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Study to Evaluate the Role of Patent Foramen Ovale in Migraine with Aura and Identification of the Predictors of Aura among Patients Attending the Neurology Outpatient Department at a Tertiary Care Centre of Eastern India

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Abstract

Introduction: Migraine is prevalent in 18.5% of the population, and migraine with aura (MA+) in 4.4% whereas patent foramen ovale is present in 27% of the general population. Multiple studies suggest that migraine with aura is more prevalent in subjects with patent foramen ovale. We aimed to investigate the role of patent foramen ovale and other independent risk factors in predicting the development of aura among migraineurs.

Methods and Materials: 200 patients over the period from January 2016 - January 2018, diagnosed as migraine with aura and without aura as per the criteria of the International Headache Society at the Neurology outpatient department, underwent transthoracic echocardiography to detect patent foramen ovale, excluding diabetics, hypertensives, alcoholics and smokers. Other pertinent investigations were also done. Two independent neurologists who were blinded to the echocardiography results diagnosed migraine with and without aura. Univariate and multivariate logistic-regression analyses were used to estimate the unadjusted and adjusted odds ratios (OR) and the corresponding 95% confidence interval. In the multivariate analyses, the most significant clinically relevant univariate variables were included. All tests were 2-sided, and $P < 0.05$ was considered to be statistically significant.

Results: Presence of PFO in patients of migraine is associated with significantly higher incidence of aura [odds ratio = 3.9 (95% confidence interval 1.505 - 10.10)]. Univariate analysis showed that female sex, younger age, previous stroke, coronary artery disease, hyperlipidemia, other hypercoagulable states and MRI brain abnormalities were significantly higher among migraine with aura patients. Multivariate analysis identified female sex [adjusted OR = 0.22, p = 0.04], previous stroke [adjusted OR = 7.8, p = 0.04], hyperlipidemia [adjusted OR = 3.88, p = 0.03], other hypercoagulable states [adjusted OR = 5.7, p = 0.032] and MRI brain abnormalities [adjusted OR = 4.4, p = 0.04] as the independent predictors of the occurrence of aura among migraine patients with PFO. Losses of working days were significantly more among migraineurs with aura (p = 0.03).

Conclusion: Aura is significantly associated with PFO and is predicted independently by female sex, previous stroke, hyperlipidemia, MRI brain abnormalities and other hypercoagulable states. Thus, it is recommended that female MA+ patients should be screened for their lipid profile and prothrombotic states and neuroimaging to identify the requirement of other therapeutic agents apart from migraine prophylaxis.

Keywords: *Aura; Patent Foramen Ovale; Echocardiography; Multivariate Logistic; Regression Analyses*

Introduction

Migraine, a complex disorder of both genetic and environmental factors, is prevalent in 18.5% of the population, and migraine with aura (MA+) in 4.4% [1]. The peak prevalence for women is reached in the third decade of life and thereafter declines with age, whereas the prevalence for men virtually plateaus [2]. The patent foramen ovale (PFO) is a slit like interatrial opening that is present in 27% of the general population [3]. Multiple studies suggest that migraine with aura is more prevalent in subjects with patent foramen ovale (PFO) and PFO is more prevalent in subjects who have migraine with aura. Possible mechanisms are subclinical embolization and metabolites (mainly serotonin) from the venous system bypassing the pulmonary circulation via the right to left shunt through PFO, thus entering the systemic circulation and resulting in irritation of the trigeminal nerve and brain vasculature, triggering migraine. Serotonin is released from aggregating platelets, which has been shown to be increased in patients with migraine. In the presence of a PFO, serotonin, which is normally metabolized by the pulmonary monoamine oxidase enzyme is shunted away from the lungs and is postulated to trigger migraine. Moreover, transient hypoxemia due to paradoxical shunting of blood through the PFO causes microinfarcts in the brain, leading to migraine [4]. But there are several arguments against the pathophysiological mechanisms of patent foramen ovale (PFO) in migraine. Although, prevalence of PFO is similar in men and women, the prevalence of migraine is twice as common in women compared to men. Embolic events are unpredictable, but migraine headaches are usually cyclical phenomena. PFO is present from birth, but migraine onsets typically in adolescence or early adulthood. Although the size of a PFO increases with age, migraine attacks typically subside with advancing age and not all migraine patients have a PFO [4]. Meta-analyses concluded that following PFO closure; approximately 83% (95% confidence interval or CI 78 - 88%) of migraineurs have improvement in migraine patterns, including 46% - 55% (95% CI 25 - 67%) who have migraine resolution. The results are similar among migraineurs with and without aura [5]. In this prospective observational study, we primarily aimed to investigate the association of the presence of PFO with the occurrence of MA+ and secondarily aimed to identify the independent risk factors predicting the development of aura among migraineurs with PFO.

