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APOE ε4 influences β-amyloid deposition in primary progressive aphasia and speech apraxia

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Abstract

Background: Apolipoprotein E ε4 (*APOE* ε4) is a risk factor for β-amyloid deposition in Alzheimer's disease dementia. Its influence on β-amyloid deposition in speech and language disorders, including primary progressive aphasia (PPA), is unclear.
Methods: One hundred thirty subjects with PPA or progressive speech apraxia underwent *APOE* genotyping and Pittsburgh compound B (PiB) PET scanning. The relationship between *APOE* ε4 and PiB status, as well as severity and regional distribution of PiB, was assessed.
Results: Forty-five subjects had an *APOE* ε4 allele and 60 subjects were PiB-positive. The odds ratio for a subject with *APOE* ε4 being PiB-positive compared with a subject without *APOE* ε4 being PiB-positive was 10.2 (95% confidence interval, 4.4–25.5; $P < .0001$). The *APOE* ε4 allele did not influence regional PiB distribution or severity.
Conclusion: *APOE* ε4 increases the risk of β-amyloid deposition in PPA and progressive speech apraxia but does not influence regional β-amyloid distribution or severity.

Keywords: Apolipoprotein; Pittsburgh compound B; Primary progressive aphasia; Logopenic aphasia; Speech apraxia

1. Introduction

The presence of the apolipoprotein E ε4 (*APOE* ε4) allele is a risk factor for Alzheimer's disease (AD) [1–3] and hence for β-amyloid deposition. Although β-amyloid deposition is usually associated with episodic memory loss and AD dementia [4], patients with progressive speech or language disorders have also been reported to have AD or β-amyloid deposition. Patients with early and prominent deficits in language are generally diagnosed with one of three variants of primary progressive aphasia (PPA) [5]. The three variants include logopenic PPA (lvPPA) in which patients present with anomia, poor word retrieval in spontaneous speech, difficulty repeating sentences, and phonological errors; semantic PPA (svPPA) in which patients present with anomia and loss of word knowledge; and agrammatic PPA (agPPA) in which patients have difficulty with grammar and syntax and can also have a motor speech disorder known as apraxia of speech [6,7]. In addition, patients with early and prominent deficits in speech in which the presenting disorder is dominated by apraxia of speech, or where apraxia of speech is the sole presenting feature [8], can be classified as progressive apraxia of speech (PAOS) [8,9]. Hence, progressive speech and language disorders can be broadly classified as PPA and PAOS [9]. β-Amyloid deposition is strongly associated with lvPPA [10–12] but has also been observed to occur in patients with svPPA [13], agPPA [11], and PAOS [8,9], although these latter PPA variants and PAOS are usually associated with frontotemporal lobar

Conflicts of interest: None.
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degeneration (FTLD) pathologies [10,14–16]. It is unclear whether the *APOE* ε4 allele is a risk factor for the presence of β-amyloid deposition in PPA or PAOS, or within the PPA variants. It is also unclear whether *APOE* ε4 influences the distribution or severity of β-amyloid deposition in these patients. Understanding the relationship between the *APOE* ε4 genotype and β-amyloid deposition in patients with speech and language disorders is important to better understand the underlying biological mechanisms that may account for pathologic variability in these patients.

The aim of this study was to use a large cohort of 130 patients with PPA or PAOS to determine the relationship between the *APOE* ε4 allele and β-amyloid deposition. We hypothesized that the presence of the *APOE* ε4 allele would strongly increase the odds of β-amyloid deposition but would not influence β-amyloid severity or distribution.

2. Materials and methods

2.1. Subjects

Between February 2010 and February 2013, we consecutively recruited subjects with a progressive speech or language disorder who presented to the Department of Neurology, Mayo Clinic, Rochester MN (n = 130). All 130 subjects underwent *APOE* genotyping as previously described [17,18] and completed ^{11}C Pittsburgh compound B (PiB) positron emission tomography (PET) scanning for determination of the β-amyloid status (see following).

