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Featured Article

The prevalence and biomarkers' characteristic of rapidly progressive Alzheimer's disease from the Alzheimer's Disease Neuroimaging Initiative database

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Abstract

Introduction: The prevalence and detailed biomarkers' characteristic of rapidly progressive Alzheimer's disease (rpAD) remain incompletely understood.
Methods: A total of 312 mild AD patients from the Alzheimer's Disease Neuroimaging Initiative database were chosen and dichotomized into rpAD and non-rpAD groups. We performed the prevalence and comprehensive biomarker evaluation.
Results: The prevalence of rpAD was 17.6% in mild AD. Compared with non-rpAD, there were no differences in *APOE* ε4/ε4, *APOE* ε3/ε4, and *APOE* ε2/ε4 genotype distribution, cerebrospinal fluid tau, phosphorylated tau (p-tau), amyloid-β, hippocampus volume, and amyloid deposition in rpAD. Yet, a lower p-tau/tau ratio was observed in rpAD ($P = .04$). rpAD showed region-specific hypometabolism ([18F]fluorodeoxyglucose-positron emission tomography [FDG-PET]) ($P = .001$). Receiver-operating characteristic analysis of FDG-PET demonstrated that left angular and left temporal cortices were the regions with higher area under the curve and predictive value for identifying clinical at-risk rpAD.
Discussion: We identified that rpAD commonly existed in mild AD. Cerebral hypometabolism could provide potential clinical differential value for rpAD in the short-term follow-up period.

Keywords: Alzheimer's disease; Biomarkers; Rapidly progressive dementia

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative dementia, which severely affects daily life [1,2]. The rapidly progressive Alzheimer's disease (rpAD) can be defined by a steeply decline on psychometric test [1–5], such as Mini-Mental State Examination (MMSE) score, (e.g., ≥4 points within 6 months) [1,5]. This definition is generally thought to select AD patients with more rapid pathophysiological and functional activity declines and high mortality rate [1–5]. The prevalence of rpAD found in the literature varied greatly across different studies and conceptual definitions [2,3]. Therefore, reliable results in large-scale populations are crucial to better characterize these set of individuals for future clinical trials designed to test interventions able to mitigate the aggressive disease progression in this population. So, studies of prevalence of rpAD in a

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[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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larger study population such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) database are highly desirable [6].

Recent studies have shown that several biomarker modalities can predict cognitive decline in AD populations, including glucose hypometabolism measured by uptake of [18F]fluorodeoxyglucose in positron emission tomography (FDG-PET) [7,8], hippocampal atrophy in magnetic resonance imaging (MRI) [9], decreased cerebrospinal fluid (CSF) amyloid-β ($A\beta_{1–42}$), increased CSF total tau (t-tau) and phosphorylated tau (p-tau) [8,10–12], and the *APOE* genotype [1,13–15]. However, parts of these results remain inconsistent. Moreover, these biomarkers were separately tested in different study during longer follow-up period. Therefore, when AD patients were dichotomized into rpAD and non-rpAD based on MMSE score loss $\geq$4 points within 6 months, for such a given population of rpAD, which biomarkers more correlate with the rapidly cognitive decline during the short-term follow-up period still need to be verified in the same AD population. Based on this idea, we decided to investigate the prevalence and comprehensive biomarkers' characteristic of rpAD patients from ADNI database in the same population, which could contribute to a better understanding of the disease in this population.

2. Methods

2.1. Study samples

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer's disease (AD). Further information can be found at http://www.adni-info.org/.

2.2. Participants

The operational definition of mild AD were patients with MMSE score of 20–26, clinical dementia rating >0.5, absence of any other neuropsychiatric disorders, and who meet the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD [16]. Further information about the inclusion/exclusion criteria of AD adopted by the ADNI is described in detail at www.adni-info.org. According to the definition of MMSE score loss $\geq$4 points within 6 months [1,5], the mild AD patients were allocated to the rpAD and non-rpAD groups. Alzheimer's Disease Assessment Scale—Cognitive Subscale consisting of 13 items (ADAS-Cog 13) and Functional Activity Questionnaire (FAQ), as gold standard comparisons of cognition and function measures, were also checked over 12 months in the present study.

2.3. CSF data

CSF $A\beta_{1–42}$, t-tau, and p-tau at threonine 181 were measured by using Innogenetics (INNO-BIA AlzBio3) immunoassay kit–based reagents in the multiplex xMAPLuminex platform (Luminex) as previously described [17]. The CSF data used in this study were obtained from the ADNI files "UPENNBIOMK5-8.csv." Further details of ADNI methods for CSF acquisition and measurements and quality control procedures can be found at www.adni-info.org.

2.4. Neuroimaging data

The neuroimaging data, including regional volume on MRI, white matter hyperintensity (WMH) on MRI, cerebral glucose metabolism on FDG uptake (FDG-PET), and cortical amyloid burden via standardized uptake values ratios (SUVRs) on Florbetapir-PET, were obtained from the ADNI files "UCSFFSL_11_02_15," "UCSFFSX51_11_02_15_V2," "UCD_ADNI1_WMH.csv," "UCD_ADNI2_WMH_10_26_15.csv," "UCBERKELEY FDG_07_30_15.csv," and "UCBERKELEYAV45_06_15_16.csv." The neuroimaging techniques used by ADNI have been reported previously [18,19]. To investigate neurodegeneration, we used the hippocampal volume and FDG-PET uptake from five brain regions (left angular gyrus, right angular gyrus, bilateral posterior cingular, left inferior temporal gyrus, and right inferior temporal gyrus). The WMH volume, a cerebrovascular disease marker, was also obtained. We also obtained the SUVR means of Florbetapir-PET from four regions (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal) and global Florbetapir-PET SUVR (average precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices) to calculate the amyloid burden. Further details regarding ADNI image acquisition and processing can be found at www.adni-info.org/methods.

2.5. Statistical analysis

Demographic, clinical, and biological data were compared between study groups using two-tailed Student *t* test for continuous variables and chi-square (χ^2) tests for categorical variables, respectively. The original data of CSF biomarkers were presented. However, the statistical analyses were further replicated after log conversion to get normal distribution. Post hoc pairwise comparisons were also performed using a general linear model. The effects of age, gender, education, and *APOE* genotype were adjusted for all pairwise comparisons. Bivariate logistic regression analysis was also performed to regress group status on CSF biomarkers. Receiver-operating characteristic (ROC) analysis was performed to find the cut-off value of biomarker. The highest area under the curve (AUC) and Youden index (Youden index = sensitivity + specificity − 1) were used to select the cut-off value of biomarker's measurement. In general, a test is acceptable in clinical efficacy if its