ELSEVIER

Alzheimer's & Dementia ■ (2017) 1-10

Alzheimer's & Dementia

Featured Article

Association of amine biomarkers with incident dementia and Alzheimer's disease in the Framingham Study

Vincent Chouraki[a,b,c,*,1], Sarah R. Preis[b,d], Qiong Yang[b,d], Alexa Beiser[a,d], Shuo Li[b,d], Martin G. Larson[b,d], Galit Weinstein[e], Thomas J. Wang[b,f], Robert E. Gerszten[g,h,i], Ramachandran S. Vasan[b,j], Sudha Seshadri[a,b,**]

[a]*Department of Neurology, Boston University School of Medicine, Boston, MA, USA*
[b]*The Framingham Heart Study, Framingham, MA, USA*
[c]*Lille University, Inserm, Lille University Hospital, Institut Pasteur de Lille, U1167 - RID-AGE - Risk factors and molecular determinants of aging-related diseases, Labex Distalz, Lille, France*
[d]*Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA*
[e]*School of Public Health, University of Haifa, Israel*
[f]*Division of Cardiovascular Medicine, Vanderbilt Heart & Vascular Institute, Nashville, TN, USA*
[g]*Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[h]*Broad Institute of MIT and Harvard, Cambridge, MA, USA*
[i]*Cardiovascular Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[j]*Department of Medicine (Sections of Preventive Medicine and Cardiology), Boston University School of Medicine, Boston, MA, USA*

Abstract

Introduction: The identification of novel biomarkers associated with Alzheimer's disease (AD) could provide key biological insights and permit targeted preclinical prevention. We investigated circulating metabolites associated with incident dementia and AD using metabolomics.

Methods: Plasma levels of 217 metabolites were assessed in 2067 dementia-free Framingham Offspring Cohort participants (mean age = 55.9 ± 9.7 years; 52.4% women). We studied their associations with future dementia and AD risk in multivariate Cox models.

Results: Ninety-three participants developed incident dementia (mean follow-up = 15.6 ± 5.2 years). Higher plasma anthranilic acid levels were associated with greater risk of dementia (hazard ratio [HR] = 1.40; 95% confidence interval [CI] = [1.15–1.70]; $P = 8.08 \times 10^{-4}$). Glutamic acid (HR = 1.38; 95% CI = [1.11–1.72]), taurine (HR = 0.74; 95% CI = [0.60–0.92]), and hypoxanthine (HR = 0.74; 95% CI = [0.60–0.92]) levels also showed suggestive associations with dementia risk.

Discussion: We identified four biologically plausible, candidate plasma biomarkers for dementia. Association of anthranilic acid implicates the kynurenine pathway, which modulates glutamate excitotoxicity. The associations with hypoxanthine and taurine strengthen evidence that uric acid and taurine may be neuroprotective.

Keywords: Dementia; Alzheimer's disease; Cohort studies; Epidemiology; Plasma biomarkers; Metabolomics; Anthranilic acid; Kynurenines; Glutamic acid; Taurine; Hypoxanthine; Uric acid

1. Background

Alzheimer's disease (AD) is the most frequent form of dementia and a growing public health burden [1]. However, to date, there is no effective preventive or curative intervention. One reason may be that AD has a long preclinical

The authors have declared that no conflict of interest exists.

[1]Current address: UMR1167, Institut Pasteur de Lille, 1 rue du Professeur Calmette 59019, Lille, France. Tel.: +33 3 20 87 73 27.
*Corresponding author. Tel.: +1 617 638 8069; Fax: ■■■.
**Corresponding author. Tel.: +1 857 389 2359; Fax: ■■■.
E-mail address: vchourak@bu.edu (V.C.), suseshad@bu.edu (S.S.)

http://dx.doi.org/10.1016/j.jalz.2017.04.009
1552-5260/

phase, starting over 2 decades before clinical onset, so that intervention after the onset of clinical dementia is too late to prevent further progression [2,3]. Therefore, the identification of novel AD biological pathways that could provide new drug targets and easily detectable circulating biomarkers predicting risk of dementia is an urgent priority [4].