Methods and Materials

Informed consent was obtained from all patients, and the institutional ethics committee approved the study. A structured headache questionnaire was composed in such a way that a neurologist could diagnose MA+ and migraine without aura (MA-), according to the criteria of the International Headache Society at the Neurology outpatient department. Transthoracic echocardiography was done for each patient at the Cardiology department. Two independent neurologists who were blinded to the patients' files and echocardiography results diagnosed MA+ and MA-, often discussing amongst them to reach consensus, when there was not a perfect agreement. The headache characteristics were analyzed by means of the headache questionnaire. The duration, frequency and the severity [measured on a scale ranging from 0 (no pain) to 10 (very severe pain)] of headache was recorded. Other relevant histories were also recorded. The neurologic and other systemic examinations were performed by 1 neurologist blinded to the echocardiography results. The complete hemograms, liver and renal function tests, lipid profiles, coagulation assay (prothrombin time, activated partial thromboplastin time, fibrinogen, protein C activity, activated protein C resistance, antithrombin III, protein S, and homocysteine levels) and autoimmune markers (antinuclear antibody, anti-citrullinated peptide, rheumatoid factor, lupus anticoagulant and antiphospholipid antibodies) were evaluated. Magnetic resonance imaging of brain was done to exclude structural causes of headache. An electrocardiogram, chest radiograph and abdominal ultrasound was also performed for all participants. 200 patients of migraine were recruited by consecutive sampling technique over the period from January 2016- January 2018. Diabetics, hypertensives, alcoholics and smokers were excluded from the study.

Descriptive statistics were used to describe patient characteristics. Continuous variables were tested on normality and presented as mean ± standard deviation (SD). Percentages were used to report categorical variables. Univariate and multivariate logistic-regression analyses were used to estimate the unadjusted and adjusted odds ratios (OR) and the corresponding 95% CI. In the multivariate analyses, the most significant clinically relevant univariate variables were included. All tests were 2-sided, and $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS 22.0 software (IBM Corp, Armonk, New York).

Results

200 patients were included in the study.

	MA+ (N = 20)	MA- (N = 180)	OR (95% CI)	p value
PFO present	12	50	3.9 (1.505 - 10.10)	0.0045
PFO absent	8	130		

Table 1: *Compares the occurrence of PFO among MA+ and MA- patients.*

[Abbreviations OR: Odds Ratio]

Thus, it is evident that the presence of PFO in patients of migraine is associated with significantly higher incidence of aura [RR i.e. risk ratio = 3.33 (1.437 - 7.76)].

Characteristics	MA+ with PFO (N = 12)	MA- with PFO (N = 50)	OR (95% CI)	p value
Females	10	26	0.2167 (0.043 - 1.1594)	0.046
Mean age ± SD (years)	34.5 ± 12.6	40.6 ± 8.8		0.0235
Mean weight ± SD (Kg)	45.0 ± 12.5	42.8 ± 10.6		0.98
Mean BMI (kg/m^2)	24.7 ± 5.2	24.3 ± 5.9		0.08
Rural residence	8	30	1.33 (0.353 - 5.02)	0.47
Duration of headache > 5 years	5	10	2.85 (0.74 - 10.91)	0.117
Family history of migraine	7	22	0.56 (0.156 - 2.011)	0.28
Previous head trauma	1	2	2.18 (0.181 - 26.27)	0.48
Previous stroke	3	2	8 (1.06 - 54.87)	0.045
Anaemia	2	8	1.05 (0.192 - 5.725)	0.624
Coronary artery disease	3	2	8 (1.166 - 54.87)	0.045
Other cardiac anomalies	0	2	0	0.64
Hyperlipidemia	7	13	3.98 (1.075 - 14.77)	0.038
ANA positivity	2	10	0.8 (0.15 - 4.24)	0.577
RA factor positivity	1	4	1.04 (0.1066 - 10.30)	0.672
Hyperhomocystenemia	4	4	0.1739 (0.036 - 0.8412)	0.038
Other hypercoagulable states	3	4	5.75 (1.18 - 27.81)	0.03
MRI brain abnormalities	5	7	4.38 (1.083 - 17.763)	0.044

Table 2: *Shows the univariate analysis of demographic and clinical characteristics and laboratory parameters of the study subjects.*

[SD: Standard Deviation]

Univariate analysis in table 2 showed that female sex [RR = 0.28 (95% CI = 0.066 - 1.16)], younger age, previous stroke [RR = 6.25 (95% CI = 1.17 - 33.35)], coronary artery disease [RR = 3.8 (95% CI = 1.49 - 9.66)], hyperlipidemia [RR = 2.24 (95% CI = 1.15 - 4.37), hyperhomocystenemia [RR = 0.725 (95% CI = 0.482 - 1.09), other hypercoagulable states [RR = 4.167 (95% CI = 1.21 - 14.31)] and MRI brain abnormalities [RR = 2.97 (95% CI = 1.14 - 7.76)] were significantly higher among MA+ patients. Among 3 MA+ patients with other hypercoagulable states, 1 had protein S deficiency, 1 had Leiden factor V, and 1 had Antithrombin III deficiency. Among 4 MA- patients with other hypercoagulable states, 1 had protein S deficiency, 1 had Leiden factor V, and 2 had antithrombin III deficiency. Other coagulation profiles investigated were normal in the study subjects. However, multivariate analysis identified female sex [adjusted OR = 0.22, p = 0.04],

previous stroke [adjusted OR = 7.8, p = 0.04], hyperlipidemia [adjusted OR = 3.88, p = 0.03], other hypercoagulable states [adjusted OR = 5.7, p = 0.032] and MRI brain abnormalities [adjusted OR = 4.4, p = 0.04] as the independent predictors of the occurrence of aura among migraine patients with PFO. Brain MRI abnormalities were white matter hyperintensities which were defined as clearly hyperintense areas relative to surrounding white matter on both FLAIR and T_2 -weighted images and identified by simultaneous inspection of both aligned images. Transthoracic echocardiography also identified small muscular ventricular septal defects among 2 MA- patients (Table 2).

6 MA+ and 30 MA- patients were employed. Among them 4 MA+ and 6 MA- patients had > 10 working days lost due to migraine attacks [OR = 8 (95%CI = 1.17 - 54.49), RR = 3.33 (95%CI = 1.33 - 8.3)] and p = 0.03.

Discussion

A meta-analysis suggests that migraineurs with aura are 4 times more likely to have a PFO [OR = 4.45] than the general population. MA- does not seem to be associated with PFO [6]. The risk of migraine with aura is higher among those with larger PFO, right-to-left shunting at rest, and atrial septal aneurysm [7]. Another meta-analysis concluded that the odds ratio of migraine in subjects with PFO is 5.19 [8], whereas in our study the odds ratio was 3.9. Atrial septal aneurysms (very mobile atrial septa) are present in people with the largest PFOs. Thus, atrial septal aneurysms, which are surrogate markers for the diameter of the PFO and hence of the degree of shunting are associated with migraine with aura. The hypothesis linking the two conditions is that microemboli or vasoactive components of platelets crossing the PFO play a causative role. This theory is supported by the observations that high-dose antiplatelet drugs improve symptoms in some migraine sufferers. A PFO with right-to-left shunt would require a susceptible neurological substrate and a vulnerability to a substance that bypasses the pulmonary circulation and induces headache. The endothelium of the pulmonary circulation has significant metabolic activity and the lung metabolizes, activates, or inactivates many compounds including vasoactive amines and other humoral substances like prostaglandins E1, E2, and F2α (completely removed from the blood); serotonin (85% to 95% removed); bradykinin (≈80% is inactivated); and 70% of angiotensin I is converted to angiotensin II. These unaltered substances increase the susceptibility of the brain to environmental or intrinsic migraine triggers, produce transient ischemia and cortical spreading depression (CSD). Microemboli from PFO or other right-to-left shunt may trigger aura by producing transient ischemia, leading to CSD [9,10]. In support of this hypothesis, injection of polystyrene microspheres into the carotid artery of anesthetized mice triggered CSD without MRI evidence of cerebral infarctions [11]. However, due to complications such as thrombus formation on the implant device, thromboembolism related to the implant device, cardiac perforation, infective endocarditis, and cardiac arrhythmias, the seriousness of the complications in comparison to the non-life threatening nature of migraine and the debatable pathophysiological relevance of PFO with aura, currently PFO closure cannot be recommended as a routine treatment for migraine [4]. Anzola [12] demonstrated that MA+ patients are more likely to have a family history of migraine than MA- patients (76% vs. 66%), suggesting a genetic link. However, in our study, although family history of migraine was higher among MA+ patients, it was not significant (58% versus 44%, p = 0.28).

Univariate analysis revealed that female sex, younger age, previous stroke, coronary artery disease, hyperlipidemia, hyperhomocystenemia and other hypercoagulable states were associated with the increased occurrence of aura in patients of migraine with PFO. The previous history of stroke and coexistence of coronary artery disease had the highest risk; patients were 8 times more prone to develop aura if associated with these features. However, multivariate analysis showed only 5 factors- female sex, previous stroke, hyperlipidemia, other hypercoagulable states and abnormalities in MRI brain to be independently associated with aura. In his large observational study on MA+ patients, Sinclair [13] described female sex, younger age, atrial fibrillation and hypercholesterolemia to be significantly associated with MA+ in univariate analysis. However, aside from the combination of PFO and atrial septal aneurysm (OR = 2.71), both female sex (OR = 2.44) and age (OR = 0.94) were independently associated with MA+ in his study. In our study, transthoracic echocardiography did not reveal any atrial septal aneurysm.

A recent metaanalysis identified migraine as an independent risk factor for ischemic stroke occurrence outside the setting of the migraine episode (pooled relative risk 1.73; 95% CI 1.31 - 2.29), but this risk was double among MA+ patients (2.16; 95% CI 1.53 - 3.03) and was further increased in women less than 45 years of age, smokers and in those taking the oral contraceptive pill [13]. Aura in migraineurs

also amplifies the mortality rates following a stroke. The significant association of aura with cerebrovascular disease raises the possibility that aura may be linked to the pathogenesis of stroke in migraine patients. Our study identified an odds ratio of 8 and relative risk of 6.25 for aura in patients with past history of stroke. Cortical spreading depression, the presumed substrate of aura, may directly predispose to brain lesions and hence there is significant and consistent association of aura with cerebrovascular disease, while for MA-, the evidence is less consistent. CSD, a self-propagating wave of neuronal and glial depolarization, marching across the cortical mantle initiates a series of cellular and molecular events, resulting in transient loss of membrane ionic gradients, and an increase of extracellular potassium, neurotransmitters, and intracellular calcium. Blood-brain barrier permeability is altered by activation of matrix metalloproteinases (MMPs). The oxygen free radicals, nitric oxide, and proteases-factors that have been implicated in MMP activation-are dramatically increased. The CSD-related MMP activation changes the vascular permeability in the CNS contributing to the migraine symptoms and reduces cerebral blood flow contributing to stroke [13].

