HIGH LIGHT

Headache, cerebrovascular symptoms, and stroke

The Atherosclerosis Risk in Communities Study

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Abstract—*Objective:* To evaluate the occurrence of stroke/TIA symptoms and ischemic stroke events among those with a lifetime history of migraine or other headaches with some migraine features in a biracial cohort of older adults. *Methods:* Participants were 12,750 African-American and white men and women from the Atherosclerosis Risk in Communities Study (1993 to 1995). The participants were queried about their lifetime headache history and characterized using modified International Headache Society diagnostic criteria. Stroke/TIA symptoms were classified using a computerized diagnostic algorithm, and ischemic stroke events were identified and validated using medical records. Multivariate logistic regression was used to assess the relationship between headache types and stroke/TIA symptoms and ischemic stroke events. *Results:* Migraine with aura was strongly associated with stroke symptoms (odds ratio [OR] 5.46, 95% CI: 3.64 to 8.18), TIA symptoms (OR 4.28, 95% CI: 3.02 to 6.08), and verified ischemic stroke events (OR 2.81, 95% CI: 1.60 to 4.92). Similarly, other headaches with aura were significantly associated with stroke symptoms (OR 3.68, 95% CI: 2.26 to 5.99) and TIA symptoms (OR 4.53, 95% CI: 3.08 to 6.67). In contrast, the associations for migraine without aura and other headaches without aura were not as consistent or robust. *Conclusions:* Migraines and other headaches, particularly those accompanied by aura, were associated with an increased occurrence of stroke/TIA symptoms and ischemic stroke events.

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Migraine and stroke share many features, including a vasospastic component, regional decreases in cerebral blood flow, platelet aggregation, and focal neurologic and ophthalmologic signs and symptoms.[1-3] Persons with a migraine history may experience a stroke not occurring during a migraine attack or a "migrainous" stroke. Although initial symptoms of both types of stroke may be similar and the clinical diagnosis only apparent over time, most strokes experienced by migraineurs are not related to a particular migraine attack because the incidence of migrainous stroke is very low.[4-6]

Studies of younger women suggest an association between migraine and stroke,[7-12] with some reporting a higher risk when migraines are accompanied by aura.[10,11] However, in older populations, findings are not consistent. Case series and case-control studies reported no association between migraine and stroke[13,14] except in the absence of other risk factors.[15] In contrast, cohort studies reported an increased risk of stroke among migraineurs.[16-18]

As migraine prevalence decreases with age, while stroke risk increases, it is important to know whether migraine confers risk in older populations as it may be a marker of more substantive systemic disease. Thus, this study evaluated the occurrence of stroke/TIA symptoms and ischemic stroke in those with a lifetime history of migraine or other headaches, by aura status, in a biracial cohort of older adults and assessed whether that relationship was affected by cardiovascular disease (CVD) risk factors.

Methods. *Study population.* The study population consisted of participants from the Atherosclerosis Risk in Communities (ARIC) Study, a prospective study designed to investigate the etiology and natural history of atherosclerosis.[19] Probability samples of men and women ages 45 to 64 years were recruited from four commu-

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nities in the United States: Forsyth County, NC; Jackson, MS; Washington County, MD; suburbs of Minneapolis, MN. African Americans were exclusively sampled in Jackson and oversampled in Forsyth County so race-specific estimates would be possible. A detailed account of the design and procedures of the ARIC Study has been published.[19]

The baseline examination, conducted during 1987 through 1989, included 15,792 participants. The current study was restricted to those who participated in the third follow-up examination (1993 to 1995), when a lifetime history of headaches was ascertained (N = 12,887). The following participants were excluded from the current study: participants who were not white or African American (n = 38); African Americans residing in Minneapolis, MN, and Washington County, MD (n = 42); and persons with missing headache information (n = 57). After these exclusions, 12,750 persons remained eligible for inclusion in this study.

Assessment of headache history. At the third clinic examination, trained interviewers asked participants about their lifetime history of headaches lasting 4 or more hours. Lifetime history of migraine headaches was defined using a modification of the 1988 International Headache Society (IHS) diagnostic criteria. The modified IHS criteria for the classification of migraine headaches in the ARIC Study included 1) headache lasting at least 4 hours; 2) headache accompanied by throbbing, pulsation, or pounding or was unilateral; 3) headaches occurring with nausea, vomiting, or sensitivity to light or sound; 4) lifetime history of 1 or more years of such headaches meeting the previous criteria. An affirmative response to a question about the occurrence of spots, jagged lines, or heat waves in one or both eyes was used to differentiate migraine with aura from migraine without aura. Headaches lasting at least 4 hours but not satisfying all the migraine criteria, referred to as "other headaches," were also evaluated. These headaches were further classified by the presence or absence of aura symptoms as previously described.

