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Blood-Based Biomarkers

Plasma phospholipids and prevalence of mild cognitive impairment and/or dementia in the ARIC Neurocognitive Study (ARIC-NCS)

Danni Li[a,*], Jeffrey R. Misialek[b], Eric Boerwinkle[c], Rebecca F. Gottesman[d], A. Richey Sharrett[e], Thomas H. Mosley[f], Josef Coresh[e], Lisa M. Wruck[g], David S. Knopman[h], Alvaro Alonso[b]

[a]*Department of Lab Medicine and Pathology, School of Public Health, University of Minnesota, Minneapolis, MN, USA*
[b]*Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA*
[c]*School of Public Health, University of Texas Health Science Center, Houston, TX, USA*
[d]*Department of Neurology, Johns Hopkins University, Baltimore, MD, USA*
[e]*School of Public Health, Johns Hopkins University, Baltimore, MD, USA*
[f]*Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA*
[g]*Collaborative Studies Coordinating Center, University of North Carolina, Chapel Hill, NC, USA*
[h]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*

Abstract

Introduction: Phospholipids are altered in brains of patients with dementia and some studies suggest their plasma levels may be useful in the detection of mild cognitive impairment (MCI) and dementia.
Methods: We measured 188 plasma metabolites in participants who underwent a detailed neuropsychological assessment and classified as normal (n = 153), MCI (n = 145), or dementia (n = 143) by expert adjudication.
Results: Among 10 phospholipids recently implicated as altered in dementia, higher concentration of PC aa C36:6 was significantly associated with decreased prevalence of dementia (odds ratio = 0.71, 95% confidence interval = 0.50–1.00 per 1−SD increase). Adding these phospholipids to a model including multiple predictors of dementia led to only minimal improvement in detection (C statistic changed from 0.702 to 0.71).
Discussion: Some phospholipids and metabolites were altered in MCI and dementia but cross-sectional association was relatively weak and did not improve detection of MCI and dementia beyond information provided by clinical variables.

Keywords: Phospholipids; Plasma; Mild cognitive impairment; MCI; Dementia; Metabolomics; Metabolites; ARIC-NCS; ARIC; Alzheimer's disease; AD

1. Introduction

There is a growing interest in discovery of plasma biomarkers for prediction and diagnosis of mild cognitive impairment (MCI) and dementia, in particular MCI and dementia due to Alzheimer's disease (AD). Currently, amnestic MCI (aMCI) and AD-type dementia, similar to other MCI and dementia, are generally diagnosed based on a full assessment of cognitive function, a neurological examination, and clinical examination of history in cognitive and behavioral changes. Positron emission tomography neuroimaging and cerebrospinal fluid proteins are important but invasive and expensive tools for verifying the diagnosis. Owing to the complexity of AD pathology, mounting evidence shows that no single biomarker can yield enough sensitivity and specificity, and multiple biomarkers may be necessary to

*Corresponding author. Tel.: +1-612-626-0299; Fax: +1-612-625-1121.
E-mail address: dannili@umn.edu

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diagnose AD and track its progression. Plasma biomarkers are less invasive and may be used as a first-step screen of AD. Moreover, the less invasive nature of plasma biomarkers makes them potentially more suitable for monitoring disease progression and treatment response to potential therapies in AD.