Interestingly, migraine with aura was similarly associated with coronary heart disease as well. In our study, MA+ patients were 8 times more prone to develop cardiovascular diseases than MA-patients. In the Women's Health Study, MA+ but not MA- approximately doubled the relative risk of major cardiovascular diseases (ischemic stroke, myocardial infarction, coronary revascularization procedures, angina, as well as death related to ischemic cardiovascular events). These associations remained significant even after adjusting for many cardiovascular risk factors [14]. Moreover, in the Physician's Health Study, both MA+ and MA- men were at increased risk for major cardiovascular diseases (RR = 1.24; 95% CI, 1.06 - 1.46), the risk of myocardial infarction increasing 42% [15]. In Atherosclerosis Risk in Communities Study, the associations were stronger even among the subset of non-hypertensive and non-diabetic migraineurs (OR = 1.79; 95% CI, 1.09 - 2.95 for MA+; and OR = 1.74; 95% CI, 1.11 - 2.71 for MA-) [16]. EPCs (endothelial progenitor cells) replace injured endothelium cells, thereby preventing the formation of atherosclerotic plaques. The number of circulating (EPC) is considered to be a surrogate biological marker of vascular function. Diminished EPC counts are associated with higher cardiovascular risk [17]. A recent study demonstrated that the mean numbers of EPC colony-forming units were significantly reduced, with reduced migratory capacity and increased cellular senescence in MA+ patients, compared to patients of other headaches, thus, predisposing MA+ patients to significantly higher incidence of cardio and cerebrovascular diseases [18].

Large cross-sectional studies confirmed that body mass index (BMI) was a risk factor for high frequency episodic migraine (OR = 2.9; 95% CI, 1.9 - 4.4 for obese; OR = 5.7; 95% CI, 3.6 - 8.8 for severe obese) [19]. Chronic migraine prevailed in 0.9% of normal weighted subjects (reference group) to 1.2% of overweight subjects (OR = 1.4; 95% CI, 1.1 - 1.8), 1.6% of obese subjects (OR = 1.7; 95% CI, 1.2 - 2.4), and 2.5% of severely obese subjects (OR = 2.2; 95% CI, 1.5 - 3.2) [15]. In their study of 2-month duration, Horev [20] found that among 27 morbidly obese women (mean BMI of 41.07), ten suffered from migraine with aura, three from migraine without aura, and four from tension headache. They concluded that the unusually high incidence of migraine with aura can be attributed to extraovarian production of estrogen and estradiol in the adipose tissue [20]. However, mean body weight and BMI were not significantly associated with the occurrence of aura in our study.

Multivariate analysis showed that hyperlipidemia is an independent risk factor of occurrence of aura in our study. The suggested mechanisms in migraine with aura are the change of cortical irritability, neural system inflammation and vascular endothelial dysfunction. Hyperlipidemia induces platelet aggregation and triggers neurogenic inflammation by inducing changes in serum serotonin and platelet serotonin levels thereby initiating the cascades of prostaglandins (mainly PGE2) and leukotrienes (LT) formation. These changes lead to vasodilatation and migraine headache. Hypertriglyceridemia is also associated with peripheral vessels vasodilatation and increased blood flow, which also predispose to migraine [21].