Assessment of stroke and TIA symptoms. To assess symptoms of stroke or TIA, participants were asked by a trained interviewer at each clinic examination whether they had experienced the sudden onset of six neurologic symptoms: loss of vision, double vision, speech dysfunction, weakness or paralysis, numbness or tingling, and dizziness. For each of the six symptoms, duration and concomitant symptoms were assessed. Participants who reported double vision, numbness, and dizziness were asked additional questions to ascertain a possible noncerebrovascular cause. A computerized diagnostic algorithm on stroke and TIA symptoms was used to simulate clinical reasoning used to differentiate vascular from other events. This diagnostic algorithm has previously been used in the Asymptomatic Carotid Atherosclerosis Study and has been evaluated as a tool for detection of stroke or TIA.[20,21] The algorithm's agreement with the diagnosis of TIA or stroke was 80%, with a reported sensitivity of 88% and specificity of 72%.[21]

Dizziness alone, numbness or paralysis in one body part alone, or double vision that did not disappear on closing one eye was not sufficient to classify a participant as experiencing stroke or TIA symptoms according to the diagnostic algorithm. Neurologic symptoms with a sudden onset and duration of at least 30 seconds were used to classify participants as having experienced stroke or TIA symptoms. TIA symptoms were differentiated from stroke symptoms based on self-report of the duration of the longest episode. Symptoms that resolved within 24 hours were classified as TIA symptoms and those that persisted longer were classified as stroke symptoms. Any persons exhibiting both stroke and TIA symptoms during clinic examinations 1 to 3 were classified as having stroke symptoms only.

Assessment of ischemic stroke. ARIC study participants received annual telephone calls from trained interviewers to ascertain any hospitalizations during the previous year and changes in health status. Local hospitals provided lists of cardiovascular disease discharges, which were monitored for the presence of ARIC participants. Cases were eligible for possible validation for stroke if any of the following occurred: 1) medical records contained discharge diagnostic codes suggestive of cerebrovascular events (International Classification of Disease, 9th Revision, Clinical Modification codes 430 to 438); 2) cerebrovascular keywords were present in discharge summary or nurse notes; 3) diagnostic CT or MRI with cerebrovascular findings; or 4) admission to neurologic intensive care unit.[22] The medical records of participants qualifying

tion, and abstracted by a trained nurse. A computer algorithm and an independent physician reviewer were used to determine the final diagnosis for each participant. A second physician-reviewer adjudicated conflicting diagnoses between the computer-determined diagnosis and the initial physician-reviewer. Due to the small number of hemorrhagic strokes, only ischemic strokes were evaluated.

Verified ischemic stroke included all stroke events occurring between 1987 and December 2001, regardless of its occurrence before or after the assessment of lifetime headache history at the third clinic examination. Incident ischemic stroke, a subset of verified ischemic stroke, was restricted to those events determined to have occurred after headache onset among participants without a history of ischemic stroke at baseline. Participants were not directly queried about when their headaches first began, so a question about the number of years with headache was used to determine whether a participant's headache history potentially predated their participation in the ARIC study. Thus, verified ischemic strokes included all strokes occurring during the ARIC Study (1987 to 2001), whereas incident ischemic stroke events were a subset of verified ischemic stroke limited to those reported to have first occurred after the onset of the headaches among participants with no history of stroke at baseline.

Statistical analysis. The sociodemographic variables included in this analysis were age, sex, and a combined race and ARIC field center variable. Additional covariates included diabetes status, smoking status (current, former, never), cigarette smoking pack-years, parental history of migraine, regular use of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), use of hypertension medications, systolic blood pressure, and total serum cholesterol. Smoking status, cigarette smoking pack-years, parental history of migraine, and regular use of aspirin and NSAIDs were self-reported. A standard sphygmomanometer was used to take blood pressure in the seated position after 5 minutes of rest, based on the average of the second and third measurements. Use of antihyptertensive medications was determined by evaluating the medication bottles that the participant brought to the clinical examination. Diabetes mellitus was defined by a fasting blood glucose level ≥126 mg/dL, a nonfasting blood glucose level of ≥200 mg/dL, self-report of physician diagnosis, or use of hypoglycemic medications. All the variables were assessed at the third clinical examination with the exception of cigarette smoking pack-years, which was obtained at the first ARIC clinical examination (1987 to 1989).

