

Stroke

American Stroke
AssociationSM

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American
Heart Association



Probable Migraine With Visual Aura and Risk of Ischemic Stroke: The Stroke Prevention in Young Women Study

Leah R. MacClellan, Wayne Giles, John Cole, Marcella Wozniak, Barney Stern,
Braxton D. Mitchell and Steven J. Kittner

Stroke 2007;38;2438-2445; originally published online Aug 9, 2007;

DOI: 10.1161/STROKEAHA.107.488395

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75114

Copyright © 2007 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online
ISSN: 1524-4628

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://stroke.ahajournals.org/cgi/content/full/38/9/2438>

Subscriptions: Information about subscribing to *Stroke* is online at
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax:
410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Probable Migraine With Visual Aura and Risk of Ischemic Stroke

The Stroke Prevention in Young Women Study

Leah R. MacClellan, PhD; Wayne Giles, MD; John Cole, MD; Marcella Wozniak, MD; Barney Stern, MD; Braxton D. Mitchell, PhD; Steven J. Kittner, MD

Background and Purpose—Migraine with aura is associated with ischemic stroke, but few studies have investigated the clinical and anatomic features of this association. We assessed the association of probable migraine with and without visual aura with ischemic stroke within subgroups defined by stroke subtype, vascular territory, probable migraine characteristics, and other clinical features.

Methods—Using data from a population-based, case-control study, we studied 386 women ages 15 to 49 years with first ischemic stroke and 614 age- and ethnicity-matched controls. Based on their responses to a questionnaire on headache symptoms, subjects were classified as having no migraine, probable migraine without visual aura, or probable migraine with visual aura (PMVA).

Results—Women with PMVA had 1.5 greater odds of ischemic stroke (95% CI, 1.1 to 2.0); the risk was highest in those with no history of hypertension, diabetes, or myocardial infarction compared to women with no migraine. Women with PMVA who were current cigarette smokers and current users of oral contraceptives had 7.0-fold higher odds of stroke (95% CI, 1.3 to 22.8) than did women with PMVA who were nonsmokers and non-oral contraceptive users. Women with onset of PMVA within the previous year had 6.9-fold higher adjusted odds of stroke (95% CI, 2.3 to 21.2) compared to women with no history of migraine.

Conclusions—PMVA was associated with an increased risk of stroke, particularly among women without other medical conditions associated with stroke. Behavioral risk factors, specifically smoking and oral contraceptive use, markedly increased the risk of PMVA, as did recent onset of PMVA. (*Stroke*. 2007;38:2438-2445.)

Key Words: migraine ■ stroke ■ transient ischemic attack ■ aura

Migraine and stroke share some common risk factors, including hypertension¹ and patent foramen ovale (PFO),^{2,3} and there is a familial basis to both.⁴⁻⁷ Furthermore, migraine has long been regarded as a risk factor for ischemic stroke.⁸⁻¹¹ Migraine could confer a predisposition to stroke occurring remote from migraine events, or stroke could occur as a direct consequence of a migraine event, as in migrainous infarction.¹² A spurious association between migraine and stroke could occur if cerebral ischemia with migraine, either transient or resulting in stroke, were misdiagnosed as migraine with aura.¹³⁻¹⁵ Few prior studies have addressed these different potential reasons for an association between migraine and stroke.

Clarifying in more detail the clinical features of the relation between migraine and stroke may provide useful insights into the basis for the migraine-stroke association. There is some evidence that the increased risk of stroke associated with

migraine may not be uniform across all migraine or stroke subgroups. For example, the association between migraine and ischemic stroke is reported to be stronger for strokes occurring among younger (ie, <50 years) than older individuals and for women than men.^{8-10,16,17} Recent evidence also suggests that migraine with aura may elevate the risk for stroke more than migraine without aura,¹⁸⁻²⁰ and some^{11,16,21} but not all^{20,22} studies suggest that the association between migraine and stroke may be elevated among women who smoke or use oral contraceptives (OCs).

The effects of migraine frequency, lifetime duration of migraine, and time of migraine onset on stroke risk are also unclear. An association between a higher frequency (>12 per year) and a longer duration (>12 years) of migraine with ischemic stroke has been reported in at least 1 study,²² and an association between higher migraine frequency and subclinical infarcts has been reported in another.¹⁷ There is some

Received March 15, 2007; final revision received May 1, 2007; accepted May 3, 2007.

From the Department of Epidemiology and Preventive Medicine (L.R.M., B.D.M.), University of Maryland School of Medicine, Baltimore, Md; the Centers for Disease Control and Prevention (W.G.), Atlanta, Ga; the VA Maryland Health Care System (J.C., M.W., S.J.K.), Baltimore, Md; the Department of Neurology (J.C., M.W., B.S., S.J.K.), University of Maryland School of Medicine, Baltimore, Md; and the Department of Medicine (B.D.M.), University of Maryland School of Medicine, Baltimore, Md.

Correspondence to Steven J. Kittner, Department of Neurology, University of Maryland School of Medicine, Bressler Research Building, Room 12-006, 655 W Baltimore St, Baltimore MD 21201. E-mail skittner@som.umaryland.edu

© 2007 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.107.488395

evidence that migrainous infarction preferentially affects the occipital lobes²³ and that a history of migraine with aura may increase the risk of subclinical posterior infarct.^{17,23} However, it is not known whether clinically recognized stroke events associated with a history of migraine have a specific anatomic predilection. The contribution of PFO to the risk of migraine-associated ischemic stroke is also uncertain. PFO is a risk factor for young-onset stroke²⁴ and is more common among migraineurs compared with nonmigraineurs²⁵; however, prior epidemiologic studies of migraine and stroke have lacked information about PFO.

