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Patent Foramen Ovale and Migraine: A Cross-Sectional Study from the Northern Manhattan Study (NOMAS)

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Abstract

Background—A causal relationship between patent foramen ovale (PFO) and migraine has been hypothesized, and improvement of migraine frequency and severity after percutaneous PFO closure has been reported. Population-based data on the relationship between PFO and migraine are however sparse. The objective of this study was to examine the association between PFO and migraine among stroke-free individuals in an urban, population-based multiethnic cohort.

Methods and Results—As a part of the ongoing Northern Manhattan study (NOMAS), 1,101 stroke-free subjects were assessed for self-reported history of migraine. The presence of PFO was assessed by transthoracic echocardiography. The mean age of the group was 69±10 years; 58% were women; 48% Caribbean Hispanic, 24% white, 26% black, and 2% other race-ethnicity. The prevalence of self-reported migraine was 16% (13% migraine with aura). The prevalence of PFO was 15%. Migraine was significantly more frequent among younger subjects, women, and Hispanics. The prevalence of PFO was not significantly different between subjects who had migraine (26/178, or 14.6%) and those who did not (138/923, or 15.0%; p=0.9). In an adjusted multivariate logistic regression model, the presence of PFO was not associated with increased prevalence of migraine (odds ratio, OR 1.01; 95% Confidence Interval, CI 0.63–1.61). Increasing age was associated with lower prevalence of migraine in both subjects with a PFO (OR 0.94, 95% CI 0.90–0.99 per year) and without PFO (OR 0.97, 95% CI 0.95–0.99 per year). The observed lack of association between PFO and migraine (with or without aura) was not modified by diabetes, hypertension, cigarette smoking, and dyslipidemia.

Conclusion—In this multiethnic elderly population-based cohort, PFO detected with TTE and agitated saline was not associated with self-reported migraine. The causal relationship between PFO and migraine remains uncertain, and the role of PFO closure among unselected patients with migraine remains questionable.

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Conflict of Interest Disclosures

Drs. Rundek, Elkind, Di Tullio Carrera Jin, and Sacco report no conflicts
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Keywords

migraine; PFO; TTE; risk factors; population study

Introduction

Migraine is a common, chronic, disabling neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, and, in some patients, an aura and neurologic symptoms (1). The prevalence of migraine is as high as 18% in the general population (2,3). Migraine is one of the most disabling chronic disorders and ranks 19th among diseases causing morbidity worldwide (2,4). The suffering associated with migraine headaches accounts for a significant loss in productivity and a substantial increase in health care-related costs. Patient foramen ovale (PFO) has a prevalence of 15–25% in the general population (5–7), and up to 60% in patients with migraine with aura (8–12) in case-control studies. However, the high prevalence of PFO in patients with migraine reported in case control studies, for a lack of population-based data, is most likely overestimated due to a biased selection of control groups.

A causal relationship between PFO and migraine has been recently hypothesized (9,10) and several mechanisms such as serotonin-platelet activation and aggregation, and embolism causing cortical spreading depression have been proposed (13,14) and genetic effects including autosomal dominant inheritance with incomplete penetrance (15) and co-inheritance (10) have been reported.

A commonly accepted endpoint of effective treatment for migraine is a 50% reduction in headache frequency after 6 months of therapy (2). The frequency of migraine attacks decreases with age (16). Reduction in migraine burden after percutaneous patient foramen ovale (PFO) closure has been reported in A few uncontrolled studies (17–22). The only prospective sham-controlled study of PFO closure for migraine with aura (The Migraine Intervention with STARFLEX Technology – MIST trial), however, did not reach its primary endpoint of a complete cessation of migraine attacks 6 months after PFO closure (23). Several clinical trials of PFO closure in refractory migraine are currently underway (MIST II, ESCAPE, PREMIUM) although the causal relationship between PFO and migraine remains uncertain, and PFO closure among patients with migraine controversial. Interestingly, population based data on the relationship between PFO and migraine are sparse and the debate on whether presence of PFO in individuals from the general population is related to migraine and stroke continues (5,24,25).