Multivariate logistic regression was used to evaluate the relationship between headache history and stroke symptoms, TIA symptoms, verified ischemic stroke, and incident ischemic stroke. The models were initially adjusted for age, sex, and race/center. Additional adjustment for parental history of migraine, smoking status, cigarette smoking pack-years, diabetes status, regular use of aspirin, regular use of NSAIDs, use of hypertension medications, systolic blood pressure, and total serum cholesterol level was performed in subsequent analyses. Interaction terms for age, race, sex, and headache history were also included in subsequent analyses but were ultimately excluded due to small strata and low power to detect effect modification. All statistical analyses were performed using SAS version 8.2 software (SAS Institute, Inc., Cary, NC).

Results. At the third clinic examination (1993 to 1995), the mean age of the study population was 60 years, with 73% of the population age 55 years and older. The population was 77% white and 56% female, and 62% had at least a high school education. Three percent of participants had a history of migraine with aura, 5% had a history of migraine without aura, 2% had a history of other headaches with aura, and 12% had a history of other headaches without aura. Additional details pertaining to the sociodemographic characteristics of ARIC participants by headache status have been published.[23]

Table 1 presents the age-adjusted prevalences or means for demographic characteristics and selected risk factors by headache status. Women comprised a large proportion of all headache groups, with the difference being most pronounced for migraine. Some of the risk factors also

Table 1 *Percentages (means) for demographic characteristics and selected risk factors by headache status in the Atherosclerosis Risk in Communities Study, 1993–1995*

	Migraine with aura, n = 345	Migraine without aura, n = 670	Other headache with aura, n = 243	Other headache without aura, n = 1446	No headache, n = 10,046
Mean age, y	58.5	58.3	59.3	58.5	60.4
% African American	15.1	8.7	25.5	16.7	24.9
% Female	83.8	80.5	72.8	63.7	51.5
% Parental history of migraines	40.1	28.7	22.6	15.0	8.1
% Current smoker*	14.4	14.2	20.6	16.1	18.3
% Diabetic*	10.8	9.4	15.6	9.3	13.5
% Regular aspirin users*	41.1	33.8	40.3	32.6	27.6
% Regular NSAID users*	29.1	26.6	28.3	21.2	15.9
% Use hypertension medications*	35.0	24.6	39.2	27.9	31.9
Systolic blood pressure (mean)*	124.3	121.5	127.0	124.1	124.8
Total cholesterol (mean)*	216.5	211.5	204.4	209.1	206.9

* Age adjusted.

NSAID = nonsteroidal antiinflammatory drug.

ication use (aspirin, NSAIDS, and antihypertensives) among participants with headaches with aura vs those with headaches without aura.

The crude prevalence of stroke symptoms, TIA symptoms, verified ischemic stroke, and incident ischemic stroke was 3.6%, 4.8%, 3.0%, and 2.8%. The age, sex, and race-adjusted prevalence of verified ischemic stroke was 7.0% for migraine with aura, 2.1% for migraine without aura, 7.1% for other headaches with aura, 3.3% for other headaches without aura, and 2.7% for no headaches. Among whites, TIA symptoms were more prevalent in women than in men (6.1% vs 4.0%). In contrast, among both whites and African Americans, verified ischemic stroke was more prevalent in men than in women. Stroke symptoms, TIA symptoms, and verified ischemic stroke were more prevalent among those with diabetes, hypertension, and higher total serum cholesterol as well as among current smokers (data not shown).

In age-, sex-, and race/center-adjusted multivariate models, migraine with aura and other headaches with aura were strongly associated with stroke symptoms and TIA symptoms (table 2). Migraine without aura and other headaches without aura were associated with both stroke and TIA symptoms; however, the magnitude of these associations tended to be modest and some were not statistically significant. No significant interaction between headache status and the included covariates was found.

In contrast, migraine without aura and other headaches without aura were not associated with verified ischemic stroke, whereas migraine with aura and other headache with aura were significantly associated with verified ischemic stroke (table 3). These associations were not modified by the selected covariates nor did they change substantially after additionally controlling for other covariates (diabetes, regular aspirin use, regular NSAID use, hypertension medication use, systolic blood pressure, pack years of smoking, current smoking status, parental history of migraine, and total serum cholesterol). When we restricted verified ischemic strokes to those determined to be

line examination and the first stroke occurred after headache onset), results did not substantively change.

Discussion. Migraines and other headaches, in particular those accompanied by aura, were associated with an increased occurrence of stroke symptoms, TIA symptoms, verified ischemic stroke, and incident ischemic stroke in this middle-aged and older study population. Previous studies of migraine and stroke have suggested an increased risk of stroke for migraineurs, particularly those with aura; however, these studies were limited to younger

Table 2 *Multivariate odds ratios (95% CI) for the association of headache history with stroke and TIA symptoms, the Atherosclerosis Risk in Communities Study, 1993–1995*

	Stroke symptoms, n = 12,065	TIA symptoms, n = 12,213
Model 1*		
Migraine with aura	6.06 (4.18–8.78)	5.06 (3.69–6.94)
Migraine without aura	2.35 (1.62–3.41)	1.43 (1.01–2.04)
Other headache with aura	4.17 (2.62–6.63)	4.66 (3.20–6.78)
Other headache without aura	1.33 (0.97–1.83)	1.41 (1.10–1.83)
Model 2†		
Migraine with aura	5.46 (3.64–8.18)	4.28 (3.02–6.08)
Migraine without aura	2.45 (1.66–3.60)	1.35 (0.93–1.96)
Other headache with aura	3.68 (2.26–5.99)	4.53 (3.08–6.67)
Other headache without aura	1.39 (1.00–1.92)	1.35 (1.03–1.76)

* Adjusted for age, sex, and race/center.
† Adjusted for age, sex, race/center, hypertension medication use, regular aspirin use, regular nonsteroidal antiinflammatory drug use, systolic blood pressure, diabetes, parental history of migraines, smoking status, pack years of smoking, and total

Table 3 *Multivariate odds ratios (95% CI) for the association of headache history with verified ischemic stroke and incident ischemic stroke, the Atherosclerosis Risk in Communities Study, 1993–1995*

	Verified ischemic stroke,* n = 12,681	Incident ischemic stroke,† n = 11,447
Model 1‡		
Migraine with aura	2.68 (1.58–4.57)	1.84 (0.89–3.82)
Migraine without aura	0.79 (0.40–1.55)	0.75 (0.33–1.71)
Other headache with aura	2.58 (1.47–4.54)	2.91 (1.39–6.11)
Other headache without aura	1.25 (0.88–1.77)	0.98 (0.57–1.70)
Model 2§		
Migraine with aura	2.81 (1.60–4.92)	2.07 (0.96–4.44)
Migraine without aura	0.82 (0.39–1.69)	0.86 (0.37–2.00)
Other headache with aura	1.84 (0.99–3.45)	2.40 (1.11–5.19)
Other headache without aura	1.39 (0.96–2.01)	1.05 (0.58–1.91)

* Includes all verified stroke events occurring after the baseline examination.
† Includes a subset of verified stroke events restricted to first stroke events and strokes occurring after the onset of headaches.
‡ Adjusted for age, gender, and race/center (373 verified ischemic strokes and 314 incident ischemic strokes).
§ Adjusted for age, gender, race/center, hypertension medication use, regular aspirin use, regular nonsteroidal antiinflammatory drug use, systolic blood pressure, diabetes, parental history of migraines, smoking status, pack-years of smoking, and total cholesterol level (358 verified ischemic strokes and 301 incident ischemic strokes).

women.[7-11] In the studies that examined the relationship in older adults,[13-18] findings have been inconsistent with the one study that ascertained aura status reporting a stronger association between migraine with aura and cerebrovascular events.[15] These inconsistent findings may be due to several methodologic variations, such as reliance on coded or recorded information concerning possible effect modifiers and confounders, use of self-reported stroke outcomes, not using symptom-based questions to assess headache history, and/or the use of a general question about a history of physician-diagnosed migraine. In this study, headache status was ascertained using a standardized symptom-based questionnaire and outcomes and other covariates were assessed using standard research protocols.

