ARIC Manuscript Proposal #2946

PC Reviewed: 02/14/17 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: MRI abnormalities in late-onset seizures

b. Abbreviated Title (Length 26 characters): MRI in late-onset seizures

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _EJ_ **[please confirm with your initials electronically or in writing]**

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:

Data analysis and manuscript preparation will take place over 1 year.

4. Rationale:

Late-onset epilepsy (i.e., recurrent unprovoked seizures starting at age 55 or older[1]) affects a large and growing number of persons worldwide. The yearly incidence of first seizure is higher in the elderly than at any other time of life[2] at 175 per 100,000 people after age 80[3]. In comparison, the incidence of epilepsy is low in earlier adulthood (20 per 100,000 from ages 20-60), and moderately high in infants under 1 year of age (100 per 100,000). In older adults without a prior history of seizures, the yearly incidence of epilepsy is 1.85% in those 80-84 and 3.25% in those 90-94[3]. Stroke and neurodegenerative diseases account for a share of late-onset epilepsy, but many patients have no obvious single cause of seizures. A large number of these patients are thought to have microvascular disease leading to seizures.

White matter hyperintensity progression is thought to be a marker for microvascular disease. ARIC brain MRI data has shown strong associations between white matter hyperintensities and hypertension[4], fasting glucose[4], and smoking[5], which are hypothesized risk factors for late-onset seizures. In the ARIC cohort, progression of white matter hyperintensities between 1996-1998 and 2004-2006 was shown to correlate to smoking history, with a dose-response relationship[5].

White matter hyperintensities on MRI are significantly more prevalent in patients with late-onset epilepsy than in age-matched controls[6]. A small case-control study of patients with late-onset seizures (16 patients) found higher volume of white matter hyperintensities and lower cortical grey matter volumes in patients with seizures (mainly in the temporal lobes)[7] than controls. A comparison of post-stroke epilepsy to "leukoaraiosis-associated epilepsy" found a higher proportion of the leukoaraiosis-associated epilepsy patients to have temporal (vs frontal) lobe epilepsy[8]; hippocampal volumes were not compared.

We propose to describe the relationship between MRI markers of cerebrovascular disease and neurodegenerative disease, as assessed on MRI from 2011-2013 (hypothesis 1), and on the MRI done in the Brain MRI ancillary (2004-2006; hypothesis 2). Specifically, we will assess whether lower hippocampal volumes, temporal lobe cortical volumes, or higher white matter hyperintensity volume – cross-sectionally, and, in the subset with cross-temporal data available, cross-temporally, – is associated with adult-onset seizures, and whether the associations differ by black versus white race (as some effect modification of blood pressure by race has been observed in this cohort for other outcomes)[9].

5. Main Hypothesis/Study Questions:

1. Participants with late-onset epilepsy will have lower hippocampal volumes, lower cortical volume in the temporal lobes, and increased white matter hyperintensity volumes on MRI scans performed at ARIC-NCS (2011-2013, cross-sectionally) than participants without late-onset epilepsy, for both black and white participants.

2. Participants with late-onset epilepsy will have had, at an MRI conducted ~10 years prior (brain MRI 1993-1995, and brain MRI 2004-2006; cross-temporal analysis), lower hippocampal volumes, lower cortical volume in the temporal lobes, and increased white matter hyperintensity volumes than participants without late-onset epilepsy, for both

black and white participants.

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: Prospective cohort study of MRI data collected at three time points (visit 3, brain MRI visit, and ARIC-NCS) between 1993-2013, and seizures retrospectively recalled by participants between 2011-2013 (and at Visit 6, when available) or documented in Medicare CMS data or hospitalization data.

Inclusion criteria: Participants queried about self-reported seizures or convulsions at the 2011-2013 ARIC-NCS visit (NHX interview).

For secondary analysis, we will use Medicare-CMS data to identify incident cases of epilepsy in the ARIC population (using a two-year look-back period to ensure preexisting cases of epilepsy are not included). ARIC participants enrolled in Medicare fee-for-service for a minimum of two years will be included.

We also plan to utilize the larger ARIC cohort in whom the TIA form was administered at visits 1-4, and which includes questions about specific neurologic symptoms and whether they were accompanied or related to seizures/ convulsions, for secondary analyses (as it is not available after visit 4). Participants treated with an anti-seizure medication will also be included in secondary analysis.

