Women.¹⁰ In that study migraine was found in 34.0% of cases, 24.0% of neighbourhood controls (odds ratio 1-7), and 33% of hospitalized controls (odds ratio 1 1). These figures of migraine prevalence are much higher than those in this study. Apart from methodological limitations, one of the possible explanations for this discrepancy is the difference in methods and criteria used for the diagnosis of migraine. In this present study history of headache was collected by trained neurologists using a structured questionnaire and the diagnosis of migraine was based on the International Headache Society criteria. It has found prevalence of migraine among our hospital based controls to be 22.0% cases. There is no large scale study data about the prevalence of migraine in Bangladesh.

For more than 3 decades, there has been a debate over whether oral contraceptive use and/or smoking among migraineurs further increases the risk of ischemic stroke. The risk of stroke in migrainous women using oral contraceptives was 3.9 compared with those without migraine not using oral contraceptives ($P < 0.001$). Of the women who used oral

contraceptives, those who had migraine still had a fourfold increased risk of ischemic stroke. With regard to the risk of stroke in migrainous patients who smoked, we decided to focus on current heavy smokers/tobacco consumers, who were at a higher risk of ischaemic stroke. The odds ratio of stroke in migrainous heavily was 2.23 compared with women without migraine who never smoked ($P < 0.001$).

The result of this case control study is consistent with another study¹⁵ who suggest that neither oral contraceptive use nor smoking alone substantially increased the odds ratio of ischemic stroke among women with migraine. However, they suggest that the combination of both resulted in a 10-fold increased risk of ischemic stroke when compared with women without migraine who did not smoke and did not use oral contraceptives.

Regarding the dyslipidaemia of the study patients, it was found that 9(17.6%) in case group had diabetes. Significant ($p < 0.05$) difference was found between two groups in chi square test. A dyslipidaemia compared to non dyslipidaemia is 4.50 times more likely to have developed ischemic stroke. Regarding the oral contraceptive, 25(49.0%) and 40(27.2%) in group I and group II patients received oral contraceptive. Significant ($p < 0.05$) difference was found between two groups in chi square test. Oral contraceptive user compared to non-oral contraceptive user is 2.57 times more likely to have developed ischemic stroke. Regarding the family history of stroke in early age, family history of stroke in early age was found in 13(25.5%) and 3(2.04%) in group I and group II respectively. Significant ($p < 0.05$) difference was found between two groups in chi square test.

Family history of stroke in early age compared to non-family. Occurrence with migraine without aura and migraine with aura were statistically significant ($P < 0.05$) between two groups. Women having history of migraine (any type) compared to women without migraine is 2.13 times more likely to have developed ischemic stroke. Women having history of migraine with aura compared to women without any migraine is 2.51 times more likely to have developed ischemic stroke. Women having history of migraine without aura compared to women without any migraine is 1.4 times more likely to have developed ischemic.

The two groups, cases and controls were similar in age, sex and BMI and the prevalence and duration of hypertension. But there were differences in prevalence of hypercholesterolaemia, and diabetes mellitus and cardiac diseases which were more common among the

patients with ischemic stroke, and the differences were significant for smoking (OR 3.4) and diabetes (OR 2.27) and for hypercholesterolaemia (OR 4.50). For cardiac disease (rheumatic heart disease, right to left shunt) (OR 12.7) in the cases of ischemic stroke.

Distribution of the study patients according to hypertension regarding the presence of hypertension of the study patients, it was found that 16(31.4%) and 32(21.8%) had hypertension in case group and control group respectively. No significant ($p > 0.05$) difference was found between two groups in chi square test. Regarding the presence of diabetes in the study patients, it was found that 14(27.5%) in case group and 21(14.3%) in control group had diabetes. Significant ($p < 0.05$) difference was found between two groups in chi square test. A diabetics compared to non-diabetics is 2.27 times more likely to have developed ischemic stroke.

Conclusion

In conclusion migraine is an independent risk factor for ischemic stroke in young women of reproductive age. The risk of ischemic stroke is higher among young women with migraine who smoked or who took oral contraceptives. Although their absolute risk of ischemic stroke is still low, young women with migraine should be advised not to smoke and, if they use oral contraceptives, to choose low dose pills. Identifying the population with migraine at highest risk of stroke should be the first step toward risk reduction and the goal of future research.

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