PC Reviewed: 12/13/11   Status: <u>A</u>   Priority: <u>2</u>
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title:

Migraine, cognition, and white matter hyperintensities: the ARIC MRI study

1.b. Abbreviated Title (26 characters):

Migraine and white matter hyperintensities

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. *AGH*

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3.   Timeline: Analyses to begin as soon as manuscript proposal is approved. Goal for abstract submission for International Stroke Conference (August 2012).

4.   Rationale

White matter hyperintensities (WMH) are a commonly noted incidental finding on magnetic resonance imaging (MRI). The prevalence of these lesions increases with age and approaches 100% by age 85[1]. WMH are associated with a number of vascular risk factors such as hypertension, hypercholesterolemia, diabetes, and tobacco use, and thus are thought to represent a form of subclinical cerebrovascular disease[2]. Recently, a growing body of evidence has emerged suggesting that migraine headaches are also a risk factor for such lesions.

Migraine has also been implicated as a risk factor for ischemic stroke, especially among women smokers with a history of migraine with aura (MA) who also use estrogen-containing oral contraceptives[3]. The same mechanisms responsible for this association may also play a causal role in the incidence of WMH. In animal models of cortical spreading depression, the physiologic substrate of the migraine aura, neurogenic inflammation at the trigeminovascular junction leads to increased expression of cytokines and other inflammatory mediators[4]. Such inflammation leads to endothelial damage and platelet aggregation, which may result in intravascular thrombosis and microinfarction[5], as well as activation of matrix metalloproteinases and disruption of the blood-brain barrier[6]. In addition, *in vivo* human studies have documented decreases in blood flow of up to 50% during acute migrainous episodes[7]. Lastly, migraineurs become dehydrated during acute episodes secondary to vomiting, which may transiently increase blood viscosity.

The first studies of migraine and WMH were small clinic-based case series or case-control studies. These studies produced highly variable results. Some found an association between migraine and WMH while others did not(Ziegler), and of those that found a significant association, some found that the association was stronger among women and among those with MA, whereas others did not find any significant effect modifiers[9]. This variability is largely attributable to heterogeneity in sample selection and study design. For example, some studies limited the study population to younger age groups in order to minimize the effect of other vascular risk factors on the development of WMH[10]. Other studies went further by excluding individuals with a history of these risk factors[9]. Still other studies limited cases to patients with MA, given the strong association between MA and stroke, whereas others did not[11].

Recently, more robust studies have provided more convincing evidence for an association between migraine and WMH. In 2004, Kruit et al. published results from the Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis (CAMERA) study, a study of 217 cases and 100 controls (mean age 48) nested within the Dutch-based Genetic Epidemiology of Migraine (GEM) population-based survey[12]. They noted a high prevalence of WMH in both cases and controls (39% and 37% respectively), with no significant difference between the two. However, after stratifying by sex, female migraineurs were significantly more likely to be in the highest quintile for WMH load compared to controls (OR = 2.1, 95% CI: 1.0-4.1). The association was stronger for those with more than one headache per month (p=0.008 for trend) but was not affected by the presence or absence of aura. Earlier this year, Kurth et al. published results from the Epidemiology of Vascular Aging MRI Study, a cohort of 780 individuals born in the same French city between 1922 and 1932[13]. They found that any history of severe headache was associated with greater WMH volume (OR = 2.0, 95% CI: 1.3-3.1). Interestingly, when distinguishing between types of headaches, the association was

stronger for non-migraine (OR = 2.7, 95% CI: 1.2-5.9) than migraine (OR = 1.8, p5% CI: 1.0-2.9). Furthermore, unlike the CAMERA study, a markedly greater association was seen for migraine with aura (OR = 12.4, 95% CI: 1.6-99.4) compared to migraine without aura (1.6, 95% CI: 0.9-2.8).