All 130 subjects underwent detailed speech and language evaluations, as previously described [8], including the Western Aphasia Battery [19] in which the Aphasia Quotient is a measure of aphasia severity, and neurologic testing that included the Mini-Mental State Examination [20] as a measure of global cognitive impairment. Subjects were classified as PAOS or as one of the three well-recognized PPA variants (agPPA, svPPA, or lvPPA), based on qualitative and quantitative speech and language data, which was influenced by the PPA consensus guidelines [5], and on recommended criteria for the diagnosis of PAOS [8,9]. Subjects who met criteria for PPA but could not be classified into one of the three PPA variants were labeled as unclassified (ucPPA).

The study was approved by the Mayo Clinic Institutional Review Board, and all patients consented for enrollment into the study.

2.2. Imaging analysis

All PiB-PET scans were performed using a PET/computed tomography scanner (General Electric, Milwaukee, WI, USA) operating in the three-dimensional (3D) mode. Each subject was injected with approximately 614 MBq of PiB, and after a 40-minute uptake period, a 20-minute PiB scan was obtained. All subjects also underwent magnetic resonance imaging (MRI) at 3.0 T, which included a 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence, within 2 days of the PiB-PET scan.

A global PiB ratio [21] was calculated for each subject to classify subjects as PiB-positive or PiB-negative. All PiB-PET images were coregistered to the MPRAGE for each patient, and the automated anatomical labeling atlas [22] was used to calculate median PiB uptake for the following six cortical regions of interest: temporal lobe, parietal lobe, posterior cingulate/precuneus, anterior cingulate, prefrontal cortex, and occipital lobe (left and right were combined for all regions). Median PiB uptake in each of the six regions was divided by median cerebellar uptake to create uptake ratios. A global cortical PiB retention summary was formed by calculating median uptake ratio values across all six regions. Patients were classified as PiB-positive using a global PiB ratio cut point of 1.5 [21].

In addition, a voxel-level comparison of PiB-PET regional distribution was performed within all PiB-positive subjects. All voxels in the PiB-PET image were divided by the median uptake of the cerebellum to form PiB uptake ratio images. The PiB-PET uptake ratio images were then normalized to a customized template using the normalization parameters from the MPRAGE normalization. Two-sided *t* tests were used to compare all the PiB-positive subjects with an *APOE* ε4 allele and the PiB-positive subjects without an *APOE* ε4 allele to an age- and gender-matched control cohort. The control cohort consisted of 30 healthy subjects who had all undergone an identical PiB-PET scan and MRI acquisition and were all PiB-negative. Results were corrected for multiple comparisons using the family-wise error correction at $P < .05$. Direct comparisons were also performed between the PiB-positive *APOE* ε4–negative and PiB-positive *APOE* ε4-positive disease groups, assessed uncorrected for multiple comparisons at $P < .001$ with an extent threshold of 100 voxels. These analyses were also repeated using only PiB-positive lvPPA subjects given that the number of PiB-positive lvPPA subjects was large enough for analysis and that the vast majority of PiB-positive PPA subjects were in fact lvPPA. Age and gender were included as covariates in all analyses.

2.3. Statistical analysis

Statistical analyses were performed using JMP computer software (JMP Software, version 9.0.0; SAS Institute Inc, Cary, NC, USA) with significance assessed at $P < .05$. Odds ratios (ORs) and confidence intervals (CIs) were calculated using logistic regression for PPA, PAOS, and as a secondary analysis for each PPA variant. For the svPPA group, to calculate a conservative OR, we had to artificially replace the 0 cell count with a count of 1, based on published recommendation [23]. Mann-Whitney *U* test was used to compare global PiB ratios between *APOE* ε4–positive PiB-positive subjects and *APOE* ε4–negative PiB-positive subjects. Given the strong association between lvPPA and β-amyloid deposition, we performed additional analyses