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Impact of apolipoprotein ε4–cerebrospinal fluid beta-amyloid interaction on hippocampal volume loss over 1 year in mild cognitive impairment

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Abstract

Background: The majority of studies relating amyloid pathology with brain volumes have been cross-sectional. Apolipoprotein ε4 (*APOE* ε4), a genetic risk factor for Alzheimer's disease, is also known to be associated with hippocampal volume loss. No studies have considered the effects of amyloid pathology and *APOE* ε4 together on longitudinal volume loss.

Methods: We evaluated whether an abnormal level of cerebrospinal fluid beta-amyloid (CSF Aβ) and *APOE* ε4 carrier status were independently associated with greater hippocampal volume loss over 1 year. We then assessed whether *APOE* ε4 status and CSF Aβ acted synergistically, testing the significance of an interaction term in the regression analysis. We included 297 participants: 77 cognitively normal, 144 with mild cognitive impairment (MCI), and 76 with Alzheimer's disease.

Results: An abnormal CSF Aβ level was found to be associated with greater hippocampal volume loss over 1 year in each group. *APOE* ε4 was associated with hippocampal volume loss only in the cognitively normal and MCI groups. *APOE* ε4 carriers with abnormal CSF Aβ in the MCI group acted synergistically to produce disproportionately greater volume loss than noncarriers.

Conclusion: Baseline CSF Aβ predicts progression of hippocampal volume loss. *APOE* ε4 carrier status amplifies the degree of neurodegeneration in MCI. Understanding the effect of interactions between genetic risk and amyloid pathology will be important in clinical trials and our understanding of the disease process.

Keywords: Apolipoprotein E4; Hippocampal atrophy; Beta-amyloid; Biomarker; MRI

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1. Introduction

Fibrillar beta-amyloid (Aβ) plaques, one of the hallmarks of Alzheimer's disease (AD), have been shown to be associated with hippocampal atrophy in multiple cross-sectional positron emission tomography (PET) studies using the amyloid ligand, Pittsburgh compound B (PiB) [1–5]. There are a few studies that have found similar correlations between cerebrospinal fluid (CSF) Aβ, an indirect measure of cerebral amyloid deposition [6,7], and hippocampal atrophy [8,9]. However, results from studies relating Aβ pathology with longitudinal volume loss have been mixed. One PiB-PET study found a strong association between brain Aβ and change in regional magnetic resonance imaging volumes in normal subjects, but only a trend in those with AD [3]. One study reported an association between CSF Aβ and the rate of hippocampal atrophy [10], although CSF p-tau was found to be a better predictor, and two other studies found no correlation between Aβ and the rate of whole brain atrophy [11,12].

The primary goal of our study was to determine whether baseline CSF Aβ level is associated with longitudinal hippocampal volume loss, incorporating data from the multicenter Alzheimer's Disease Neuroimaging Initiative (ADNI; www.loni.ucla.edu\ADNI). Because apolipoprotein ε4 (*APOE* ε4), a well-documented genetic risk factor for developing AD [13,14], is known to be associated with increased brain Aβ [15–18] and hippocampal atrophy [19–21], we further explored whether *APOE* ε4 modifies the relationship between abnormally low CSF Aβ and hippocampal volume loss.

2. Methods

2.1. Participants

The participants in this study were recruited through the ADNI between 2005 and 2008, a longitudinal study including 56 centers in the United States and Canada was conducted with the purpose of identifying biomarkers of early AD for clinical trials (www.adni-info.org). The ADNI was funded by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a 5-year public–private partnership.

2.2. APOE *genotyping and clinical assessment*

All participants underwent *APOE* genotyping at the baseline visit. Approximately 6 mL of blood were collected from each participant in an ethylenediamine tetraacetic acid-containing tube, gently mixed by inversion, and shipped at an ambient temperature to a single designated laboratory within 24 hours of collection for analysis.

Participants ranged in age from 55 to 90 years, did not have major depression or severe systemic illnesses that would interfere with participation, and did not take investigational or psychometric medications. The normal control (NC) subjects had no memory complaint, had preserved activities of daily living, scored between 26 and 30 on a baseline Mini-Mental State Examination (MMSE) [22], scored a 0 on the Clinical Dementia Rating (CDR) scale [23], and scored within the normal range on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-Revised [24]. Subjects with mild cognitive impairment (MCI) had a memory complaint that was verified by a study partner, had preserved activities of daily living, and scored between 24 and 30 on the MMSE, 0.5 on the CDR, and below the normal range on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-Revised. Subjects with AD scored between 20 and 26 on the MMSE, between 0.5 and 1 on the CDR, and met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD [25]. Written consent was obtained from all subjects participating in the study, and the study was approved by the institutional review board at each participating site.

2.3. CSF analysis

As described in the ADNI protocol (www.adni-info.org), all 56 participating centers were asked to perform lumbar punctures on a minimum of 20% of their participants. Approximately one-half of the participants recruited at each center underwent lumbar puncture for CSF analysis. CSF samples were banked and batch-processed at a single laboratory, as described previously [26]. Briefly, lumbar puncture was performed with a 20- or 24-gauge spinal needle at the baseline visit after an overnight fast. The CSF samples were then transferred to polypropylene transfer tubes, frozen on dry ice within an hour after collection, and shipped on dry ice overnight to a single designated laboratory. After thawing for 1 hour at room temperature and gentle mixing, 0.5 mL aliquots were prepared from these samples. The aliquots were then stored in bar code-labeled polypropylene vials at −80°C and measured using the xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNOBIA AlzBio3, Ghent, Belgium) immunoassay kit-based reagents, which included the monoclonal antibody specific for $A\beta_{1\text{-}42}$ (4D7A3).

In our analysis, the baseline CSF Aβ level was dichotomized as either abnormal (i.e., reflective of underlying AD pathology) or normal (Fig. 1). It was previously published that using a threshold CSF Aβ value of 192 pg/mL yielded a sensitivity of 96% for detecting AD, on the basis of a sample of non-ADNI NC subjects and subjects with AD using the same CSF assay [27]. Furthermore, this cutoff value showed 91% agreement with evidence of brain amyloid using PiB in PET imaging [28].

2.4. MRI acquisition

Participants underwent the following standardized 1.5-T MRI protocol (http://www.loni.ucla.edu/ADNI/Research/