We sought to address many of these issues by evaluating the association between prior migraine and ischemic stroke on data from a population-based, case-control study of young white and African-American women. In our analyses, we considered traditional vascular risk factors as well as clinical and anatomic features of the association.

Methods

The Stroke Prevention in Young Women Study (SPYW) is a population-based, case-control study initiated to examine risk factors for ischemic stroke in young women. Study recruitment and data collection occurred in 2 waves: recruitment for SPYW-1 was conducted between 1992 and 1996, resulting in an enrollment of 228 case and 392 control subjects, and recruitment for SPYW-2 was conducted between 2001 and 2003, resulting in an enrollment of 263 case and 225 control subjects in addition to those enrolled during SPYW-1. In both waves, case patients were women hospitalized with a first cerebral infarction identified by discharge surveillance from 1 of 59 hospitals in the Greater Baltimore–Washington area and direct referral from regional neurologists. The methods for discharge surveillance, chart abstraction, case adjudication, and assignment of probable and possible underlying causes have been described elsewhere.^{26–28}

Control subjects were women with no history of stroke identified by random-digit dialing and were matched to cases by age (within 10 years) and geographic region of residence in both waves and additionally matched for race in SPYW-2. SPYW-1 included cases age 15 to 44 years recruited within 1 year of stroke and was designed with a 1:2 case-to-control ratio. SPYW-2 included cases age 15 to 49 years recruited within 3 years of stroke and was designed with a 1:1 case-to-control ratio. For both study periods, additional cases were recruited after completion of control recruitment.

Lifetime headache history was collected from case and control subjects by standardized questionnaire. Subjects were classified as having probable migraine with visual aura (PMVA) if they (1) reported ever seeing spots, lines, or flashing lights around the time of their probable migraine or (2) if they reported ever experiencing loss of vision and also reported a frequency of PMVA of at least twice per year. Subjects were identified as having probable migraine without visual aura if they reported no history of visual aura and reported nausea, vomiting, or sensitivity to light during a probable migraine and probable migraine frequency of at least 5 times per year. Our questionnaire-based definitions for probable migraine with and without visual aura are less specific than the International Headache Society (IHS) criteria for definite or probable migraine with or without aura. These definitions differ from IHS criteria in that they do not refer to phonophobia, they do not specify the untreated duration of migraine or migraine features, nor do they specify the time criteria of aura symptoms (IHS 1.6).¹²

To evaluate the impact of lifetime duration of probable migraine on stroke risk and to assess the possibility that reported PMVA was due to an unrecognized transient ischemic attack, we classified stroke patients with probable migraine into 3 groups according to the duration of exposure for subanalyses: (1) first probable migraine occurred within 1 year of stroke onset; (2) first probable migraine occurred >1 but <12 years before stroke onset; and (3) first probable migraine occurred >12 years before stroke onset. Fre-

TABLE 1. Demographic and Clinical Characteristics of Stroke Cases and Controls in the SPYW

	Cases (n=386)	Controls (n=614)
Age, y	39.2±7.6	36.8±7.8
African-American	182 (47%)	233 (38%)
Hypertension	134 (35%)	84 (14%)
Diabetes	51 (13%)	23 (4%)
MI or angina	45 (12%)	21 (3%)
Smoking	279 (51%)	294 (28%)
Use OCs	48 (12%)	64 (10%)
Probable migraine		
No migraine	206 (53%)	360 (59%)
Probable migraine without aura	35 (9%)	79 (13%)
PMVA	145 (38%)	175 (29%)

quency and duration of probable migraine were collected by subject report during the interview process. Probable migraine severity was assessed by responses to the questions, “How often are you unable to work, parent, or go to school for all or part of the day due to your headaches?” and “How often do you require bedrest?” If the subject responded “more than half the time” to either question, the probable migraines were classified as severe.

Traditional stroke risk factors and other study variables, including age, ethnicity, and history of hypertension, diabetes, myocardial infarction (MI), current smoking status, and current OC use (both defined as use within 1 month of an event for cases and at the time of interview for controls), were also collected during the standardized interview and were included as covariates in our analyses.

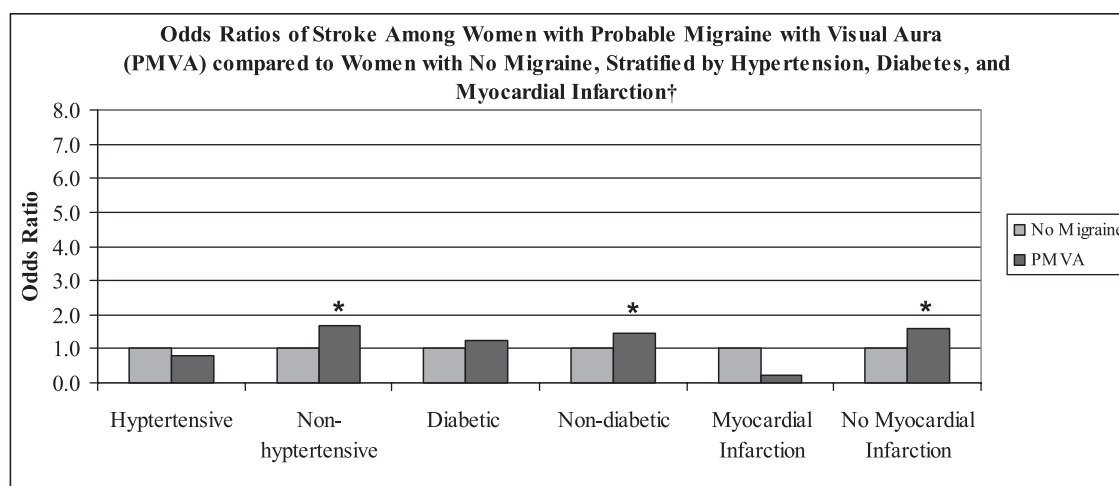
Of 491 adjudicated cases and 617 controls, 25 subjects (23 cases and 3 controls) were excluded because they had proxy or assisted interviews, and 82 cases were excluded because they lacked definitive evidence of stroke-related abnormalities on computed tomography or magnetic resonance imaging scans, leaving 386 cases and 614 controls. A pair of neurologists determined ischemic stroke subtype and vascular distribution. Stroke subtype categories were as follows: (1) large-artery atherosclerosis, (2) cardioembolism, (3) lacunar stroke, (4) stroke of other determined cause, and (5) stroke of undetermined cause.^{26,28} Probable migrainous infarction²⁹ was categorized as stroke of undetermined cause. Based on both clinical and neuroimaging data, lesion location was classified into (1) anterior circulation, (2) posterior circulation, (3) both, or (4) unknown. For the subset of cases (n=163) with an air contrast transthoracic or transesophageal echocardiogram, the presence or absence of a PFO was recorded.