Multivariate analysis established hypercoagulable states as an independent predictor of occurrence of aura, with almost 6 times higher risk. Hyperhomocystenemia was found to be significantly associated with aura in univariate analysis, but was not found to be an independent factor in multivariate analysis. Although definitive studies are lacking, a growing body of literature suggests that migraine patients, and especially MA+ patients, have increased levels of estradiol, thrombo- and erythrocytosis, increased von Willebrand factor (vWF) antigen, fibrinogen, tissue plasminogen activator (tPA) antigen, and endothelial microparticles [22]. Studies evaluating a link of migraine to hyperhomocysteinemia, low protein S, and the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism have conflicting reports. Several meta-analyses found that within a large, young ischemic stroke sample, migraine with aura was associated with a thrombophilic state and with patent foramen ovale (PFO) [22]. Kutai showed high incidence of Leiden factor V mutation (F5 A1691G) and prothrombin gene mutation (F2 G20210A) and significantly increased factor VIII activity in a group of pediatric migraine patients compared with the control group amongst a Jewish population, the risk being even higher among MA+patients [23]. Mantelet demonstrated that there was a significant association between MA+ and Leiden factor V mutation and prothrombin gene mutations [adjusted OR = 1.76 (95% CI 1.02-3.06), p = 0.04] whereas this association in MA- and in non-migrainous headache women was not significant [24].

In our study, the presence of MRI brain abnormalities among migraineurs was associated with approximate 4.5 times higher risk of developing aura. Meta-analysis of six population-based and 13 clinic-based studies identified that structural brain changes, including white matter abnormalities, silent ischemia like lesions, and volumetric changes in both gray and white matter regions were more common in migraineurs than in control groups and the results were strongest for MA+ [25]. The meta-analysis of white matter abnormalities showed an association for MA+ (OR 1.68; 95% CI 1.07 - 2.65; p = 0.03) but not for MA- (OR 1.34; 95% CI 0.96 - 1.87; p = 0.08). The association of ischemia like lesions was greater for MA+ (OR 1.44; 95% CI 1.02 - 2.03; p = 0.04) than for MA-, but no association was found for MA+ (p = 0.52) and MA- (p = 0.08) compared to controls [26]. White matter abnormalities results from acute ischemia due to disruption of blood flow in the perforating artery or chronic ischemia in the periventricular and deep white matter regions of the brain, which are watershed regions with low perfusion. The load of such hyperintensities exponentially increases with the duration and frequency of migraine attacks, suggesting that migraine is a progressive brain disorder [27].

Migraine attacks can be severe enough to limit activities both at work and at home, and there may be significant psychological impact between attacks. In south Asia, the years lived with disability due to migraine was 569 per 100,000 people. According to the Global Disease Burden study published in 2015, migraine is the third cause of disability in under 50s. Until recently, little work has been done on the impact of migraine on the quality of life [28]. Losses of working days were significantly (8 times) higher among MA+ patients in our study. Clarke [24] described 158 migraineurs, diagnosed according to International Headache Society (IHS) criteria, had estimated 2.0 days/year absence from work, and an equivalent of 5.5 days/year lost by reduced effectiveness at work caused by their migraine at an estimated financial cost of over £50,000 to their employer [29].

Limitations

This study is limited by the fact that the confounders like hypertension, diabetes, smoking and alcoholism were not taken into account while evaluating the patients with history of stroke and patients with MRI brain abnormalities. For ANA positive patients, their subprofiles were not investigated. Moreover, we performed transthoracic echocardiography, whereas in other studies, transesophagic echocardiography were performed, which is more sensitive in diagnosing PFO and assessing its size.

Conclusion

Hence, this study presents the fact that PFO is significantly higher in migraineurs with aura in our local population. Female sex, previous stroke, hyperlipidemia, MRI brain abnormalities and other hypercoagulable states are the independent predictors of the occurrence of aura in migraine patients with PFO. Although the association of these factors with migraine has already been described in previous studies, the demonstration of their significant association with the occurrence of aura is the originality of this study. Thus, it is recommended that female MA+ patients should be screened for their lipid profile and prothrombotic states. Further studies are needed to investigate whether antiplatelet therapy, statins, and anticoagulants in pertinent cases could reduce the frequency of attacks of migraine with aura.

Conflict of Interest

None stated.

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