Previous work has documented altered concentrations of phospholipids in brains of aging, cognitive function decline, MCI, and dementia [1–3]. Furthermore, plasma phospholipids were associated with cognitive function during middle adulthood [4], the risk of decline in verbal fluency [5], and a significant reduction in risk of developing all-cause dementia [6]. Recently, Mapstone *et al.* reported a panel of plasma phospholipids that identified cognitive normal adults who would progress to either aMCI or AD within 2–3 years from those who remained cognitively normal (the area under curve [AUC] of the receiver-operating characteristic [ROC] analysis was 0.96 [95% confidence interval, 0.93–0.99]) [7]. In addition to the index finding, these 10 phospholipids also discriminated aMCI/AD from cognitive normal with an AUC of 0.827 in the initial discovery (n = 88) and an AUC of 0.77 in an independent validation (n = 41) [7]. Subsequently, three publications suggested that plasma phospholipids and metabolites might aid in the clinical diagnosis of MCI and dementia [8–10]. With the general aim of validating the biomarkers identified by Mapstone et al. for detection of MCI and dementia and not for prediction, we examined the cross-sectional association of concentrations of selected phospholipids with the prevalence of MCI or dementia in a subset of participants in the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study (ARIC-NCS).

2. Methods

2.1. ARIC-NCS study

The ARIC study is a prospective cohort study investigating the etiology of atherosclerotic diseases in a middle-aged, predominantly biracial population. A detailed study design description was published [11].

2.2. Standard protocol approvals and patient consents

The ARIC Study and ARIC-NSC protocols were approved by the institutional review board of each participating center, and informed consent was obtained from participants at each study visit.

2.3. Measures of cognitive performance

As part of the ARIC-NCS, all participants underwent a physical examination, collection of blood samples, and a detailed neurocognitive assessment in 2011–2013. Measures of cognitive function in ARIC-NCS have been described in detail [12].

Participants who had a low mini mental state examination (MMSE) score ($<$21 in whites, $<$19 in African Americans), those with low scores in the cognitive testing ($<$1.5 standard deviations below norms applicable to our specific populations in any single domain) and cognitive decline (as evidenced by decrease in cognitive tests from previous examinations), together with a random subset of participants without evidence of cognitive impairment, underwent a neurological examination, and were administered the Clinical Dementia Rating (CDR) scale, both the informant and the subject interviews. A subset of participants without contraindications underwent a brain magnetic resonance imaging (MRI) study, as described elsewhere [13]. Briefly, MRI scans were provided in each site on 3-Tesla scanners using a common set of sequences including 3-D volumetric magnetization and fluid-attenuated inversion recovery sequences.

2.4. Diagnosis and adjudication of MCI and dementia

Two study reviewers, a neurologist and a neuropsychologist, reviewed independently data on each participant and rendered a diagnosis of normal cognition, MCI, or dementia. After the established of the syndromic diagnosis, an etiologic diagnosis was made for participants with MCI or dementia diagnoses. Discordant cases were assigned to a third independent reviewer [13].

Functional assessment questionnaire (FAQ) and CDR were used. Although the FAQ score was not administrated as a distinct scale, the items for the FAQ were embedded with the CDR. A diagnosis of MCI was assigned in persons without dementia who met the three criteria below: (1) FAQ $\leq$5 or CDR sum of boxes $\leq$3, (2) at least one neuropsychological cognitive domain Z score <-1.5 or clock time perception reading failure, and (3) documented decline in ARIC serial cognitive test battery of these tests: delayed word recall (DWR), digit symbol substitution (DSS), and word fluency (WF) (i.e., falling at or below the worst 20th percentile of change on $>$1 test or below the worst 10th percentile on at least 1 test; with change calculated as current score minus the highest prior score). Dementia diagnosis was made either (1) by a low MMSE score ($<$21 in whites, $<$19 in African Americans), even in the absence of more complete cognitive testing, if, in the judgment of the Classification Committee, any prior DWR, DSS, and WF scores were not indicative of dementia, or (2) by meeting all three of the following criteria: FAQ $\geq$ 5 or CDR sum of boxes $>$3, at least two neuropsychiatric cognitive domain scores < -1.5, and documented decline in ARIC serial cognitive test battery (as defined above).

Etiologic diagnoses were recorded as primary or secondary. Primary diagnoses and all vascular diagnoses, whether primary or secondary, were adjudicated. The diagnosis of AD as an etiologic diagnosis of MCI or dementia as a primary diagnosis was a clinical one and