We compared risk factor distributions between cases and controls by *t* tests for continuous variables and χ^2 tests for categorical variables. We used multivariate logistic regression to evaluate the relation between history of PMVA and ischemic stroke; to assess a 3-way interaction between PMVA, smoking, and OC use; and to adjust for covariates. Two-tailed probability values of <0.05 were considered statistically significant. All statistical analyses were performed with SAS version 8.2 software.³⁰

This study was approved by institutional review boards at the University of Maryland, the Centers for Disease Control and Prevention, and at all participating hospitals. Each patient gave written, informed consent before enrollment.

Results

Clinical characteristics of stroke cases (n=386) and non-stroke controls (n=614) are shown in Table 1. Cases were significantly older on average compared with controls and were more likely to be African-American. As expected, cases were also more likely than controls to report a history of hypertension, diabetes, and MI and were more likely to be

* $p < 0.05$

† Odds ratios adjusted for age, race, geographic region and study period

Figure 1. ORs for stroke among women with PMVA compared with women with no migraine, stratified by hypertension, diabetes, and MI.

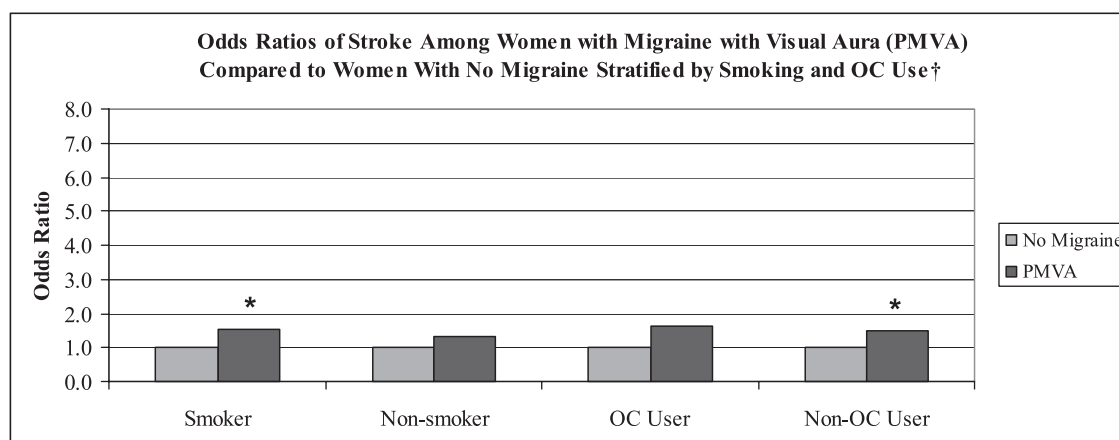
current smokers and current OC users. A higher proportion of cases reported a history of PMVA compared with controls; however, there was no significant difference between the proportion of cases and controls reporting a history of probable migraine without visual aura.

There were no statistically significant interactions between age, race, geographic region, and study period and the reported associations; therefore, the minimally adjusted model controlled for these factors. Women with PMVA had 1.5-fold greater odds of having a stroke compared with women with no migraine (95% CI, 1.1 to 2.0). There was no association between stroke and probable migraine without visual aura (odds ratio [OR], 1.0; 95% CI, 0.6 to 1.5). Subsequent analyses were therefore focused on assessing the clinical and anatomic characteristics of the PMVA-stroke association.

Figure 1 shows adjusted ORs for stroke among women with PMVA compared with women without migraine, stratified by hypertension, diabetes, and MI. PMVA was a

significant risk factor for stroke among women without a history of hypertension (OR, 1.7; 95% CI, 1.2 to 2.4), without a history of diabetes (OR, 1.5; 95% CI, 1.1 to 2.0), and among women without a history of MI (OR, 1.6; 95% CI, 1.2 to 2.2) compared with women with no migraine. Statistical tests for effect modification were significant for a history of MI or angina ($P=0.01$) and a history of diabetes ($P=0.03$) but not for a history of hypertension ($P=0.23$). Additional analyses indicated that there was no association between stroke and probable migraine without visual aura in any of these strata (data not shown).