   Despite the results of these studies, many unanswered questions remain. First, no study has examined the progression of migraine-associated WMH over time. WMH that are associated with vascular risk factors accumulate over time, but whether this is true of migraine-associated WMH is unknown. The functionality of migraine-associated WMH is also unclear. In the general population, WMH are associated with cognitive impairment and can be thought of as a subclinical form of vascular dementia[14]. Some studies have found subtle associations between migraine and cognitive impairment, though others, such as the Epidemiology of Vascular Aging Study, did not. Moreover, studies of migraine and cognition have not considered WMH as a potential intermediary. At the core of these questions is the issue of whether migraine-associated WMH are truly the same as the WMH associated with traditional risk factors. Assessing these similarities and differences can further our knowledge of the underlying vascular pathophysiology of migraine, as well as clarify the clinical significance of WMH.

5.   Main Hypothesis/Study Questions

I. The presence of migraine will be associated with WMH volume at visit 3 and at the Brain MRI ancillary study visit. The strength of this association will be stronger for those with migraine with aura and weaker for those with non-migraine headache (with or without aura).
   a. History of migraine ascertained via headache questionnaire at visit 3 as previously published[16], which fulfills the International Headache Society's International Classification of Headache Disorders (ICHD-2) criteria for probable migraine[17].
      i. Headache status will be classified as one of the following: migraine with aura, migraine without aura, non-migraine headache with aura, non-migraine headache without aura, or no severe headache. An individual is defined as having migraine if he or she has 1) headaches of at least 4 hours' duration; 2) headache accompanied by throbbing, pounding, pulsing, or was unilateral; 3) headache occurred with nausea, vomiting, or sensitivity to light or sound; and 4) one or more years with history of such headaches. Headaches lasting at least 4 hours but not meeting all of the other criteria are defined as non-migraine headaches. A separate question about the occurrence of visual aura (i.e. spots, jagged lines, or heat waves in one or both eyes) was also included in the questionnaire.
   b. WMH volume ascertained via categorical measurement at both visits and volumetric measurements at Brain MRI visit..
II. Migraine will be associated with the progression of WMH volume between visit 3 and Brain MRI visit. The strength of this association will be greater in those with migraine with aura as compared to those with migraine without aura; and greater

in all migraineurs (with or without aura) as compared to those with non-migraine headache or without headache.

    a. Using categorical WMH measurements, progression is defined as an increase of 2 or more in WMH score.

    b. Using volumetric measurement, progression is defined as either the difference in WMH volume (linear regression) or being in the highest quintile of WMH volume differences (logistic regression). Difference in WMH volume is calculated using previously published techniques where the relationship between the Brain MRI visit categorical white matter scale rating and the volumetric WMH volume rating are related using a quadratic equation, and this equation is used to estimate a visit 3 volume based on visit 3 WMH categorical ratings[15]. Visit 3 estimated WMH volume is then subtracted from Brain MRI actual WMH volume to get an estimated volume of progression.

III. Migraine will be associated with impaired cognition at visit 4 and at Brain MRI visit, as well as cognitive decline between visit 4 and Brain MRI visit, though we expect the magnitude of change to be small. The association will remain significant after adjusting for WMH volume.

    a. Cognition ascertained via word fluency test (WFT), digit symbol substitution test (DSST), and delayed word recall test (DWRT) administered at visit 4 and Brain MRI visit.

    b. Depending on the results of these analyses, we will consider examining the association between migraine and a more detailed cognitive battery performed at the Brain MRI ancillary study visit.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design: cross-sectional data collection on exposure, prospective data collection on other risk factors, cross-sectional definition of outcome at visit 3 and Brain MRI visit

Inclusion: For the part of hypothesis III dealing with migraine and cognitive outcomes at visit 4, we will use all ARIC participants for whom these data are available. For all other hypotheses, our study will be limited to individuals in the ARIC Brain MRI cohort (n=1134).

