ARIC Manuscript Proposal #4071

PC Reviewed: 7/12/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

Cognitive predictors in late-onset epilepsy

b. Abbreviated Title (Length 26 characters):

Cognitive predictors - LOE

2. Writing Group Members:

Anny Reyes (First author)
Emily Johnson (Co-senior author)
Carrie McDonald (Co-senior author)
Rebecca Gottesman
Andrea L. C. Schneider
Anna Kucharska-Newton
Alena Stasenko
Others welcome

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

First Author: Anny Reyes
anr086@health.ucsd.edu

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: Building 10, room B1D73
10 Center Dr
Bethesda, MD 20814

3. Timeline:

Data for analyses are currently available. Data analysis, conference abstract submission, and manuscript preparation and submission will take place over one year from manuscript proposal acceptance (2022-2023).

4. Rationale:

Late-onset epilepsy (LOE; that is, recurrent seizures starting in older adulthood) occurs in a large and growing number of adults, with an estimated burden of 100,000 new cases every year

in adults eligible for Medicare[1]. The incidence of epilepsy is higher in older adulthood than at any other time of life[2], at 175 per 100,000 people after age 80[3]. There is a bidirectional relationship with individuals with epilepsy being at increased risk for cognitive impairment and cognitive decline and individuals with dementia at risk for seizures[4, 5]. We have previously shown in ARIC participants that persons with LOE are at increased risk of dementia compared to individuals without LOE, and have earlier changes on specific subtests (e.g., the delayed word recall score) than do those without LOE[5, 6].

In older adults with epilepsy, standard MCI classification protocols may not accurately capture cognitive dysfunction due to the unique features of epilepsy affecting cognition. In adults with temporal lobe epilepsy (TLE), Drs. Reyes and McDonald have previously validated the application of a comprehensive neuropsychological approach to diagnosing MCI and identified unique neuropsychological profiles among patients with early and late onset epilepsy[4]. This approach has been used to improve the diagnostic stability and classification of amnestic mild cognitive impairment (aMCI), the prodromal stage to Alzheimer's disease (AD)[7-9], to identify unique cognitive profiles or subtypes of MCI (i.e., amnestic, dysexecutive, dysnomic), and to identify patients who later revert to normal in large-scale clinical trials[10]. These criteria define MCI as having 1) an impaired score on two or more measures within at least one cognitive domain or 2) one impaired score in each of the domains sampled. In Reyes et al. (2021), the nature and prevalence of cognitive disorders in older adults with TLE (TLE-related mild cognitive impairment: TLE-MCI) was explored and cognitive profiles were compared between older adults with TLE and aMCI. We found that approximately 60% of older adults with epilepsy met the above criteria for TLE-MCI, and that these patients demonstrated a neuropsychological profile consisting of primarily language impairments. A subset of the patients with TLE-MCI demonstrated amnestic profiles similar to participants with aMCI with impairments primarily in memory, suggesting that a high proportion of adults with TLE may be on a progressive course to AD[4]. These findings demonstrate that by identifying unique neuropsychological profiles among those that meet criteria for MCI, we could identify patients that may be at risk for a comorbid neurodegenerative disorder. Further, our work demonstrated that the majority of persons who met criteria for TLE-MCI had at least one cerebrovascular risk factor (e.g., hypertension, diabetes, leukoaraiosis), raising concern for a vascular cognitive impairment in dementia (VCID) syndrome in addition to TLE. Additionally, those individuals with TLE-MCI that demonstrated a more amnestic profile had a higher prevalence of cerebrovascular risk factors combined with a worse epilepsy phenotype. Similarly, in ARIC, our colleagues have shown that conditions such as hypertension and diabetes are associated with earlier cognitive decline[11]. An examination of detailed neuropsychological profiles has the potential to identify older adults with epilepsy at risk for further cognitive decline and progression to AD or vascular dementia, which could lead to more tailored clinical interventions. In this study, we will identify unique neuropsychological profiles among individuals who meet criteria for MCI/dementia and we will investigate whether vascular risk factors are more strongly associated with progression to dementia in older adults with epilepsy than in those without.