The risk of stroke associated with PMVA, stratified by smoking and OC use, is shown in Figure 2. PMVA was a significant risk factor for stroke among smokers (OR, 1.5; 95% CI, 1.1 to 2.3). The point estimate for PMVA was similar among OC users and nonusers, but the association among nonusers attained statistical significance owing to a larger sample size (OR, 1.5; 95% CI, 1.1 to 2.1). Neither current smoking nor OC use was an independent effect



OC indicates oral contraceptive

* $p < 0.05$

† Odds ratios adjusted for age, race, geographic region, and study period

Figure 2. ORs for stroke among women with PMVA compared with women with no migraine, stratified by smoking and OC use.

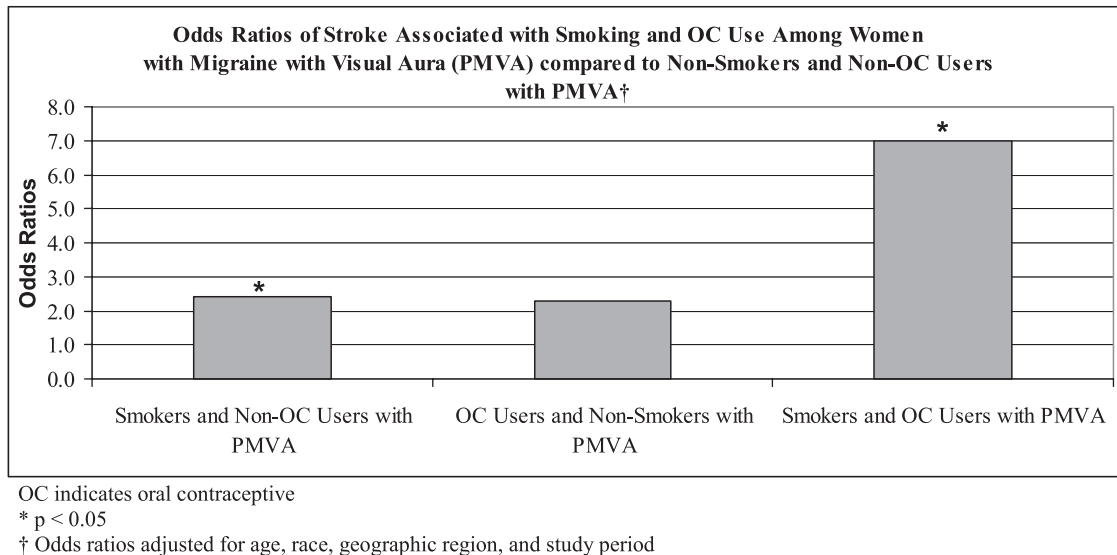


Figure 3. ORs for stroke associated with smoking and OC use among women with PMVA compared with nonsmokers and non-OC users with PMVA.

modifier of the association between PMVA and stroke ($P=0.45$ and $P=0.87$, respectively). To evaluate the combined effect of smoking and use of OCs among women with PMVA on stroke risk, we included a 3-way interaction term for these covariates in our model. After controlling for age, race, geographic region, and study period, women with PMVA who smoked and used OCs had 7.0-fold higher odds of stroke (95% CI, 1.4 to 22.8) compared with women with PMVA who were nonsmokers and non-OC users (Figure 3). When compared with women with no migraine history who were nonsmokers and non-OC users, women with PMVA who smoked and used OCs had 10.0-fold higher odds of stroke (95% CI, 1.4 to 73.7).

ORs of probable migraine-associated stroke, stratified by stroke subtype, are shown in Table 2. Results are shown for the minimally adjusted model and for a full model additionally adjusted for vascular risk factors. In the risk factor-adjusted model, women with PMVA had 1.3 greater adjusted odds of all ischemic strokes than women with no migraine (95% CI, 0.9 to 1.8) and odds of 1.5 for stroke of undetermined cause (95% CI, 1.0 to 2.2). The adjusted OR for lacunar stroke was also 1.5, but this failed to achieve statistical significance owing to a smaller sample size. PMVA was not associated with large-artery atherosclerosis or cardioembolic stroke.

ORs of probable migraine-associated stroke, stratified by frequency, severity, and duration, are shown in Table 3. Results are shown for the minimally adjusted model and for a full model additionally adjusted for vascular risk factors. In the risk factor-adjusted model, women experiencing a higher frequency of PMVA (>12 per year) had 1.7-fold higher odds of stroke (95% CI, 1.1 to 2.8), and women having severe PMVA (requiring bed rest or absence from work) had 1.3-fold higher odds of stroke (95% CI, 0.8 to 1.9) compared with women with no history of migraine, although this was not statistically significant. Compared with women who had no history of migraine, women with a lifetime duration of PMVA of >12 years had 1.2-fold higher odds of stroke (95% CI, 0.8 to 1.9), whereas women who experienced their first PMVA onset within a year of the index date (stroke date for cases, within 1 week of the interview date for controls) had 8.3 (2.6 to 25.7)-fold higher odds of stroke.

We found no evidence for a differential association between PMVA and stroke with posterior (OR 1.1; 95% CI, 0.6 to 1.8) or anterior (OR 1.4; 95% CI, 0.9 to 2.0) circulation involvement. Similarly, there was no evidence for a stronger association between PMVA and stroke in the small subgroup ($n=21$) with known PFO (OR 2.1; 95% CI, 0.8 to 5.3) compared with the small subgroup ($n=142$) whose air con-

TABLE 2. Effect of PMVA on Stroke Risk, Stratified by Stroke Subtype (OR and 95% CI)

	Proportion of Cases With PMVA	Proportion of Controls With PMVA	OR (95% CI)*	OR (95% CI)†
All ischemic stroke	0.38	0.29	1.5 (1.1–2.0)	1.3 (0.9–1.8)
Large-artery atherosclerotic ($n=47$)	0.32	0.29	1.3 (0.7–2.7)	1.1 (0.5–2.2)
Cardioembolic ($n=42$)	0.31	0.29	1.2 (0.6–2.5)	0.8 (0.3–1.7)
Lacunar ($n=45$)	0.40	0.29	1.8 (0.9–3.8)	1.5 (0.7–3.3)
Undetermined cause ($n=192$)	0.39	0.29	1.6 (1.1–2.3)	1.4 (0.9–2.0)

*Adjusted for study period, age, race, and geographic region.