The aim of this study was to examine the association of PFO and migraine among stroke-free individuals from an urban, population-based multiethnic cohort

Subjects and Methods

The Northern Manhattan Study (NOMAS) is an ongoing prospective cohort study of stroke-free individuals designed to determine stroke incidence, risk factors, and outcomes in a multi-ethnic urban population of the northern Manhattan area. The methods of subject recruitment and enrollment into NOMAS have been previously described (26,27). Briefly, community subjects from Northern Manhattan were eligible if they (1) had never been diagnosed with a stroke, (2) were over age 39, and (3) resided in Northern Manhattan for at least 3 months in a household with a telephone. Stroke-free subjects were identified by random digit dialing utilizing dual frame sampling to identify both published and unpublished telephone numbers. Of the prospective study participants that were contacted telephonically, 90% agreed to come

in for an in-person visit. A total of 3298 subjects were recruited and enrolled in NOMAS between1993 and 2001. The study was approved by the Institutional Review Board at the Columbia University Medical Center and all participants gave written informed consent.

Information about risk factors was collected through interviews by trained research assistants, and physical and neurological examinations were performed by study physicians. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System (28) of the Centers for Disease Control and Prevention regarding the following conditions: hypertension, diabetes, hypercholesterolemia, cigarette smoking, peripheral vascular disease and cardiac diseases. Assessments were conducted in English or Spanish depending upon the primary language of the participant. Race-ethnicity was based upon self-identification through a series of interview questions modeled after the US census and conforming to the standard definitions outlined by Directive 15 (29). Standard techniques were used to measure blood pressure, height, weight, and fasting glucose as described in prior publications (26,27,30). Fasting lipid panels (including total cholesterol, LDL, HDL and triglyceride) were measured using a Hitachi 705 automated spectrometer (Boehringer; Mannheim, Germany). Risk factors were defined as in prior publications (26,27,30). Hypertension was defined as a systolic blood pressure recording of 140 mmHg or higher or a diastolic blood pressure recording of 90 mmHg or higher or the patient's self-report of a history of hypertension or antihypertensive use. Diabetes mellitus was defined by a fasting blood glucose level ≥ 126 mg/dL, the subject's self-report of such a history, or insulin or oral hypoglycemic use. Dyslipidemia was defined as a history of elevated cholesterol, taking medications for elevated cholesterol or a total cholesterol level > 240. Current smoking was defined by smoking within the past year.

Definition of Migraine

A consecutive sample of 1,101 subjects (34% of the parent NOMAS cohort) enrolled into NOMAS from 1997–2001 we asked to respond to a questionnaire regarding self-reported diagnosis of migraine. All NOMAS subjects were interviewed in person in a neurology research clinic. The subjects were questioned regarding self-reported migraine by trained research assistants. Individuals were asked the following questions: "*Have you ever had migraine headaches?"*, for a past history of migraine ; and "*In the past year have you had at least one headache, other than those caused by head injury, hangover, or a bad cold or flu?"*, for the current symptoms. Self-reported migraine was defined as a positive answer to either of these two questions. If self reported migraine was described by a research assistant, a study neurologist (a stroke fellow or an attending) interviewed the subjects regarding migraine history at the time of neurological examination using a short 15 minutes questionnaire adopted from the *International Headache Society (IHS) Classification, 2nd Edition* (2), in order to record frequency and duration of headache, pain type, sensitivity to light and sound, visual disturbances, nausea, focal neurological symptoms, and medications. According to the recorded answers, the self-reported migraine was defined as close as possible to the IHS criteria as *migraine without aura* (recurrent headache with attacks lasting 4–72 h; unilateral, pulsating, aggravating by physical activity and associated with nausea and/or photophobia and phonophobia), and *migraine with aura* (recurrent headache with attacks of completely reversible focal neurological symptoms lasting less than 60 min following the aura symptoms). Typical aura was visual and/or sensory with or without speech symptoms.

Echocardiographic Evaluation of Patent Foramen Ovale

Transthoracic 2-dimensional echocardiography (TTE) was performed in all study subjects according to the published protocol adopted form the recommendations of the American Society of Echocardiography (5). Saline contrast injection (aerated saline solution) with provocative maneuvers (Valsalva maneuver, sniff, cough) was used for PFO detection. A PFO

was considered to be present if any microbubble was seen in the left-sided cardiac chambers within 3 cardiac cycles from maximum right atrial opacification (5).

Statistical analyses

The distribution of the variables of interest and of the other risk factor variables was examined. Means were calculated for continuous variables and proportions for categorical variables. Simple and multiple logistic regression were used to analyze the association between presence of PFO and self-reported migraine before and after adjusting for potential confounding demographics (age, sex, and race-ethnicity) and vascular risk factors (hypertension, diabetes, dyslipidemia, current smoking) that are associated with endothelial dysfunction, a presumed mechanism in migraine. Statistical significance was determined at the alpha level of 0.05 using two-sided tests. Statistical analyses were conducted using SAS Version 9.1 (SAS Institute, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A sample of 1,101 stroke-free individuals were analyzed in this study. Demographics and clinical characteristics of this group did not significantly differ from the characteristics of the parent cohort (26). The mean age in this sample was 69±10 years (vs. 69±10 years in the parent cohort); 58% were women (vs.62%); 48% Caribbean Hispanics (vs.53%), 26% African-American (vs.24%), and 22% Caucasian (vs. 20%). The prevalence of hypertension was 67% (vs. 73% in the parent cohort), diabetes 18% (vs. 21%), and current and former smoking 54% (vs. 53%).

The prevalence of self-reported migraine in the cohort was 16% (178); 13% (140) with aura. The prevalence of PFO was 15% (164). In the cohort, only 26 subjects (2%) had PFO and reported a history migraine.

The distribution of demographics and risk factors among all subjects, subjects with migraine, and subjects without migraine is shown in Table 1. The subjects with self-reported migraine were younger than those without self-reported migraine (mean age 61 vs. 71 years, $p<0.01$), were more likely women (72% vs. 55%, $p<0.01$), and Caribbean Hispanics (58% vs. 46%, $p<0.01$). There were no other significant differences between subjects with and without self-reported migraine. The prevalence of PFO was not significantly different between subjects who had migraine (26/178, or 14.6%) and those who did not (138/923, or 15.0%; $p=0.91$). In addition, the prevalence of PFO did not differ between subjects with migraine with aura (22/140, or 19%) and those with migraine without aura (4/38, or 11%; $p=0.42$). In an adjusted multivariate model (Table 2), the presence of PFO was not associated with increased prevalence of migraine (odds ratio, OR 1.01; 95% Confidence Interval, CI 0.63–1.61). In addition, we have calculated OR and 95% CI for the adjusted association of PFO with migraine with aura alone in comparison to no migraine (OR 1.01; 95% CI, CI 0.71–1.69). Although the result is not significant, the upper confidence limit for the OR is consistent with a slightly higher elevation in risk of migraine with aura among people with PFO.

Increasing age was associated with lower prevalence of migraine in both subjects with a PFO (OR 0.94, 95% CI 0.90–0.99 per year) and without PFO (OR 0.97, 95% CI 0.95–0.99 per year). The lack of association between migraine and PFO was not modified by age or sex (in a model adjusted for age and sex only: OR 1.00; 95% CI, 0.61–1.74). No significant interaction was observed on the relationship between PFO and migraine for diabetes, hypertension, dyslipidemia, and cigarette smoking (data not shown).

Discussion

In this cross-sectional analysis from an elderly urban multi-ethnic population-based cohort of 1,101 stroke-free individuals, we did not find an association between presence of PFO detected with TTE and agitated saline and self-reported migraine. The prevalence of PFO of about 15% was observed among individuals with self-reported migraine as well as among those without self-reported migraine. PFO was slightly more prevalent in migraine with aura (19%) than in migraine without aura (11%) but the number of subjects with migraine subtypes was not large enough to make a definitive statement about this difference In addition, risk factors did not affect the relationship between PFO and self-reported migraine.

We could not confirm previous reports of the association of PFO with migraine, or migraine with aura (8–12,31–33). There are several possible reasons for this discrepancy. Unlike our population-based study, most of the previous studies were case reports, case-control studies, or case series of highly selected patients with migraine and therefore the true associations in the populations could not be ascertained. The study populations differed according to subject characteristics, diagnostic criteria for migraine, and methods for PFO detection (Table 3). A half of our cohort consisted of Caribbean Hispanics, among which the prevalence of migraine was more than twice that of blacks and whites. Although the prevalence of PFO in migraine differed considerably between the studies, the most consistent finding is an increased prevalence of PFO among individuals with migraine with aura. Although association of PFO with migraine in our study was not statistically significant, the upper 95% confidence limit for the adjusted OR for PFO in the multivariate logistic model showed that increases in the odds of migraine among those with PFO as large as 61% cannot be entirely ruled out. The small number of subjects with PFO and migraine may explain the wide the confidence intervals for the OR for their association.

In our study, the prevalence of PFO was 15% and of self-reported migraine 16% (13% with aura), but the coexistence of both conditions in an individual was quite uncommon: only 2% of subjects had both PFO and self-reported migraine. There is currently insufficient evidence to support a causal link between PFO and migraine. Vasoactive substances and platelet emboli, and their paradoxical bypass of the lung through a PFO, have been proposed to trigger the cortical spreading depression of the aura in subject with PFO (14). A pattern of autosomal dominant inheritance in families with large PFOs or atrial septal defects have been identified. (13) Co-inheritance of PFO, endothelial and platelet abnormalities have been proposed to predispose an individual to migraine (15). These abnormalities and genetic determinants may be responsible for migraine, its type and severity, and resistance to medical treatment. In addition, PFO has been proposed as potential explanation of the migraine-stroke association. Based on recent data of a lack of an association between PFO and cryptogenic stroke in elderly individuals, such explanation is unlikely (5).

PFO Closure and Migraine

The results of several uncontrolled PFO closure studies (17–22) have suggested a beneficial effect of the procedure on reduction of migraine frequency and duration. The first double blind randomized trial MIST I, however, did not achieve the primary efficacy endpoint of cessation of headache attacks during 3 and 6 months after the procedure (23). The study also filed to achieve secondary predefined endpoint. However, in the exploratory analysis after exclusion of 2 patients in the implant group who accounted for more than one third of all migraine headache days throughout the entire study period, a significant reduction of 37% in median total migraine headache days for the implant group was observed in comparison to 26% reduction in the sham group. Several randomized PFO closure trials in migraine are currently underway, but at present there is no convincing scientific evidence to support PFO closure for treatment of migraine. Furthermore, PFO closure procedure is associated with significant

complications. Most of the patients in the MIST trial had at least one adverse event; 16 (11% of the intent-to-treat population) patients experienced serious adverse events, and 10 (7%) had serious adverse event definitely or possibly related to device or procedure (23). In addition, PFO closure also may trigger migraine. Recently, a substantial number of patients developed *de novo* migraine attacks after PFO closure (34). These individuals were younger and bigger devices were used. Platelet activation, adhesion, and aggregation at the site of the occlusion device may release increased levels of serotonin, which triggers migrainous attacks, and these patients may benefit from antithormbotic therapy (34). Migraine is a complex neurological disorder with many possible exogenous and endogenous triggers, so any simple "cure" such as PFO closure is unlikely to exist. Therefore, until there is more evidence from ongoing large controlled trials, PFO closure should not be used as a treatment of migraine in clinical practice (24).

Study Limitations

Several limitations of our study exist. First, the presence of migraine in our study was defined by self-reported history of signs and symptoms of migraine. Although we have tried to maximize the accuracy of diagnosis by asking the questions used in the IHS classification of migraine and our study neurologists have reviewed the charts, a certain proportion of cases could have been misclassified. In addition, the recall bias in an older cohort such as ours could have contributed to underreporting of the symptoms. However, the prevalence of the self-reported migraine in our study is similar to the prevalence expected in a general population. The higher prevalence of migraine with aura may be overestimated however due to a recall bias. Second, our study population is older in comparison to most previous studies, and an association between migraine and PFO cannot be excluded in younger individuals from these data. Third, we used TTE to detect PFO instead of the more sensitive transesophageal echocardiography (TEE). This resulted in a lower prevalence of PFO (15%) than previously reported (17–26%) (7,35). However, TEE is a semi-invasive technique not suited for use in a large epidemiological studies or in a low-risk population, and therefore, our results are more relevant for general medical practice. Moreover, the PFOs that are missed by TTE have been shown to be small and characterized by small interatrial shunts (36), therefore possibly less relevant from a clinical standpoint. The other alternative could have been to perform transcranial Doppler (TCD) contrast studies, which in conjunction with TTE would have increased the sensitivity of PFO detection. TCD data was not systematically collected in our study. Finally, under-ascertainment of both PFO and migraine in our study, while plausibly non-differential, would also be expected to attenuate the observed association, again slightly weakening the negative finding of the study.