The longitudinal ARIC neurocognitive evaluations provide an ideal source of information for identification of individuals with epilepsy at high risk for cognitive decline. Furthermore, the ARIC study contains vital health-related and socio-cultural variables that can further inform the risk for cognitive decline and progression to dementia in this population.

5. Main Hypothesis/Study Questions:

Aim 1: To identify unique neuropsychological profiles (e.g., amnestic, dysexecutive, dysnomic/language, generalized), using comprehensive neuropsychological criteria in participants with and without LOE who meet criteria for MCI/dementia. We will examine whether distinct cognitive profiles during visit 5 differ between participants with and without LOE.

Aim 2: To examine whether different neuropsychological profiles identified in Aim 1 are related to unique clinical profiles (e.g., vascular factors) in participants with and without LOE. To determine whether higher burden of vascular risk factors is associated with progression to dementia at subsequent visits (visit 6, 7, or surveillance through 2017) across cognitive subtypes. We hypothesize that participants that demonstrate an amnestic cognitive profile will have a higher burden of vascular risk factors and higher rates of progression (MCI to dementia). If we do not identify unique phenotypes in Aim 1, we will still determine if higher burden of vascular risk factors is associated with progression to dementia.

Aim 3: To examine whether a higher burden of vascular risk factors in participants with LOE who do not meet criteria for MCI/dementia at visit 5 is associated higher rates of progression (normal to MCI or normal to dementia).

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 proposed analysis of a prospective cohort study, with analysis of cognitive status at Visit 5 in those with and without LOE.

Inclusion/Exclusion Criteria:
Since the definition of LOE relies on CMS FFS claims codes, Black (from NC and MS) and white (from MD, MN, and NC) participants with at least 2 years of continuous CMS FFS coverage and who attended Visit 5 will be included in Aim 1 analyses. In Aim 2, those with CMS FFS coverage above who attended Visit 5 and either Visit 6 or Visit 7 (or both) or dementia via surveillance through 2017 will be included.

Exposures:
The primary exposure of interest will be LOE. We will study multiplicative interactions between vascular risk factors and epilepsy, as below. We have previously identified LOE in ARIC through the use of merged CMS codes[12, 13], using the definition of 2 or more seizure-related codes in the first 5 diagnostic positions, with the first seizure-related code occurring after at least 2 years of CMS coverage without a seizure-related code (to identify incident epilepsy).

Baseline characterization:

Participants will first be classified as having MCI, dementia, or cognitively normal based on the definitions at Visit 5 as previously ascertained in ARIC[14, 15]. MCI is defined as at least one domain score worse than -1.5 Z, a CDR sum of boxes >0.5 and ≥ 3, an FAQ 5, and decline below the 10 percentile on one test or below the 20th percentile on two tests in the serial ARIC cognitive battery. Dementia is defined as >1 cognitive domain worse than −1.5 Z, a CDR sum of boxes >3 and FAQ >5, and decline below the 10 percentile on one test or below the 20th percentile on two tests in the serial ARIC cognitive battery. Cognitive normality was defined as not meeting criteria for MCI or dementia. Specifically, the diagnosis of cognitive normality required that all ARIC-NCS cognitive domain scores were better than -1.5 Z and that there was an absence of decline below the 10 percentile on one test or below the 20th percentile on two tests in the serial ARIC cognitive battery. The CDR sum of boxes was required to be ≤0.5 and the FAQ ≤5.

Participants with MCI or dementia will be classified into different neuropsychological profiles based on the pattern of impairment across tests of memory, language, and executive function. The following neuropsychological profiles were based on subtypes that have been previously identified in the MCI/aging literature[9] and that have also been observed in young-to-middle-aged adults with epilepsy[16, 17]. An amnestic profile will be defined as having impairment (i.e., ≤-1.5 Z for MCI; ≤-2 for dementia) on tests of memory (DWRT recall and Logical Memory 2); dysnomic profile will be defined as having impairment on tests of language (BNT and Animal Naming); dysexecutive profile will be defined as having impairment on tests of executive function (Trails B and FAS). Given evidence from the cognitive phenotype literature that a proportion of patients with epilepsy demonstrate “generalized” cognitive profiles (e.g., impairment across multiple domains)[16, 17], we will also identify participants that demonstrate a generalized neuropsychological profile defined as having impairment on 4 or more of the 6 tests included or at least one test per cognitive domain.