†Adjusted for study period, age, race, geographic region, smoking, diabetes, hypertension, MI, and OC use.

TABLE 3. Effect of Severity, Frequency, and Duration of PMVA on Stroke Risk (OR and 95% CI)

	Cases With PMVA/Cases Without Migraine	Controls With PMVA/Controls Without Migraine	OR (95% CI)*	OR (95% CI)†
Frequency				
≤12 per year	65/206	111/360	1.1 (0.7–1.6)	0.9 (0.6–1.4)
>12 per year	80/206	64/360	2.2 (1.5–3.3)	1.7 (1.1–2.8)
Severity‡				
Nonsevere	78/206	97/360	1.5 (1.0–2.2)	1.3 (0.8–1.9)
Severe	64/206	77/360	1.4 (0.9–2.1)	1.1 (0.7–1.8)
Lifetime duration§				
>12 years	62/206	68/360	1.5 (1.0–2.3)	1.2 (0.8–1.9)
1–12 years	52/206	92/360	1.0 (0.6–1.5)	0.7 (0.5–1.2)
<1 year	17/206	5/360	6.8 (2.4–20.0)	8.3 (2.6–25.7)

*Adjusted for study period, age, race, and geographic region.

†Adjusted for study period, age, race, geographic region, smoking, diabetes, hypertension, MI, and OC use.

‡Three cases and 1 control with missing data.

§Fourteen cases and 10 controls with missing data. Index date was stroke date for cases and within 1 week of interview date for controls.

trast echocardiograms had shown no evidence of PFO (OR 1.5; 95% CI, 1.0 to 2.2).

After exclusion of 7 cases with clinically diagnosed migrainous infarction, the risk factor-adjusted OR for women with PMVA was 1.2 (95% CI, 0.9 to 1.7) and, in the subset of women who experienced their first PMVA onset within a year of the index date, the risk factor-adjusted OR was 6.0 (95% CI, 1.9 to 18.6).

Discussion

In this population-based, case-control study of young African-American and white women, PMVA was significantly associated with increased odds of ischemic stroke, particularly stroke of undetermined origin. Risk of stroke was highest for women who reported new-onset PMVA within 1 year before stroke or study enrollment. These findings were not materially altered after exclusion of patients with probable migrainous stroke. Overall and subgroup analyses did not indicate any association between probable migraine without visual aura and stroke. Our data are consistent with existing evidence that migraine with aura is associated with an increased risk of ischemic stroke from several case-controls studies of young-onset stroke^{11,16–18} and from 2 prospective studies carried out in middle-aged and older populations.^{17,20,31} A recent prospective study of women 45 years and older reported a significant association between migraine with aura and risk of ischemic stroke but no increased risk of stroke among women with migraine without aura, compared with women with no migraine history.²⁰ Similarly, a recent nested case-control study that included African-American and white men and women between 45 and 64 years of age reported that a history of migraine or other probable migraine with aura, but not migraine or other probable migraine without aura, was associated with ischemic stroke.³¹

Subgroup analyses of our data indicated that women without a history of hypertension, diabetes, and MI were at greatest risk for PMVA-associated stroke. This is consistent with previous findings among younger women¹⁰ and middle-

aged and older¹⁹ women suggesting that PMVA may contribute to the etiology of ischemic stroke independently of atherogenic risk factors. Although smoking or OC use did not independently modify the effect of PMVA on stroke risk, these factors had a multiplicative effect on the risk of stroke. Our data support previous studies that reported an increase in stroke risk associated with smoking and the use of OCs among young women^{11,16,18,21} and clinical recommendations to modify these risk factors in the presence of migraine with aura.^{32,33}

There were 145 ischemic stroke patients among women with PMVA. When we stratified our analyses by ischemic stroke subtype, we found that PMVA was associated with strokes of undetermined origin and showed a strong trend toward an association with lacunar stroke, which is more a descriptive than an etiologic category. Associations were not present for subtypes with a clear etiology, such as atherosclerotic and cardioembolic strokes.

Our data suggest that women who reported a frequency of PMVA of >12 episodes per year have an increased risk of stroke compared with women who reported no migraine history. These findings are consistent with previous reports of increased migraine frequency as a risk factor for clinically recognized stroke²² and subclinical infarcts.¹⁷ In contrast, the Women's Health Study recently reported that high migraine frequency within the previous year was not associated with increased ischemic stroke risk.¹⁹

In the 22 participants whose onset of PMVA occurred within the previous year, we observed a strong association with ischemic stroke, with an adjusted OR of 8.3 (2.6 to 25.7) compared with women with no migraine. It is possible that unrecognized acute cerebral ischemia could have clinical features of PMVA and thus, could confound the association between PMVA and stroke. Prior case-control studies have not addressed this issue. The prospective Women's Health Study,¹⁹ which found an association between migraine with aura and ischemic stroke in women under age 55, constructed time-varying models that updated information about migraine

attacks in the previous year, analyzed their data with different follow-up time periods, and found no evidence for an increased association for specific follow-up periods. Furthermore, consistent with at least 1 other case-control study,²² we observed a trend toward an association between longstanding PMVA and stroke. We also considered the possibility that the strong association between recent-onset PMVA and stroke was due to migrainous infarction. However, of 7 cases adjudicated as having migrainous infarction, only 1 reported onset of PMVA in the year before study enrollment, and exclusion of this case did not materially change the findings.