In conclusion, PFO and migraine are relatively frequent conditions in the general population but their coexistence in an individual is uncommon. We did not find a significant association between PFO detected with TTE and agitated saline and migraine among elderly individuals from an urban, population-based multiethnic cohort. The causal relationship between PFO and migraine remains uncertain. Scientific evidence for PFO closure in order to reduce frequency of migraine is lacking. Our study did not evaluate the effect of PFO closure but indirectly supports the notion that the role of PFO closure among patients with refractory migraine remains questionable.

CLINICAL PERSPECTIVE

While a causal relationship between patent foramen ovale (PFO) and migraine has been hypothesized, and improvement of migraine severity after percutaneous PFO closure has been reported, population-based data on this relationship is sparse. This study reports on the lack of the significant association between PFO detected with TTE and agitated saline

and migraine among 1,101 stroke-free elderly individuals derived from an urban, population-based multiethnic cohort. In this population, the prevalence of self-reported migraine was 16% (13% migraine with aura); the prevalence of PFO was 15%, and 2% of individuals with migraine had PFO. Migraine was significantly more frequent among younger individuals, among women, and Hispanics. The observed lack of association between PFO and migraine (with or without aura) was not modified by other traditional risk factors such as diabetes, hypertension, cigarette smoking, and dyslipidemia. This study demonstrates that PFO and migraine are relatively frequent conditions in the general population but their coexistence in an individual is uncommon. Although this study did not evaluate the effect of PFO closure, it indirectly supports the notion that the role of PFO closure among patients with refractory migraine is questionable as a “true” relationship between PFO and migraine remains uncertain.

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Table 1

Demographics and risk factors in an overall cohort of 1,101 subjects, and among subjects with self-reported migraine and without self-reported migraine

	ALL N=1,101	MIGRAINE 178 (16%)	NO MIGRAINE 923 (84%)	P
Age (years)	69±10	61 ± 9	71 ± 10	<0.01
Women, n (%)	639 (58)	128 (72)	508 (55)	<0.01
African American, n (%)	286 (26)	36 (20)	249 (27)	
Hispanic, n (%)	528 (48)	103 (58)	425 (46)	<0.01
White, n (%)	264 (24)	36 (20)	231 (25)	
Hypertension, n (%)	738 (67)	123 (69)	618 (67)	0.58
Diabetes, n (%)	198 (18)	27 (15)	175 (19)	0.23
Dyslipidemia, n (%)	528 (48)	79 (44)	462 (50)	0.17
Current smoking, n (%)	198 (18)	36 (20)	148 (16)	0.17
PFO, n (%)	164 (15)	26 (14.6)	138 (15)	0.91
		With aura 22/140 (19%)		0.42
		Without aura 4/38 (11%)		

Table 2

Predictors of self-reported migraine, including a presence of PFO (multivariate logistic regression)

	OR	95% CI	P
PFO	**1.01**	**0.63 – 1.61**	**0.90**
Age	0.97	0.95 – 0.99	<0.01
Women	2.34	1.61 – 3.40	<0.01
Hispanics vs. white	1.18	0.75 – 1.87	0.47
Black vs. white	0.76	0.45 – 1.27	0.29
Hypertension	1.13	0.78 – 1.64	0.52
Diabetes	0.66	0.43 – 1.02	0.07
Dyslipidemia	1.12	0.78 – 1.59	0.55
Current smoking	1.36	0.99 – 2.10	0.16

Table 3

Prevalence of PFO among subjects with migraine selected from the literature including data from the current NOMAS study

STUDY	PFO Method	Migraine With Aura	Migraine Without Aura	NO Migraine
Del Sette et al. (10) Cerebrovas Dis. 1998	TCD	18/44 (41%)	NA	8/50 (16%)
Anzola et al. (9) Neurology. 1999	TCD	54/113 (48%)	12/53 (23%)	5/25 (20%)
Schwerzmann et al. (8) Neurology. 2005	TEE	44/93 (47%)	NA	16/93 (17%)
Dalla Volta et al. (31) J Headache Pain. 2005	TCD	161/260 (62%)	12/74 (16%)	NA
Carod-Artal FJ et al. (33) Cephalalgia. 2006	TCD	25/48 (51%)	32/93 (34%)	NA
Domitrz et al. (11) Headache. 2007	TCD	33/61 (54%)	15/60 (25%)	16/65 (25%)
NOMAS	TTE	26/140 (19%)	4/38 (11%)	138/923 (15%)