Outcome:

The primary outcome of interest for Aim 1 will be a characterization of the cognitive phenotypes at Visit 5 (i.e., proportion in each group). The primary outcome of interest for Aim 2 will be vascular risk factors (as described below) in participants with MCI/AD, with and without epilepsy. For Aim 3, the primary outcome of interest will be vascular risk factors in participants without MCI/AD with LOE. For aims 2 and 3, we will use Level 3 dementia as previously ascertained in ARIC in our primary analysis, with cases of dementia ascertained from neuropsychology testing, telephone calls, CMS code surveillance, and death certificate surveillance[11].

Covariates:

Covariates of interest will include: demographic information (age, sex, level of education, combined field center-race variable) and socioeconomic/sociocultural factors (income, insurance coverage, occupational categories coded in ARIC) from Visit 5 or the most recent available and medical comorbidities (history of hypertension, diabetes, hyperlipidemia, obesity), lifestyle factors (smoking, alcohol use) from Visit 5. Hypertension will also be acquired from earlier visits as duration of hypertension and midlife hypertension has been associated with cognitive decline. We will also include prevalent and incident stroke (continuously collected in ARIC), the Apolipoprotein E4 genotype which was identified at Visit 1, and history of head injury (as

ascertained by Dr. Schneider)[18]. A burden of vascular risk score will also be calculated and will be defined by the number of vascular risk factors present (e.g., 0/1/2+).

We will use ARIC definitions of hypertension (mean SBP>140, mean DBP>90, or use of an antihypertensive medication), diabetes (fasting glucose >126, non-fasting glucose >200, hemoglobin A1c >6.5, or use of medications to control blood sugar), obesity (body mass index >30), hyperlipidemia (total cholesterol > 200), and smoking (self-reported at each visit). We will construct a vascular risk factor score with categories of 0, 1, or 2+ of these vascular risk factors.

Statistical Analyses:
Primary analysis
Aim 1: We will conduct chi-square t-tests and analysis of variance (ANOVA) to determine whether classification of MCI/dementia subtypes and performance on individual neuropsychological tests differ between participants with and without LOE.

Aim 2: We will conduct chi-square t-tests and analysis of variance (ANOVA) to compare clinical variables and the burden of vascular risk factors across MCI/dementia subtypes with and without LOE. We will conduct chi-square t-tests to determine if the proportion of participants that progressed (MCI to dementia) differed across subtypes. We will conduct multiple linear regressions to examine the contribution of the burden of vascular risk factors to progression.

Aim 3: We will conduct multiple linear regressions to examine the contribution of the burden of vascular risk factors to progression.

Limitations:
A limitation of this study is the reliance on ICD-9/10 codes to define LOE. The use of ICD-9/10 codes leads to a risk for misclassification; however, we expect misclassification bias to be towards the null as this would weaken any true differences between participants with and without LOE. For aim 1, the samples sizes for each cognitive phenotype may be small, however, based on prior literature we may have enough power to detect a medium to large effect sizes within the white matter analyses. For example, in Reyes et al.[4], the total sample of older adults with epilepsy was 71 with 43 patients meeting criteria for MCI.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No __X__ N/A
(The 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
APOE ε4 genotype

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

_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)?

#2215: Development of longitudinal measures of general and domain-specific latent factors for cognitive performance (Alden Gross)
#3181: Cognitive Trajectories and Cognition in Late-onset Epilepsy (Emily Johnson)
#3435: Late-onset Epilepsy and Risk of Later Dementia or Mild Cognitive Impairment (Emily Johnson)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X_ Yes ____ No
2008.06: The ARIC Neurocognitive study

11.b. If yes, is the proposal
_x__ A. primarily the result of an ancillary study (list number* _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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

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