With regard to location of the infarct, there is some evidence of increased posterior circulation involvement for clinically recognized migrainous infarction²³ and for subclinical infarcts¹⁷ associated with migraine, whereas other studies have reported no evidence for anatomic predilection among stroke cases with migraine compared with stroke cases without migraine.¹⁹ In our data, we found no appreciable difference in risk of stroke between the anterior and posterior regions in relation to PMVA.

PFO has been implicated as a possible mechanism for the association between migraine and stroke because it is a risk factor for young-onset stroke² and is associated with migraine prevalence^{3,34} and frequency.³⁵ In our study, there was no evidence for a substantially stronger association between PMVA and ischemic stroke among the small subset of women with known PFO compared with women without evidence of a PFO. However, we had limited ability to address this issue, because there were PFO data for only 163 women, some of whom might have been misclassified as having no PFO owing to the limited sensitivity of air contrast transthoracic echocardiograms as a diagnostic tool for PFO. It should be noted that the presence of a PFO does not explain recent findings of an association between migraine with aura and cardiovascular events other than stroke.²⁰

There are several strengths of our study. We used a population-based design, which is optimal for studying early-onset stroke owing to the low incidence of stroke in this age range. Cases selected by this approach are likely to be more representative of young stroke cases from the defined study area than are cases selected from tertiary care referral centers only. We included both white and African-American women; few studies have examined migraine and stroke risk among African-Americans. Our study population consisted of young women, the group that has had the greatest risk of migraine-associated stroke in previous studies.^{8–11,18–20} Finally, the large number of strokes allowed examination of risk stratified by ischemic stroke subtype.

Limitations of our study include self-reported migraine history, which did not include data on untreated duration of headache or headache features, phonophobia, or time and duration of aura symptoms, and therefore, was not sufficient to classify migraine status according to IHS criteria.¹² Lipton and colleagues³⁶ performed a validation study of migraine classification wherein subjects were considered to have migraine if they reported at least 1 severe probable migraine in the previous 12 months with unilateral or pulsatile pain and either nausea, vomiting, or phonophobia with photophobia, or visual or sensory aura before probable migraine. These

criteria differed from those of IHS, which specify an attack duration of 4 to 72 hours for untreated attack and a lifetime number of attacks of at least 5. Nevertheless, the criteria used by Lipton et al³⁶ were 100% specific for migraine as validated by follow-up assessment and definitive diagnosis by a physician with expertise in probable migraine. Probable migraine with aura (probable migraine that lasted at least 4 hours but did not satisfy all other IHS criteria for migraine) has also been associated with stroke in a prospective analysis.³¹ Because the only other headache disorder besides migraine that may be preceded by aura is cluster headache, which is rare,³⁷ these were likely undiagnosed migraines or transient ischemic attacks.³⁸ Similarly, the PMVAs reported by women in our study likely represent migraine with aura.

The proportion of subjects who reported PMVA was high in our study compared with the prevalence of migraine with aura in the general population.³⁹ This was likely due in part to misclassification of migraine status. However, this misclassification is an unlikely explanation for the significant associations found in our study. Nondifferential misclassification of probable migraine would tend to underestimate the true association between migraine and stroke. We note that our ORs were weaker than risk estimates reported from other studies of migraine and stroke^{18,20,31} and may be underestimated for this reason.

The potential for recall bias between case and control subjects is also a study limitation. It is possible that case patients more frequently recalled migraine history due to the experience of their stroke event. Finally, we did not control for factors such as medication use, cholesterol, alcohol consumption, and physical activity in our model, which may have resulted in unmeasured or residual confounding of our risk estimates.

In summary, we found an association between PMVA and ischemic stroke of undetermined cause. The association of smoking, OC use, and PMVA with ischemic stroke indicates a high-risk population for which appropriate management strategies are warranted.

Acknowledgments

We are indebted to the following members of the SPYW research team for their dedication: Esther Berrent, Julia Clark, Mohammed Huq, Nasrin Huq, Ann Maher, Tamar Pair, Mary Jane Seipp, Mary Simmons, Mark Waring, Latasha Williams, Mary J. Sparks, and Nancy Zappala.

The authors appreciate the following individuals who sponsored the SPYW at their institutions: Clifford Andrew, MD, PhD; Brian Avin, MD; Merrill Ansher, MD; Harjit Bajaj, MD; Robert Baumann, MD; Christopher Bever, MD; David Buchholz, MD; Nicholas Buendia, MD; Young Ja Cho, MD; James Christensen, MD; Kevin Crutchfield, MD; Remzi Demir, MD; Terry Detrich, MD; Mohammed Dughly, MD; Boyd Dwyer, MD; Christopher Earley, MD; John Eckholdt, MD (deceased); Nirmala Fernback, MD (deceased); Jerold Fleishman, MD; Benjamin Frishberg, MD; Stuart Goodman, MD, PhD; Adrian Goldszmidt, MD; Kalpana Hari Hall, MD; Norman Herschkowitz, MD, PhD; Aleem Iqbal, MD; Constance Johnson, MD; Luke Kao, MD, PhD; Walid Kamsheh, MD; John Kelly, MD; Andrew Keenan, MD; Harry Kerasidis, MD; Mehrullah Khan, MD; Ramesh Khurana, MD; Ruediger Kratz, MD; John Kurtzke, MD; Somchai Laowattana, MD; William Leahy, MD; Alan Levitt, MD; William Lightfoot II, MD; Bruce Lobar, MD; Paul Melnick, MD; Michael Miller, MD, PhD; Harshad Mody, MBBS; Marvin Mordes, MD; Seth

Morgan, MD; Howard Moses, MD; Francis Mwaisela, MD; Sivarama Nandipati, MD; Mark Ozer, MD; Roger Packer, MD; Maciej Poltorak, MD; Thaddeus Pula, MD; Phillip Pulaski, MD; Naghbusan Rao, MD; Marc Raphaelson, MD; Neelupali Reddy, MD; Perry Richardson, MD; Solomon Robbins, MD; David Satinsky, MD; Elijah Saunders, MD; Michael Sellman, MD, PhD; Arthur Siebens, MD (deceased); Barney Stern, MD; Harold Stevens, MD, PhD; Jack Syme, MD; Richard Taylor, MD; Dean Tippet, MD; Roger Weir, MD; Michael Weinrich, MD; Richard Weisman, MD; Laurence Whicker, MD; Robert Wityk, MD; Don Wood, MD (deceased); Robert Varipapa, MD; James Yan, MD; Mohammed Yaseen, MD; and Manuel Yepes.

In addition, the study could not have been completed without the support from the administration and medical records staff at the following institutions: in Maryland, Anne Arundel Medical Center, Bon Secours Hospital, Calvert Memorial Hospital, Carroll Hospital, Chester River Hospital, Civista Medical Center, Department of Veterans Affairs Medical Center in Baltimore, Doctors Community Hospital, Dorchester Hospital, Franklin Square Hospital Center, Frederick Memorial Hospital, Good Samaritan Hospital, Greater Baltimore Medical Center, Harbor Hospital Center, Hartford Memorial Hospital, Holy Cross Hospital, Johns Hopkins Bayview, Johns Hopkins Hospital, Howard County General Hospital, Kernan Hospital, Laurel Regional Hospital, Maryland General Hospital, McCready Memorial Hospital, Memorial Hospital at Easton, Mercy Medical Center, Montgomery General Hospital, North Arundel Hospital, Northwest Hospital Center, Peninsula Regional Medical Center, Prince George's Hospital Center, Saint Agnes Hospital, Saint Joseph Medical Center, Saint Mary's Hospital, Shady Grove Adventist Hospital, Sinai Hospital of Baltimore, Southern Maryland Hospital Center, Suburban Hospital, The Union Memorial Hospital, Union Hospital Cecil County, University of Maryland Medical System, Upper Chesapeake Medical Center, Washington Adventist Hospital and Washington County Hospital; in Washington, DC: George Washington University Medical Center, Georgetown University Hospital, Hadley Memorial Hospital, Howard University Hospital, National Rehabilitation Hospital, Providence Hospital, Sibley Memorial Hospital, Veteran's Affairs Medical Center; and the Washington Hospital Center; in Pennsylvania: Gettysburg Hospital.

Sources of Funding

This material is based on work supported in part by the Office of Research and Development, Medical Research Service, and the Research Enhancement Award Program in Stroke, the Geriatrics Research, Education, and Clinical Center, Department of Veterans Affairs; a cooperative agreement with the Cardiovascular Health Branch, Division of Adult and Community Health, Centers for Disease Control and Prevention; the National Institute of Neurological Disorders and Stroke and the National Institutes of Health Office of Research on Women's Health R01 NS45012; the National Institute on Aging Pepper Center grant P60 12583; and the University of Maryland General Clinical Research Center Grant M01 RR 165001, General Clinical Research Centers Program, National Center for Research Resources, National Institutes of Health.

Disclosures

None.

