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
Jeanette Simino, PhD
Thomas Mosley, PhD
Anna Kucharska-Newton, PhD, MPH
David Knopman, MD
Rebecca Gottesman, MD, PhD
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]**

First author: Emily Johnson, M.D.
Address: The Johns Hopkins Hospital
Department of Neurology
600 N. Wolfe St, Meyer 2-147
Baltimore, MD 21287
ejohns92@jhmi.edu
Office phone: 410-550-0630
Office fax: 410-550-0539

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).

Name: **Rebecca Gottesman**
Address: Phipps 446D
600 N. Wolfe St
Baltimore, MD 21287

Phone: 410-614-2381 Fax: 410-955-0672
E-mail: rgottesm@jhmi.edu

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[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 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[4]. The APOE4 genotype is associated with amyloid beta (Aβ) deposition, also with a dose-dependent relationship[5], even in cognitively normal individuals[6–8]. 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[9], 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[10–12]. Human studies with brain PET-Pittsburgh Compound B (PiB) imaging have found increased Aβ in patients with earlier-life epilepsy compared to controls[13], 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[14]. 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[15–18]. This Aβ42/40 ratio has been posited to be a biomarker for cognitive decline and dementia[19]. 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 Aβ 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 Aβ collected at 2 time points (Visit 3 and Visit 5), between 1993-2013, and the development of seizures.

Inclusion criteria:
Participants with Aβ 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 Aβ 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:
Aβ 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 Aβ levels from Visit 3 and Visit 5 samples, we will use weighted survey methods in Stata orpfor all analysis of Aβ measurements. To compare cross-sectional Aβ 42/40 plasma ratios (H1),we will use logistic regression, with LOE status as the primary outcome and Aβ 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[4]. 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)

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* 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:

1. Josephson CB, Engbers JDT, Sajobi TT, et al. Towards a clinically informed, data-driven definition of elderly onset epilepsy. Epilepsia [online serial]. 2016;57:298–305. Accessed at:

http://www.ncbi.nlm.nih.gov/pubmed/26648047. Accessed April 25, 2016.
2. Cloyd J, Hauser W, Towne A, et al. Epidemiological and medical aspects of epilepsy in the elderly. Epilepsy Res [online serial]. 2006;68 Suppl 1:S39-48. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/16384689. Accessed May 4, 2016.
3. Hesdorffer DC, Logroscino G, Benn EKT, Katri N, Cascino GD, Hauser WA. Estimating risk for developing epilepsy: A population-based study in Rochester, Minnesota. Neurology. 2011;76:23–27.
4. Johnson EL, Krauss GL, Lee AK, et al. Association Between Midlife Risk Factors and Late-Onset Epilepsy. JAMA Neurol [online serial]. Epub 2018 Jul 23. Accessed at: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/jamaneurol.2018.1935. Accessed July 24, 2018.
5. Kok E, Haikonen S, Luoto T, et al. Apolipoprotein E-dependent accumulation of Alzheimer disease-related lesions begins in middle age. Ann Neurol [online serial]. Wiley-Blackwell; 2009;65:650–657. Accessed at: http://doi.wiley.com/10.1002/ana.21696. Accessed July 13, 2018.
6. Reiman EM, Chen K, Liu X, et al. Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. Proc Natl Acad Sci U S A [online serial]. National Academy of Sciences; 2009;106:6820–6825. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/19346482. Accessed August 25, 2017.
7. Morris JC, Roe CM, Xiong C, et al. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Ann Neurol [online serial]. Wiley Subscription Services, Inc., A Wiley Company; 2010;67:122–131. Accessed at: http://doi.wiley.com/10.1002/ana.21843. Accessed August 25, 2017.
8. Lim YY, Mormino EC, Alzheimer's Disease Neuroimaging Initiative F the ADN, et al. APOE genotype and early β-amyloid accumulation in older adults without dementia. Neurology [online serial]. Lippincott Williams & Wilkins; 2017;89:1028–1034. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/28794245. Accessed September 24, 2017.
9. Vossel KA, Tartaglia MC, Nygaard HB, Zeman AZ, Miller BL. Epileptic activity in Alzheimer's disease: causes and clinical relevance. Lancet Neurol [online serial]. 2017;16:311–322. Accessed at: http://linkinghub.elsevier.com/retrieve/pii/S1474442217300443. Accessed August 23, 2017.
10. Palop JJ, Mucke L. Amyloid-β–induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nat Neurosci [online serial]. 2010;13:812–818. Accessed at: https://www.nature.com/neuro/journal/v13/n7/pdf/nn.2583.pdf. Accessed August 23, 2017.
11. Minkeviciene R, Rheims S, Dobszay MB, et al. Amyloid β-Induced Neuronal Hyperexcitability Triggers Progressive Epilepsy. J Neurosci [online serial]. 2009;29:3453–3462. Accessed at: http://www.jneurosci.org/content/29/11/3453.long. Accessed August 23, 2017.
12. Reyes-Marin KE, Nuñez A. Seizure susceptibility in the APP/PS1 mouse model of Alzheimer's disease and relationship with amyloid β plaques. Brain Res [online serial]. 2017;1677:93–100. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/28963050. Accessed July 11, 2018.
13. Joutsa J, Rinne JO, Hermann B, et al. Association Between Childhood-Onset Epilepsy and Amyloid Burden 5 Decades Later. JAMA Neurol [online serial]. 2017;74:583. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/28346588. Accessed June 19, 2017.
14. Song F, Poljak A, Smythe GA, Sachdev P. Plasma biomarkers for mild cognitive impairment and Alzheimer's disease. Brain Res Rev [online serial]. Elsevier; 2009;61:69–80. Accessed at: https://www.sciencedirect.com/science/article/pii/S0165017309000551?via%3Dihub. Accessed June 19, 2018.
15. Fei M, Jianghua W, Rujuan M, Wei Z, Qian W. The relationship of plasma Aβ levels to dementia in aging individuals with mild cognitive impairment. J Neurol Sci [online serial]. Elsevier; 2011;305:92–96. Accessed at: https://www.sciencedirect.com/science/article/pii/S0022510X11001146?via%3Dihub. Accessed July 13, 2018.
16. Graff-Radford NR, Crook JE, Lucas J, et al. Association of Low Plasma Aβ42/Aβ40 Ratios With Increased Imminent Risk for Mild Cognitive Impairment and Alzheimer Disease. Arch Neurol [online serial]. American Medical Association; 2007;64:354. Accessed at: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/archneur.64.3.354. Accessed July 13, 2018.
17. Blennow K, De Meyer G, Hansson O, et al. Evolution of Abeta42 and Abeta40 levels and Abeta42/Abeta40 ratio in plasma during progression of Alzheimer's disease: a multicenter assessment. J Nutr Health Aging [online serial]. 2009;13:205–208. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/19262954. Accessed July 13, 2018.
18. Nakamura A, Kaneko N, Villemagne VL, et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature [online serial]. Nature Publishing Group; 2018;554:249–254. Accessed at:

http://www.nature.com/doifinder/10.1038/nature25456. Accessed March 2, 2018.
19. Rembach A, Watt AD, Wilson WJ, et al. Plasma Amyloid-β Levels are Significantly Associated with a Transition Toward Alzheimer's Disease as Measured by Cognitive Decline and Change in Neocortical Amyloid Burden. J Alzheimer's Dis [online serial]. 2014;40:95–104. Accessed at: http://www.ncbi.nlm.nih.gov/pubmed/24334723. Accessed July 13, 2018.