The presence of aura was strongly associated with the occurrence of stroke/TIA symptoms and ischemic stroke events for both migraines and other headaches. This finding is consistent with previous studies[8-11] of migraine reported in younger, predominantly female populations. One study[15] has postulated that the relationship between migraine with aura and ischemic stroke may be due to an interaction between migraine and other stroke risk factors. We assessed effect modification of the migraine-stroke association by age and other stroke risk factors but did not find meaningful variations. However, our power to detect interactions was limited, so we cannot exclude the possibility that such variations may exist. Migraine without aura and other headaches without aura had significant but more modest associations with stroke and TIA symptoms but no significant association with verified ischemic stroke.

There are several possible limitations to our study. Because we assessed lifetime history of headache, recall error may have occurred. Migraine, especially with aura, and cerebrovascular events share many clinical features that may make it difficult for sodes. For example, TIAs, especially those involving the posterior circulation, are often accompanied by headache.[24] Similarly, because our aura question was framed within the context of headaches, it may be difficult for a participant to distinguish individual symptoms of migraine or its accompaniments as being part of a headache syndrome because some symptoms may occur independent of headache. This would not be a rare occurrence as others have shown that migraineous visual accompaniments occur in 1.2% of the population, typically after age 50 years.[25] Because the strength of the association between stroke and TIA symptoms and headaches with auras is strong, these data suggest that some fraction of stroke and TIA symptoms may indeed represent migraine phenomena, whereas the reverse is also possible. In this study, aura was defined purely as a visual phenomenon, so we were unable to identify additional participants with nonvisual aura symptoms (i.e., sensorimotor). This may have affected our observed associations with cerebrovascular symptoms. This misclassification probably would have attenuated the association between aura and cerebrovascular symptoms. The strong association found for other headaches with aura and cerebrovascular events may also have been due to a propensity for these participants to report aura symptoms associated with their usual headaches when these symptoms may actually have occurred independent of their usual headaches but as part of a cerebrovascular event.

It is also possible that participants who experienced a cerebrovascular event that was preceded by headache or headache symptoms were more likely to report headache. However, this is unlikely, as one would have expected to see a higher rate of migraine or headache in general in this analysis than what has been reported. In addition, headache history was not obtained

possibility because 19% of participants from the first clinic examination who subsequently died or did not attend the third clinical examination were not included in this study. This may have caused an underestimation of the true association between migraine and stroke. Of the four cerebrovascular outcomes evaluated, incident stroke was the only one for which the exposure, by definition, had to occur before the outcome and is the outcome for which the association with migraine was weakest. For both verified ischemic stroke and incident stroke, the association with headache types was consistent and of the same magnitude; however, the temporal requirement for headache, coupled with the relatively small number of outcomes, may have selected participants in whom competing risks for these events attenuated the impact of headache type found for the other outcomes.

The association between migraine and stroke was slightly attenuated after adjusting for risk factors. This suggests that the strength of the association between aura and cerebrovascular outcomes may be independent of classic risk factors and may act through a separate mechanism. However, because risk factor status was obtained at the same time as migraine history, we cannot infer that risk factor status at that time reflects cumulative history.

It has been suggested that migraine may be part of a more generalized vasospastic syndrome because of its possible association with Raynaud phenomenon[26,27] and Prinzmetal angina.[28] This explanation is plausible, because migraine in general and aura specifically are believed to be manifestations of the spreading depression of Leao,[29] a spreading wave of depolarization across the cortex that is accompanied by decreases in blood flow.[30] The decreased blood flow in combination with increased platelet aggregability may increase the likelihood of stroke in the migraineur. Thus, migraineurs may have an increased vascular instability that persists long after the classic symptoms of migraine have ended. Although the current study cannot prove or disprove this theory, it does add additional evidence to the predictive value of headache and aura for cerebrovascular symptoms and ischemic stroke in an older population with increased risk of cerebrovascular events. Because aura represents a distinct clinical and physiologic finding, its strong association with cerebrovascular outcomes can potentially be related to either the shared common mechanism of reduced blood flow or diagnostic misclassification. Aura itself may be such a striking clinical finding that the patient is less likely to have difficulty recalling its occurrence, which results in higher specificity and sensitivity of aura symptoms. In addition, the underlying physiology of aura, apparently directly related to changes in blood flow, would appear to increase the risk of cerebrovascular events in those patients most sensitive to these effects.

Further research that focuses on the potential mechanisms underlying the complex relationship between headaches, particularly when accompanied by

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