References

- Scher AI, Terwindt GM, Picavet HS, Verschuren WM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: the GEM population-based study. *Neurology*. 2005;64:614–620.
- Lamy C, Giannesini C, Zuber M, Arquizan C, Meder JF, Trystram D, Coste J, Mas JL. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA study: atrial septal aneurysm. *Stroke*. 2002;33:706–711.
- Schwedt TJ, Dodick DW. Patent foramen ovale and migraine: bringing closure to the subject. *Headache*. 2006;46:663–671.
- Merikangas K. Genetic epidemiology of migraine. In: Sandler M, Collins, GM, eds. *Migraine: A Spectrum of Ideas*. Oxford, England: Oxford University Press; 1990:40–47.
- Russel M, Hilden J, Sorensen SA, Olesen J. Familial occurrence of migraine without aura and migraine with aura. *Neurology*. 1993;43:1369–1373.
- Russell MB, Iselius L, Olesen J. Inheritance of migraine investigated by complex segregation analysis. *Hum Genet*. 1995;96:726–730.
- MacClellan LR, Mitchell BD, Cole JW, Wozniak MA, Stern BJ, Giles WH, Brown DW, Sparks MJ, Kittner SJ. Familial aggregation of ischemic stroke in young women: the stroke prevention in young women study. *Genet Epidemiol*. 2006;30:602–608.
- Tzourio C, Iglesias S, Hubert JB, Visy JM, Alperovitch A, Tehindrazanarivelo A, Biousse V, Woimant F, Bousser MG. Migraine and risk of ischaemic stroke: a case-control study. *BMJ*. 1993;307:289–292.
- Merikangas KR, Fenton BT, Cheng SH, Stolar MJ, Risch N. Association between migraine and stroke in a large-scale epidemiological study of the United States. *Arch Neurol*. 1997;54:362–368.
- Carolei A, Marini C, De Matteis G. History of migraine and risk of cerebral ischaemia in young adults: the Italian National Research Council study group on stroke in the young. *Lancet*. 1996;347:1503–1506.
- Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case-control study: the World Health Organisation collaborative study of cardiovascular disease and steroid hormone contraception. *BMJ*. 1999;318:13–18.
- Headache Classification Committee of the International Headache Society. The international classification of headache disorders. *Cephalalgia*. 2004;24:1–160.
- Biousse V, Touboul PJ, D'Anglejan-Chatillon J, Levy C, Schaison M, Bousser MG. Ophthalmologic manifestations of internal carotid artery dissection. *Am J Ophthalmol*. 1998;126:565–577.
- Welch KM, Levine SR. Migraine-related stroke in the context of the International Headache Society classification of head pain. *Arch Neurol*. 1990;47:458–462.
- Ramadan NM, Tietjen GE, Levine SR, Welch KM. Scintillating scotomata associated with internal carotid artery dissection: report of three cases. *Neurology*. 1991;41:1084–1087.
- Tzourio C, Tehindrazanarivelo A, Iglesias S, Alperovitch A, Chedru F, d'Anglejan-Chatillon J, Bousser MG. Case-control study of migraine and risk of ischaemic stroke in young women. *BMJ*. 1995;310:830–833.
- Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, Launer LJ. Migraine as a risk factor for subclinical brain lesions. *JAMA*. 2004;291:427–434.
- Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ*. 2005;330:63.
- Kurth T, Slomke MA, Kase CS, Cook NR, Lee IM, Gaziano JM, Diener HC, Buring JE. Migraine, headache, and the risk of stroke in women: a prospective study. *Neurology*. 2005;64:1020–1026.
- Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. *JAMA*. 2006;296:283–291.
- Schwartz SM, Petitti DB, Siscovick DS, Longstreth WT Jr, Sidney S, Raghunathan TE, Quesenberry CP Jr, Kelaghan J. Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of 2 US studies. *Stroke*. 1998;29:2277–2284.
- Donaghy M, Chang CL, Poulter N. Duration, frequency, recency, and type of migraine and the risk of ischaemic stroke in women of child-bearing age. *J Neurol Neurosurg Psychiatry*. 2002;73:747–750.
- Hoekstra-van Dalen RA, Cillessen JP, Kappelle LJ, van Gijn J. Cerebral infarcts associated with migraine: clinical features, risk factors and follow-up. *J Neurol*. 1996;243:511–515.
- Lechat P, Mas JL, Lascault G, Loran P, Theard M, Klimczak M, Drobinski G, Thomas D, Grosgeat Y. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med*. 1988;318:1148–1152.
- Schwarzmann M, Nedeltchev K, Lagger F, Mattle HP, Windecker S, Meier B, Seiler C. Prevalence and size of directly detected patent foramen ovale in migraine with aura. *Neurology*. 2005;65:1415–1418.
- Johnson CJ, Kittner SJ, McCarter RJ, Sloan MA, Stern BJ, Buchholz D, Price TR. Interrater reliability of an etiologic classification of ischemic stroke. *Stroke*. 1995;26:46–51.
- Kittner SJ, Stern BJ, Feaser BR, Hebel R, Nagey DA, Buchholz DW, Earley CJ, Johnson CJ, Macko RF, Sloan MA, Wityk RJ, Wozniak MA. Pregnancy and the risk of stroke. *N Engl J Med*. 1996;335:768–774.
- Kittner SJ, Stern BJ, Wozniak M, Buchholz DW, Earley CJ, Feaser BR, Johnson CJ, Macko RF, McCarter RJ, Price TR, Sherwin R, Sloan MA,

- Wityk RJ. Cerebral infarction in young adults: the Baltimore-Washington cooperative young stroke study. *Neurology*. 1998;50:890–894.
29. Rothrock JF, Walicke P, Swenson MR, Lyden PD, Logan WR. Migrainous stroke. *Arch Neurol*. 1988;45:63–67.
30. SAS Institute Inc. The SAS system for Windows. 1999–2001.
31. Stang PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, Szklo M. Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. *Neurology*. 2005;64:1573–1577.
32. Bousser MG, Conard J, Kittner S, de Lignieres B, MacGregor EA, Massiou H, Silberstein SD, Tzourio C. Recommendations on the risk of ischaemic stroke associated with use of combined oral contraceptives and hormone replacement therapy in women with migraine: the International Headache Society task force on combined oral contraceptives and hormone replacement therapy. *Cephalalgia*. 2000;20:155–156.
33. Tzourio C, Kittner SJ, Bousser MG, Alperovitch A. Migraine and stroke in young women. *Cephalalgia*. 2000;20:190–199.
34. Post MC, Thijs V, Herroelen L, Budts WI. Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine. *Neurology*. 2004;62:1439–1440.
35. Schwerzmann M, Wiher S, Nedeltchev K, Mattle HP, Wahl A, Seiler C, Meier B, Windecker S. Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. *Neurology*. 2004;62:1399–1401.
36. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American migraine study II. *Headache*. 2001;41:646–657.
37. Silberstein SD, Niknam R, Rozen TD, Young WB. Cluster headache with aura. *Neurology*. 2000;54:219–221.
38. Diener HC, Kurth T. Is migraine a risk factor for stroke? *Neurology*. 2005;64:1496–1497.
39. Scher AI, Stewart WF, Liberman J, Lipton RB. Prevalence of frequent headache in a population sample. *Headache*. 1998;38:497–506.