Existing biomarkers have been developed based on the "amyloid cascade" hypothesis of AD in which the disease results from the aggregation of amyloid β peptides in the brain, leading, through a cascade of events, to the hyperphosphorylation of tau proteins, axonal loss, neuronal death, and clinical onset [5]. Biomarkers derived from those peptides, when measured in the cerebrospinal fluid (CSF) or used as targets in positron emission tomography (PET) scans, are used to refine the diagnosis of AD. But the cost of PET scans is still very high, and the acceptability of lumbar puncture is low in an asymptomatic population, thus limiting their use in AD risk prediction.

Outside the amyloid cascade, other biomarkers studied in the Framingham cohorts using a candidate approach have shown some significant associations with risk of AD and led to additional studies of their role in AD pathophysiology [6–9]. Given the expected complexity of AD and the relative success of agnostic genome-wide association studies, which suggested that additional biological pathways may modulate the risk of AD [10,11], a broader selection of circulating biomarkers might further improve our understanding of AD biology and risk prediction.

The metabolomics approach studies the products of cell and organismal metabolism. Assessing simultaneously the circulating levels of a large number of metabolites allows the construction and comparison of metabolic profiles between pathological conditions and enhances the discovery of new biomarkers. Using those techniques in animal models and in human participants, in blood, CSF, or postmortem brain, several previously unsuspected mechanisms have been implicated in the pathophysiology of AD, such as phospholipids and the tryptophan, purine, and tyrosine pathways [12–14]. Nevertheless, the results have been inconsistent, likely due to differences in analytical platforms, choice of outcome measures and frequently, cross-sectional study designs that make it difficult to assess whether the observed changes preceded or are consequent to the dementia process.

In this study, we used data from a prospective community-based cohort to perform an exploratory analysis of plasma metabolomics data and to identify individual circulating biomarkers and biological pathways associated with risk of developing dementia and AD.

2. Methods

2.1. Study samples

The Framingham Heart Study (FHS) is an ongoing community-based prospective cohort study initiated in 1948 with the enrollment of 5209 women and men aged 28 to 74 years (Original Cohort) [15]. In 1971, offspring of the Original Cohort and the spouses of these offspring (n = 5124; age, 5–70 years; 3548 biological offspring, and 1576 offspring spouses) were enrolled in the Framingham Offspring Cohort [16]. They have been examined every 4 to 8 years since, nine times to date, for a core examination [17]. In addition, the Offspring Cohort has been under ongoing surveillance for cognitive decline and dementia since the fifth examination (1991–1995, n = 3799). A total of 2526 participants among those who attended this fifth examination had their plasma metabolome measured. We excluded participants with prevalent dementia (n = 133), no follow-up (n = 43), or missing values for selected covariates (education level, APOEε4 status, and/or homocysteine; n = 629) yielding a subsample of up to 2067 participants for longitudinal assessment of dementia and AD risks related to metabolite concentrations (see Supplementary Methods for the complete flowchart of the study). The study protocol was approved by the Institutional Review Board of the Boston University Medical Center, and all participants provided written informed consent.

2.2. Dementia and AD assessment

Detailed procedures for dementia screening and assessment have been published previously [18]. We screened participants at each examination for possible cognitive decline using serial administrations of the Folstein Mini–Mental Status Examination (MMSE) [19]. Any of the following participant scores resulted in an MMSE flag: an absolute score of <23 for all persons, a score <24 for persons with a high school education, and a score <26 for college-educated persons; a decline of 3 points since the participant's previous examination; or a decline of 5 points from their personal best score. Participants could also be flagged through 45-minute neuropsychological tests that they underwent every 5 or 6 years since 1999. Finally, participants might also be "flagged" by self-, family-, or physician-expressed concern either spontaneously or at a health status update, that is, an FHS ancillary study examination or an FHS baseline examination.

Persons flagged as having possible cognitive decline or otherwise being at risk for developing dementia underwent a more detailed neuropsychological and neurological evaluation, and when required, a structured family interview was administered to one or more family members and caregivers over the telephone. All persons were assigned a Clinical Dementia Rating [20] scale score. We then determined whether each person fulfilled criteria for a diagnosis of dementia, the probable date of onset, and type of dementia at a consensus review conducted by a panel comprising at least one behavioral neurologist and one neuropsychologist. Participants with dementia met criteria outlined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders criteria [21]. Participants with AD met National Institute