Exclusion: missing Brain MRI or migraine questionnaire data

Data Analysis:

I. Ordinal logistic regression of categorical WMH score at visit 3 and Brain MRI visit vs. history of migraine. Linear regression of WMH volume at Brain MRI visit vs. history of migraine.

- Adjusted for age, race/center, sex, diabetes, hyperlipidemia, blood pressure, smoking, history of CHD, marital status, and income.
- Will perform separate analyses for all headache, all migraine headaches, migraine with aura, migraine without aura, non-migraine headache with aura, and non-migraine headache without aura as separate exposures.

- For migraine, we will perform additional analyses based on headache frequency ($\geq$2/month and <2/month) and duration (top tertile and bottom two tertiles). These analyses will be performed both for all participants and separately for those with a history of headache.

II. Logistic regression of $\geq$2 units change in categorical WMH score vs. history of migraine. Linear regression of change in WMH volume vs. history of migraine.
- Adjusted for age, race/center, sex, diabetes, hyperlipidemia, blood pressure, smoking, history of CHD, marital status, and socioeconomic status.
- Will perform separate analyses for all headache, all migraine headaches, migraine with aura, migraine without aura, non-migraine headache with aura, and non-migraine headache without aura as separate exposures.
- For migraine, will perform additional analyses based on headache frequency ($\geq$2/month and <2/month) and duration (top tertile and bottom two tertiles) as described above.

III. Linear regression of WFT, DSST, and DWR at visit 4 and Brain MRI visit vs. history of migraine. Linear regression of change in WFT, DSST, and DWR vs. history of migraine.
- Adjusted for age, race, sex, diabetes, hyperlipidemia, hypertension, smoking, education, family income, and ApoE genotype. Will adjust additionally for WMH volume to see if adjustment affects strength of association.
- Will perform separate analyses for all headache, all migraine headaches, migraine with aura, migraine without aura, non-migraine headache with aura, and non-migraine headache without aura as separate exposures.
- For migraine, will perform additional analyses based on headache frequency ($\geq$2/month and <2/month) and duration (top tertile and bottom two tertiles) as described above.

Limitations: Our power will be limited by the prevalence of migraine in the study population, which previous studies have estimated as 2.7% for MA, 5.3% for migraine without aura, 1.9% for other headaches with aura, and 11.3% for other headaches without aura. We will also be limited by the relatively short interval between migraine evaluation and white matter evaluation. It is possible that a stronger association might exist if the relationship were over a longer time interval. In addition, there is not likely to be a great deal of decline in cognitive performance from visit 4 to the brain MRI visit, and individuals are relatively young at the time of their visit 4 evaluations so might not have much cognitive impairment. Finally, there is the potential for unmeasured confounders.

7.a. Will the data be used for non-CVD analysis in this manuscript?   Y/N
8.a. Will DNA data be used in this manuscript?   Y/N

ApoE genotype will be used for the cognitive outcome hypotheses.

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this

proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:
http://www.cscc.unc.edu/ARIC/search.php

Y/N

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MP399. Paton CC et al. A study of MRI-diagnosed white matter lesions and infarcts among migrainers participating in a population-based study of cardiovascular disease: the ARIC study, 1993-94.

Gottesman RF, Coresh J, Catellier DJ, Sharrett AR, Rose KM, Coker LH, Shibata DK, Knopman DS, Jack CR, Mosley TH,Jr. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. Stroke . 2010;41:3-8.

Carson AP, Rose KM, Sanford CP, Ephross SA, Stang PE, Hunt KJ, Brown CA, Szklo M. Lifetime prevalence of migraine and other headaches lasting 4 or more hours: the Atherosclerosis Risk in Communities (ARIC) study. Headache . 2004;44:20-28.

Stang PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, and Szklo M. Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. Neurology. 2005;64:1573-7.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Y/N

11.b. If yes, is the proposal
          A. primarily the result of an ancillary study (ARIC Brain MRI: 1999.01)
          B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list numbers)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

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