Exclusion criteria: clinical stroke or neurodegenerative disorder prior to first seizure; brain tumor or multiple sclerosis; no MRI of sufficient quality from 2011-2013 (hypothesis 1), and/or no MRIs of sufficient quality from 1993-1995 or 2004-2006 (hypothesis 2). In analysis of Medicare data, participants without at least 2 years of data prior to the first code for epilepsy or seizures will be excluded.

Analysis will exclude individuals with seizure history but onset prior to age 45.

Outcome: The primary outcome variable of interest is the presence or absence of adult-onset seizures.

Independent variables:
Hypothesis 1: Hippocampal volume, white matter hyperintensity volume, and cortical volumes on MRI data from the ARIC-NCS ancillary study.

Hypothesis 2: Hippocampal volumes, volume of white matter hyperintensities, cortical volumes, and/or 0-9 categorical grade from 1993-1995 MRI and/ or 2004-2006 MRI. We will consider MRI at either time point, with the understanding that the visit 3 MRI had less precise quantification of brain volumes (so we will use categorical grades as needed for that analysis), but will primarily focus on the brain MRI visit for this hypothesis.

Other variables of interest:
Age at first seizure, sex, race-center
Hypertensive status
Diabetic status
Educational level
Smoking history
Alcohol abuse history

Planned data analysis:
For hypothesis 1, we will use logistic regression models to estimate the association between white matter hyperintensity volumes, cortical volumes, and hippocampal volumes and late-onset epilepsy. For hypothesis 2, we will use logistic regression models to assess the cross-temporal association between MRI measures of white matter hyperintensities volume, and hippocampal and cortical volume, from the Brain MRI 2004-2006 visit) and late-onset epilepsy. In the subset with visit 3 MRI scans, we will repeat the analysis but using the 0-9 categorical grade for white matter hyperintensities, ventricular volume, and sulcal measurements as a surrogate for global cortical atrophy. We will first perform univariate analysis, then a combined multivariable analysis of variables significant on univariate analysis for all hypotheses.

Models will be compared using maximum likelihood ratio tests. We will use multiplicative interaction terms, likelihood ratio tests, and stratified analyses to assess effect modification by sex, race, hypertensive status, and diabetic status.

Potential limitations:
One potential limitation is that the number of patients reporting seizures starting at age 45 or later may be low, which may limit the power of our analysis. The addition of visit 6 data and Medicare data will allow ascertainment of seizures in a larger proportion of the cohort. A further limitation is that participant self-reported seizures may not be accurate, as in older patients seizures may be underdiagnosed (or, alternatively, other events may be misdiagnosed as seizure). In addition, by examining late-onset seizures and MRIs done at different time points (1993-1995 MRI and/ or 2004-2006, and 2011-2013), we will not always be able to show a directional relationship between white matter changes and seizures, but will instead identify associations.

Some misclassification of MRI markers is expected; however, as MRI classification is done without respect to seizure status, we expect any bias to be towards the null.

7.a. Will the data be used for non-CVD analysis in this manuscript? _x_ Yes ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? _x_ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __x_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

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

___x___ Yes _____ No

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)?

MS351: Population-based study of seizures in blacks and whites, Rich, submitted 5/22/2012

MS368: Prevalence of seizures in blacks and whites, Rich, submitted 5/22/2012

These studies use data from Visits 1-3 only, and only examine the differences in prevalence of seizures between race and in patients with and without a history of stroke. No mention is made of other risk factors. There are no publications from these proposals.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _x__ Yes ____ No

11.b. If yes, is the proposal

_x_ A. primarily the result of an ancillary study (list number* 1999.01, 2008.06)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

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

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this

policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _x__ No.

References:

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6. Maxwell H, Hanby M, Parkes LM, Gibson LM, Coutinho C, Emsley HCA. Prevalence and subtypes of radiological cerebrovascular disease in late-onset isolated seizures and epilepsy. *Clin Neurol Neurosurg*. 2013;115(5):591-596. doi:10.1016/j.clineuro.2012.07.009.
7. Hanby MF, Al-Bachari S, Makin F, Vidyasagar R, Parkes LM, Emsley HCA. Structural and physiological MRI correlates of occult cerebrovascular disease in late-onset epilepsy. *NeuroImage Clin*. 2015;9:128-133. doi:10.1016/j.nicl.2015.07.016.
8. Gasparini S, Ferlazzo E, Beghi E, et al. Epilepsy associated with Leukoaraiosis mainly affects temporal lobe: a casual or causal relationship? *Epilepsy Res*. 2015;109(1):1-8. doi:10.1016/j.eplepsyres.2014.10.012.
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