ARIC Manuscript Proposal # 3354

PC Reviewed: 2/12/19  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Plasma beta-amyloid and late-onset epilepsy: The ARIC Neurocognitive Study

b. Abbreviated Title (Length 26 characters): Amyloid and LOE

2. Writing Group:
   Writing group members:
   Emily Johnson, MD
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   Others welcome

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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3. **Timeline:**
Data analysis and manuscript preparation will take place over 2 years.

4. **Rationale:**

Late-onset epilepsy (LOE; i.e., recurrent unprovoked seizures starting at age 60 or older) 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, at 175 per 100,000 people after age 80. 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. Stroke and neurodegenerative diseases account for a share of late-onset epilepsy, but many patients have no obvious single cause of seizures. A number of these patients are thought to have seizures related to neurodegeneration, specifically Alzheimer’s disease (AD).

Using data from the ARIC cohort, my colleagues and I previously found that the APOE4 genotype is associated with LOE, with a dose-dependent risk, after adjusting for demographics and medical comorbidities, even in the absence of clinically recognized dementia. The APOE4 genotype is associated with amyloid beta (Aβ) deposition, also with a dose-dependent relationship, even in cognitively normal individuals. Therefore, we hypothesize a relationship between Aβ and LOE.

Amyloid beta deposition, which by leading hypotheses contributes to AD, is a possible cause of this increased risk of epilepsy, potentially due to altered synaptic transmission. Animal models with excess Aβ have a high incidence of epileptiform discharges on electroencephalogram (EEG) and electrical and clinical seizures. Human studies with brain PET-Pittsburgh Compound B (PiB) imaging have found increased Aβ in patients with earlier-life epilepsy compared to controls, but whether differences in Aβ might be responsible for the development of LOE is unknown. Two peptides derived from amyloid precursor protein which are 42 and 40 peptides in length, Aβ-42 and Aβ-40, are major components of amyloid plaques in the brain. Aβ can be detected in cerebrospinal fluid (CSF) and in plasma, and a decreased plasma Aβ42/40 ratio is found in cognitively normal individuals with a genetic predisposition to AD, as well as in persons with MCI who go on to develop sporadic AD. This Aβ42/40 ratio has been posited to be a biomarker for cognitive decline and dementia. Numbers of individuals with LOE and amyloid PET in the ARIC-PET study are too small to test hypotheses for this proposal, but the promise of plasma markers of Aβ points to the potential value of testing hypotheses with this plasma biomarker.

Therefore, we propose to examine the relationship between plasma Aβ and LOE in ARIC, using Aβ measured at Visits 3 and 5.

5. **Main Hypothesis/Study Questions:**

**Hypothesis 1:** Cross-sectionally, individuals with LOE diagnosed at any time will have a lower Aβ 42/40 ratio than do participants who are never diagnosed with LOE.

**Hypothesis 2a:** Longitudinally, lower Aβ 42/40 ratio measured between the ages 49-72 will be associated with subsequent development of LOE.
Hypothesis 2b: A greater change in A\(\beta\) 42/40 ratio from Visit 3 to Visit 5 will be associated with an increased risk of LOE after Visit 5.

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: This is a prospective cohort study of A\(\beta\) collected at 2 time points (Visit 3 and Visit 5), between 1993-2013, and the development of seizures.

Inclusion criteria:
Participants with A\(\beta\) measurements at Visit 3 and/or Visit 5, with at least 2 years of Medicare fee-for-service (FFS) data available.

Exclusion criteria:
Participants without A\(\beta\) measurements available will be excluded from pertinent analyses. As is standard in ARIC, I will exclude participants with race other than black or white, and exclude white participants from Jackson MS and black participants from Minneapolis suburbs, MN.

Outcome:
Late-onset epilepsy (LOE), defined as two or more seizure-related diagnostic codes (from CMS Medicare claims for inpatient and outpatient encounters and from ARIC hospitalization data) with the first code occurring at or after age 60, and at least 2 years of hospitalization and/or CMS claims data prior to the first seizure-related code (to exclude prevalent cases). This definition has been used previously to define LOE cases in ARIC\(^4\). We will perform a sensitivity analysis will be performed in which LOE cases will be defined as presence of a first seizure-related diagnostic code at age 67 or later. This is the earliest age at which a participant would qualify for the definition of LOE using only Medicare CMS data (rather than ARIC hospitalization data), to include a 2-year look-back period of seizure-free codes data after Medicare eligibility at age 65.

Independent variables:
A\(\beta\) measured at Visit 3 and Visit 5; age, sex, race, field center, hypertension, diabetes, hypercholesterolemia, smoking history, stroke history, and dementia history

Planned data analysis:
To account for the sampling strategy used to select ARIC participants for measurement of plasma A\(\beta\) levels from Visit 3 and Visit 5 samples, we will use weighted survey methods in Stata or for all analysis of A\(\beta\) measurements. To compare cross-sectional A\(\beta\) 42/40 plasma ratios (H1), we will use logistic regression, with LOE status as the primary outcome and A\(\beta\) 42/40 as an independent variable, adjusting for demographic factors and medical comorbidities. For this analysis, we will include participants who develop LOE at any time.
To compare Aβ 42/40 plasma ratios and subsequent development of LOE (H2a), we will use Cox proportional hazards models with time-to-LOE as the dependent variable, adjusting for demographic factors and medical comorbidities. For this analysis, we will exclude participants with LOE developing prior to Visit 3 or Visit 5 (for the respective analyses).

To compare change in Aβ 42/40 ratio over time in those with and without LOE (H2b), we will use a logistic model with LOE as the dependent variable, and change in Aβ 42/40 ratio over time (visit 3-visit 5) as the primary independent variable of interest. For this analysis, we will include participants who develop LOE at any time as well as only after Visit 5.

For all models, we will assess interactions between Aβ and sex, and between Aβ and race, hypothesizing no interactions. The demographic factors to be included as covariates are age, sex, race, and field center. The medical comorbidities to be included as covariates are hypertension, diabetes, hypercholesterolemia, body mass index, smoking history, stroke history, and dementia history.

**Sensitivity Analyses:**

We will perform a sensitivity analysis using LOE cases defined as onset of first seizure-related code at age 67 or later, the first age at which a participant would qualify for the definition of LOE using only Medicare CMS data (rather than ARIC hospitalization data).

**Potential limitations:**

There may be a relatively small number of participants with seizures developing after Visit 3 (or in general). We will use Medicare CMS claims for inpatient and outpatient services and ARIC Hospitalization data to attempt to maximize identification of ARIC participants with LOE. We previously identified LOE in 596 participants using the above-described algorithm. At Visit 3, 2,558 participants had plasma Aβ measured. At Visit 5, 2,576 participants had plasma Aβ measured.

**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?**  
__x__ Yes  ____ 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”?  
__x__ 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)?

#2947: Late-onset seizures and cardiovascular risk factors (Johnson EL et al)
#3011: Systemic inflammation and brain amyloid deposition: the ARIC-PET study (Walker K et al)
#3181: Cognitive trajectories and cognition in late-onset epilepsy (Johnson EL et al)

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

11b. If yes, is the proposal

   _x_   A. primarily the result of an ancillary study (list number* ARIC-NCS: )
   ____ 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 _x___ Yes _____ No.

References:


