Apolipoprotein E4, Amyloid, and Cognition in Alzheimer's and Lewy Body Disease

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Research

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Abstract

Background: The role of *APOE4* in the risk of Alzheimer's disease, Lewy body disease, and their mixed diseases have not been evaluated in antemortem patients. Also, the *APOE4* effect on β-amyloid deposition and cognition, with consideration of both Alzheimer's and Lewy body diseases, remains unclear. We aimed to determine the *APOE4* effects on the risk of Alzheimer's disease, Lewy body disease, and their mixed diseases, as well as on β-amyloid deposition and cognition after adjusting for the effect of Alzheimer's disease and Lewy body disease.

Methods: Based on clinical features and ^{18}F-Florbetaben and dopamine transporter PET, we recruited 126 controls, 90 patients with typical Alzheimer's disease (57 pure Alzheimer's disease, 32 Lewy body variant of Alzheimer's disease), 77 with typical Lewy body disease (56 pure Lewy body disease, 21 dementia with Lewy bodies with amyloid deposition), and 42 with typical Alzheimer's disease/dementia with Lewy bodies. We used logistic regression analysis to investigate the effect of *APOE4* on the risk of each disease and general linear models to investigate the independent and interaction effects of *APOE4*, Alzheimer's disease, and Lewy body disease on *β*-amyloid deposition and cognition.

Results: *APOE4* was associated with increased risks of all disease subtypes except pure Lewy body disease. *APOE4* was associated with increased frontal *β*-amyloid burden, typical Alzheimer's disease was associated with increased *β*-amyloid burden in all lobar regions, and typical Lewy body disease interacted with *APOE4* to increase the occipital *β*-amyloid burden. The interaction of *APOE4* and typical Alzheimer's disease was associated with more severe memory dysfunction, while that of *APOE4* and typical Lewy body disease was associated with poorer Clinical Dementia Rating Sum of Boxes.

Conclusions: Our findings suggest that the *APOE4* effect on disease risk is dependent on *β*-amyloid deposition and *APOE4* is associated with *β*-amyloid deposition regardless of the clinical diagnosis; however, *APOE4* further interacts with typical Lewy body disease to induce worse general cognition and higher occipital *β*-amyloid deposition and it interacts with typical Alzheimer's disease to decrease memory function. This study highlights the possible interaction of *β*-amyloid and Lewy body pathologies converging in the occipital cortex through the *APOE4* effect.

Background

Alzheimer's disease (AD) and Lewy body disease (LBD) are the two most common causes of dementia. The *apolipoprotein E4* (*APOE4*) allele poses a genetic risk for AD [1] via increased β-amyloid accumulation [2] or a non-amyloidogenic mechanism that contributes to neurodegeneration by interacting with tau [3]. Further, *APOE4* is a genetic risk factor for LBD [4, 5]. Previous autopsy studies have reported that *APOE4* increases the pathologic α-synuclein burden [6, 7], however other studies have yielded contrasting results [8, 9]. Frequent AD and LBD co-occurrence in patients with cognitive impairment [10, 11] could be attributed to the association between *APOE4* and LBD risk [12]. Advances in amyloid and dopamine transporter imaging have allowed the *in vivo* diagnosis of AD [13], LBD [14], and their mixed diseases [15]; however, the role of *APOE4* in the risk of AD and LBD, with consideration of their mixed diseases, remains unclear.

β-amyloid accumulation is a key phenomenon in patients with AD [16] and LBD [17]. Given the association of *APOE4* with α-synuclein spreading [6, 18] and the interaction between α-synuclein and β-amyloid [19], *APOE4* could be involved in the relationship between α-synuclein and β-amyloid deposition. Amyloid positron emission tomography (PET) has allowed *in vivo* β-amyloid burden quantification [20]. There remains no reliable *in vivo* biomarker for α-synuclein quantification or LB pathology; however, sufficient LB pathology that causes cognitive dysfunction can be detected based on the clinical diagnostic criteria and dopamine transporter imaging, which have high specificity for detecting dementia with Lewy bodies (DLB) [14]. Amyloid PET is superior to autopsy evaluation with regards to thorough topographical β-amyloid quantification without *a priori* evaluation for specific AD pathology sites. Therefore, we hypothesized that amyloid PET could be used to determine the effects of LBD, *APOE*, and their interaction on regional β-amyloid deposition.

Tau, α-synuclein, and β-amyloid have a synergistic interaction in cognitive decline [21]. AD and LBD independently contribute to cognitive dysfunction [22]; however, the role of *APOE4* in cognitive dysfunction with AD and LBD considered simultaneously remains unclear. Thus, we aimed to determine the effects of *APOE4* on the risk of each disease subtype as well as on β-amyloid deposition and cognitive dysfunction after adjusting for AD and LBD. We hypothesized that the association between disease risks and *APOE4*

is dependent on β-amyloid deposition and that *APOE4* is associated with *β*-amyloid deposition regardless of the clinical diagnosis. Moreover, we hypothesized that *APOE4* interacts with AD or LBD to increase *β*-amyloid deposition and cognitive dysfunction.

Methods

Participants

We enrolled 126 participants with normal cognition (NC) and 208 patients with cognitive impairment (AD and/or LBD). The NC participants lacked any subjective cognitive impairment symptoms or history of neurologic or psychiatric illnesses and underwent neurological and neuropsychological examination, brain magnetic resonance imaging (MRI), and *APOE* genotyping. Their neurological and neuropsychological findings were normal, and they lacked structural brain lesions. Eleven NC participants underwent ^{18}F-Florbetaben (FBB)-PET, which did not indicate significant β-amyloid deposition.

The patients with AD and/or LBD underwent neurological examination, *APOE* genotyping, neuropsychological tests, 3T MRI, fluorodeoxyglucose (FDG)-PET, and FBB-PET scans at the dementia and movement clinics of Yonsei University Severance Hospital, Seoul, Korea, between April 2012 and May 2019. Using semi-structured questionnaires, caregivers evaluated the presence of clinical features of AD, including slow-progressive memory dysfunction, and those of LBD, including parkinsonism, rapid eye movement sleep behavior disorder, visual hallucinations, and cognitive fluctuation. Parkinsonism severity was assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (UPDRS) motor score, with a score of >16 indicating moderate severity. The exclusion criteria were (1) pure vascular cognitive impairment; (2) other degenerative dementia causes, including frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy; (3) drug-induced cognitive impairment; and (4) other adequate cognitive impairment causes, including epilepsy, psychiatric disorder, normal-pressure hydrocephalus, and structural brain lesions (e.g., tumor or hemorrhage).

All patients with AD dementia met the criteria for probable AD dementia with high levels of biomarker evidence [13], while all patients with mild cognitive impairment (MCI) due to AD met the criteria for a high likelihood of MCI due to AD based on the National Institute on Aging-Alzheimer's Association workgroups guidelines for AD [23]. These patients were regarded as having "typical AD." Specifically, all patients with typical AD had progressive memory problems with insidious onset, biomarker evidence of neuronal injury based on FDG-PET, and significant cerebral β-amyloid deposition confirmed by a global FBB standardized uptake value ratio (SUVR) of >1.478 [20].

All patients with Parkinson's disease (PD) satisfied the United Kingdom PD Brain Bank diagnostic criteria [24] and presented with decreased dopamine transporter uptake on ^{18}F-fluorinated N-3 fluoropropyl-2-beta-carboxy-methoxy-3-beta-(4-iodophenyl) nortropane (FP-CIT)-PET. Patients with PD-MCI and PD dementia (PDD) met the Movement Disorder Society criteria for PD-MCI [25] and probable PDD [26], respectively. All patients with DLB fulfilled the 2017 revised criteria for probable DLB [14] and exhibited decreased dopamine transporter uptake on FP-CIT-PET. To identify early brain changes in patients with DLB, we included patients with MCI [27] who met all of the diagnostic criteria for probable DLB, except the presence of dementia. These patients were regarded as having LBD-related cognitive impairment (LBCI).

Based on clinical features and biomarker evidence, patients with mixed disease were categorized into the AD-dominant, LBD-dominant, and equally dominant mixed disease subgroups. Patients with LBCI who presented with β-amyloid deposition, but not memory problems, as their chief complaint, were considered to have LBD-dominant mixed disease or DLB with amyloid deposition. Conversely, patients with typical AD who presented with moderate/severe parkinsonism and abnormal FP-CIT-PET but lacked other LBD features, including cognitive fluctuation and visual hallucination, were considered to have AD-dominant mixed disease or LB variant of AD (LBVAD) [28]. If patients with typical AD satisfied the diagnostic criteria for DLB, they were regarded to have an equally dominant mixed disease or AD/DLB. Finally, there were 57, 32, 56, 21, and 42 patients with pure AD (PAD), LBVAD, pure LBD (PLBD), DLB with amyloid deposition (DLBA), and AD/DLB, respectively. Patients with PAD and LBVAD were considered to have typical AD; patients with PLBD and DLBA were considered to have typical LBD; and patients with AD/DLB were considered to have both typical AD and typical LBD.

AD-related cognitive impairment (ADCI) was defined to include patients with PAD, LBVAD, AD/DLB, and DLBA. Given the progressive nature of AD [29], we defined ADCI solely based on amyloid PET-positivity and differentiated it from typical AD that corresponds to

the symptomatic AD stage. Similarly, LBCI was defined to include patients with LBVAD, AD/LBD, DLBA, and PLBD to differentiate it from typical LBD corresponding to LBD-dominant disease.

APOE genotyping

Genomic DNA was extracted from peripheral blood leukocytes using the DiaPlexQ^{TM} ApoE Genotyping Kit following the manufacturer's instructions (SolGent co., Ltd.). Two single nucleotide polymorphisms (rs429358 for codon 112 and rs7412 for codon 158) in the *APOE* gene were genotyped using CFX 96 Real-time PCR system (Bio-Rad) following the manufacturer's instructions.

MRI acquisition

All MRI scans were acquired using the same 3T MRI scanner (Philips Achieva; Philips Medical System, Best, The Netherlands) with a SENSE head coil (SENSE factor = 2). A high-resolution, T1-weighted MRI volume dataset was obtained for all participants with a three-dimensional T1-turbo field echo sequence configured with the following acquisition parameters: axial acquisition with a 224 × 224 matrix; 256 × 256 reconstructed matrix with 182 slices; 220 mm field of view; 0.98 × 0.98 × 1.2 mm^3 voxels; echo time of 4.6 ms; repetition time of 9.6 ms; flip angle of 8°; and slice gap of 0 mm. Moreover, axial fluid-attenuated inversion recovery images were obtained to evaluate white matter hyperintensity (WMH) using the following parameters: matrix, 224 × 224; section thickness, 1 mm; echo time, 335 ms; repetition time, 8000 ms; and flip angle, 90°.

Regional WMH measurement and lacune counting

A visual rating scale of WMHs was modified from the Fazekas scale [30]. Periventricular WMH (PWMH) areas were classified as P1 (cap and band <5 mm), P2 (cap ≥5 mm or band <10 mm), and P3 (cap or band ≥10 mm); deep WMH (DWMH) areas were classified as D1 (maximum diameter of deep white matter lesion <10 mm), D2 (10 mm≤ lesion <25 mm), and D3 (lesion ≥25 mm). The number of lacunes was determined as previously described [31]. Manual ratings of WMHs and lacunes were performed by three blinded neurologists (J.H.J., K.B., S.H.J.).

Acquisition of ^{18}F-FBB- and ^{18}F-FP-CIT-PET imaging

PET scans were obtained using a Discovery 600 system (GE Healthcare, Milwaukee, WI). Doses of 185 MBq (5 mCi) of FP-CIT, 300 MBq (8 mCi) of FBB, and 4.1 MBq per body weight (kg) of FDG were intravenously injected during the procedure. At 90 min after the injection, images were acquired during a 20 min session after a computed tomography (CT) scan for attenuation correction. The parameters for the spiral CT scan were as follows: 0.8 s per rotation at 120 kVp, 10 mA, 3.75 mm slice thickness, 0.625 mm collimation, and 9.375 mm table feed per rotation. The images were reconstructed using the ordered subset expectation maximization algorithm with four iterations and 32 subsets. A Gaussian filter with 4 mm full-width at half maximum (256 × 256 matrix with 0.98 mm pixels and 0.98 mm slice thickness) was applied to reconstructed PET images.

Assessment of ^{18}F-FBB- and ^{18}F-FP-CIT-PET images

Quantitation of ^{18}F-FBB-PET/CT images was based on surface-based PET analysis methods. First, we processed all T1-weighted MR images using the CIVET pipeline (http://mcin.ca/civet) to classify gray/white matter tissues and extract cortical surfaces. Subsequently, we co-registered the FBB-PET scans to individual T1-weighted images using rigid-body transformation. We performed partial volume correction within gray and white matter regions using the idSURF method [32]. Next, the corrected FBB values were normalized to the crus-I/II gray matter reference region, which yielded an SUVR. Finally, we extracted the global FBB SUVR value as the cortical volume-weighted average of the following cortical regions of interest: frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices. FP-CIT-PET was interpreted using visual ratings as previously described [33]. FBB-PET was regarded as amyloid-positive if the global FBB SUVR was >1.478, as described in a previous autopsy-validation study [20].

Quality assurance for image processing

All MR images and processing results were visually inspected by three researchers blinded to participant information (J.H.J., S.J., B.S.Y.) for quality assurance.

Neuropsychological evaluation

All participants were assessed using the standardized Seoul Neuropsychological Screening Battery, which assesses attention, language, visuospatial function, memory, and frontal/executive function [34, 35]. Standardized z scores were available for all scorable tests based on age- and education-matched norms. The following tests were performed for analyses: the digit span backward for the attention domain; Korean version of the Boston Naming Test for the language domain; copying item of the Rey–Osterrieth Complex Figure Test (RCFT) for the visuospatial domain; immediate recall, 20 min delayed recall, and recognition items of the RCFT and Seoul Verbal Learning Test for the memory domain; and semantic and phonemic Controlled Oral Word Association Test and Stroop color reading test for the frontal/executive domain. Moreover, global cognitive performance was assessed using the Korean version of the Mini-Mental State Examination (K-MMSE) and Clinical Dementia Rating Sum of Boxes (CDR-SOB).

Statistical analysis

An analysis of variance and the c^2 test were performed for cross-group comparisons of clinical features. Logistic regression analyses were performed to evaluate the effect of *APOE4* (carrier vs. non-carrier) on disease risk after controlling for age, sex, education, hypertension, diabetes mellitus, hyperlipidemia, DWMH, PWMH, and the lacune number. Model 1 analyses evaluated the *APOE4* effect on the risk of each disease (PAD, LBVAD, AD/LBD, DLBA, PLBD, ADCI, LBCI, typical AD, or typical LBD) in a combined NC and each disease group. Model 2 analyses evaluated the effect of *APOE4* on the risk of ADCI and LBCI in all participants after adjusting for LBCI and ADCI, respectively. Model 3 analyses evaluated the effect of *APOE4* on the risk of typical AD and typical LBD in all participants after adjusting for typical LBD and typical AD, respectively.

To determine the effect of *APOE4* on β-amyloid deposition, we used general linear models to investigate the independent and interactive effects of *APOE4*, typical AD, and typical LBD on the global and mean FBB SUVR in the frontal, temporal, parietal, and occipital cortices with the same covariates as the logistic regression analyses. Model 1 analyses evaluated the independent effects of *APOE4*, typical AD, and typical LBD. Model 2 analyses tested the significance of each pair of interaction terms, including *APOE4* * typical AD, *APOE4* * typical LBD, and typical AD * typical LBD. Model 3 analyses used *APOE4*, typical LBD, typical AD, and significant interaction terms from Model 2 as predictors.

To determine the effect of *APOE4* on cognitive dysfunction, the effects of *APOE4*, typical AD, and typical LBD on composite cognitive scores were evaluated using general linear models with similar covariates. Model 1 analyses evaluated the independent effects of *APOE4*, typical AD, and typical LBD. Given the significant interaction effects of AD and LBD on neuropsychological test scores, the interaction term of typical AD * typical LBD was further included in Model 1 analyses [22]. Model 2 analyses tested the significance of interaction terms, including *APOE4* * typical AD and *APOE4* * typical LBD. Model 3 analyses used *APOE4*, typical LBD, typical AD, typical AD * typical LBD, and significant interaction terms from Model 2 as predictors. Statistical analyses were performed using SPSS software (version 23.0; IBM Corp., Armonk, NY, USA) and significance was set at $p<0.05$.

MATLAB-based SurfStat toolbox was used for statistical analyses of vertex-wise FBB uptake [36]. To identify regional β-amyloid deposition patterns associated with *APOE4*, typical AD, and typical LBD, the independent and interactive effects of *APOE4*, typical AD, and typical LBD on the vertex-wise FBB SUVR were investigated using general linear models after adjustment for same covariates as for global and lobar FBB SUVRs. Given the significant interaction effects of *APOE4* * typical LBD and typical AD * typical LBD on the mean lobar FBB SUVR, they were included in the models.

Results

Demographics and clinical characteristics

Table 1 presents the demographic and clinical characteristics of the participants. The AD/DLB, LBVAD, and PLBD groups were older than the NC group; however, there was no significant among-group age difference. Male patients were more common in the LBVAD and DLBA groups than in the NC group. There were no significant among-group differences in education, hypertension, and hyperlipidemia; however, diabetes mellitus was more common in the PLBD group than in the NC, PAD, and AD/DLB groups. The lacune number and DWMH severity were comparable among groups. PWMH was more severe in the AD/DLB group than in the NC group and was similar across the remaining groups. The proportion of patients with dementia was higher in the AD/DLB group than in the PAD, LBVAD, and PLBD groups; moreover, it was higher in the DLBA group than in the PAD group. All disease groups had

poorer K-MMSE and CDR-SOB scores than the NC group. The AD/DLB group had poorer K-MMSE scores than the PAD, LBVAD, and PLBD groups. The AD/DLB and DLBA groups had higher mean CDR-SOB scores than the PAD and LBVAD groups; moreover, the PLBD group had a higher mean CDR-SOB score than the PAD group. Compared to the NC and PLBD groups, the PAD, LBVAD, AD/DLB, and DLBA groups had higher global, frontal, parietal, temporal, and occipital FBB SUVRs. The *APOE4* carrier proportion was highest in the PAD group (73.7%), followed by the AD/DLB (59.5%), LBVAD (53.1%), DLBA (47.6%), PLBD (19.6%), and NC (17.5%) groups. The PAD, AD/DLB, LBVAD, and DLBA groups had higher proportions of *APOE4* carriers than the PLBD and NC groups; however, the proportion of *APOE4* carriers was comparable between the PLBD and NC groups.

Effect of *APOE* genotype on disease risk

Table 2 shows the associations between the *APOE* genotype and the risk of each disease compared to the NC group (Model 1). *APOE4* was associated with increased risks of PAD, LBVAD, AD/DLB, and DLBA but not PLBD. The odds ratio (OR) associated with *APOE4* was highest in the PAD group (OR, 95% confidence interval [CI]: 14.71, 6.54-33.10), followed by the AD/DLB (OR, 95% CI: 9.07, 3.52-23.37), LBVAD (OR, 95% CI: 7.73, 2.85-21.02), and DLBA (OR, 95% CI: 5.52, 1.68-18.13) groups. *APOE4* was associated with an increased risk of ADCI (OR, 95% CI: 8.90, 4.78-16.56), LBCI (OR, 95% CI: 4.06, 2.13-7.74), typical AD (OR, 95% CI: 9.39, 4.98-17.71), and typical LBD (OR, 95% CI: 3.58, 1.80-7.10). The effect of *APOE2* on the risk of PAD was not evaluated since there were no *APOE2* carriers in the PAD group. Further, *APOE2* was not associated with LBVAD, AD/DLB, DLBA, and PLBD risk. However, *APOE2* was associated with a decreased risk of ADCI (OR, 95% CI: 0.29, 0.11-0.73) and typical AD (OR, 95% CI: 0.24, 0.09-0.70). Sensitivity analysis involving the evaluation of the association between *APOE4* and LBCI after excluding patients with typical AD indicated that *APOE4* was associated with an increased LBCI risk (OR, 95% CI: 2.30, 1.04-5.08). However, sensitivity analysis excluding patients with ADCI revealed that *APOE4* was not associated with LBCI risk (OR, 95% CI: 1.37, 0.54-3.47).

Evaluation of the effect of *APOE4* on the risk of ADCI and typical AD (Model 2 and Model 3) showed that *APOE4* was associated with a higher risk of ADCI and typical AD after controlling for LBCI and typical LBD, respectively. Meanwhile, *APOE4* was not associated with a risk of LBCI or typical LBD after controlling for ADCI and typical AD, respectively. *APOE2* was associated with a lower risk of ADCI and typical AD after controlling for LBCI and typical LBD, respectively. However, *APOE2* was not associated with LBCI or typical LBD risk after controlling for ADCI and typical AD, respectively.

Effects of *APOE4*, AD, and LBD on the global and regional FBB SUVR

Table 3 presents the effects of *APOE4*, typical AD, and typical LBD on the global and regional FBB SUVR. Model 1 analyses showed that typical AD was associated with the global SUVR and mean lobar SUVR in all four lobar regions, *APOE4* was associated with the mean frontal SUVR, and typical LBD was associated with the mean occipital SUVR. Model 2 analyses revealed that the interaction of typical AD and typical LBD was associated with a lower mean parietal SUVR. Further, the interaction of *APOE4* and typical LBD was associated with a higher mean occipital SUVR. Model 3 analyses indicated that typical LBD and typical AD were associated with a higher mean parietal SUVR, and only typical AD was associated with the mean occipital SUVR.

There was a significant interaction effect between typical LBD and *APOE4* on occipital β-amyloid (Figure 1). Typical AD had a significant effect on whole-brain cortices, while typical LBD and *APOE4* lacked independent effects on the vertex-wise FBB SUVR.

Effects of *APOE4*, typical AD, and typical LBD on cognition

Model 1 analyses showed that typical AD and typical LBD were independently associated with poorer cognitive scores in all neuropsychological domains as well as poorer K-MMSE and CDR-SOB scores. Further, *APOE4* was independently associated with poorer CDR-SOB scores (Table 4). Typical AD and typical LBD had significant interaction effects on all neuropsychological domains with the exception of the attention domain. However, the interaction direction implied that the degree of cognitive dysfunction was comparable across the typical AD, typical LBD, and typical AD/typical LBD groups. Model 2 analyses indicated that the interaction of *APOE4* and typical AD was associated with poorer memory scores, while the interaction of *APOE4* and typical LBD was associated with poorer CDR-SOB scores. Effects of typical AD, typical LBD as well as the interaction effect of typical AD and typical LBD in Model 3 were similar to those in Model 1.

Discussion

We evaluated the relationship between *APOE4*, AD, LBD, β-amyloid deposition, and cognition in patients with cognitive impairment and NC participants who underwent clinical assessment and FDG-PET, amyloid PET, and dopamine transporter PET. *APOE4* was associated with increased risk of PAD, AD/DLB, LBVAD, and DLBA, but not PLBD. Further, typical LBD was associated with increased occipital β-amyloid burden via the interaction with *APOE4*. Moreover, the interactions of *APOE4* with typical LBD and AD were associated with poorer CDR-SOB scores and severe memory dysfunction, respectively. This suggests that the *APOE4* effect on disease risk is dependent on β-amyloid deposition; however, *APOE4* interacted with typical LBD to worsen general cognition and increase occipital β-amyloid deposition.

It remains unclear whether *APOE4* is associated with an increased risk of PLBD [4] [12], which could be attributed to the definition of AD pathology. Previous autopsy studies identified AD pathology based on a Braak neurofibrillary tangle stage of >III and a Consortium to Establish a Registry for Alzheimer's Disease plaque score of C, with both requiring significant tau accumulation. Since β-amyloid ligands bind to diffuse and neuritic plaques [20, 37, 38], our PLBD definition implied the absence of neuritic and diffuse plaques regardless of the tau burden. Specifically, antemortem amyloid PET scans of autopsy-confirmed PLBD were found to be amyloid-positive with a diffuse plaque being the primary contributor [37, 38]. This perspective is consistent with our sensitivity analyses excluding patients with typical AD or ADCI. *APOE4* was significantly associated with LBCI risk after excluding patients with typical AD, but not after excluding patients with ADCI. Therefore, the *APOE4* effect on disease risk across AD and LBD depends on β-amyloid deposition.

We found an association of LBD with increased occipital β-amyloid deposition after adjusting for typical AD. This is consistent with previous reports of relatively higher occipital amyloid deposition in patients with LBD than in patients with AD [17]. Previous studies have reported a synergistic relationship between cortical α-synuclein and β-amyloid accumulation [8, 39, 40] and a positive correlation between striatal dopamine depletion and occipital β-amyloid deposition in patients with LBD [41]. Therefore, the association of LBD with occipital β-amyloid deposition could reflect a possible interaction between β-amyloid and α-synuclein-related brain changes. Patients with AD with LBD and LBD without AD have previously exhibited relatively sparse occipital β-amyloid deposition compared to patients with AD without LBD on Pittsburgh Compound B PET [38]. Given the same brain reserve, the extent of LBD pathology is negatively associated with the AD pathology required for a similar degree of cognitive dysfunction [42]. Patients with AD with LBD reportedly present with lower β-amyloid deposition than patients with AD without LBD; however, this difference was smallest in the occipital cortex [38]. Therefore, careful interpretation should be applied regarding our finding of an association between the presence of typical LBD and higher occipital β-amyloid deposition than control participants after controlling for AD.

The effect of LBD on occipital β-amyloid deposition could be attributed to the significant interaction between LBD and *APOE4*. Since *APOE4* is also involved in the spread of α-synuclein or LB pathology [6, 18, 43, 44], as well as the co-existence of α-synuclein and β-amyloid pathologies [11, 45], *APOE4* could play a pivotal role in the interaction between α-synuclein and β-amyloid [19]. In our study, the interaction of *APOE4* with LBD was associated with poorer CDR-SOB scores. Notably, no specific cognitive domains were affected by the interaction. Since general cognition in patients with LBD is affected by several factors, including visual hallucinations, cognitive fluctuation, parkinsonism severity, and various psychiatric symptoms, there is a need for further studies on the association between *APOE4* and other LBD features.

The interaction of *APOE4* and typical AD was associated with greater memory dysfunction. Although we could not perform tau imaging, all of the patients with typical AD presented with typical clinical AD features and significant β-amyloid deposition. Further, FDG-PET confirmed AD-relevant neurodegeneration. Given the close correlation between tau accumulation and clinical and neurodegenerative changes in AD [46], typical AD in our study could be considered to involve AD-specific tau accumulation. Therefore, our findings could constitute clinical evidence of the interaction between *APOE4* and tau pathology. This is consistent with previous reports of a direct interaction of *APOE4* with tau [47] and tau phosphorylation [48], as well as of a significant association between *APOE4* and medial temporal lobe tau independent of β-amyloid burden [3].

The interaction effects of typical AD and typical LBD on cognitive dysfunction were significant, but they were not additive nor synergistic. The degree of cognitive deficit in the AD/DLB group was mostly comparable to that in the PAD and the PLBD groups. This result could also be explained by the concept of brain reserve [42] and dichotomization of our participants into those with and without typical AD and those with and without typical LBD. Although we cannot measure the burden of α-synuclein or LB pathology because of the lack of feasible *in vivo* biomarkers, the pathologic LB burden could be reduced in the mixed AD/DLB group compared to that in the PLBD group. Conversely, it is noteworthy that the interaction effect between typical AD and typical LBD was not

significant in the attention domain. The attention domain could be a particularly vulnerable domain that typical AD and typical LBD additively deteriorate.

This study has several limitations. First, we did not perform tau PET nor measure the LB pathology burden, which impeded the establishment of the dose-dependent relationship of AD and LB pathologies with cognitive dysfunction and β-amyloid burden. Second, we could not adjust for the effect of the β-amyloid burden on cognitive dysfunction since only 11 NC participants underwent FBB-PET. Third, LBVAD could have been under-diagnosed since we did not perform dopamine transporter PET for patients with PAD without significant parkinsonism (UPDRS motor scale of >16). Moreover, dopamine transporter PET has suboptimal sensitivity for LBD detection [49], particularly if LB pathology does not involve the nigrostriatal dopaminergic system [50]. Inconsistent with our finding that the highest *APOE4* prevalence was in the PAD group, a previous autopsy study reported that the *APOE4* prevalence was highest in the AD with LB group, followed by the AD without LB group [11]. This inconsistency could be attributed to our possible LBVAD underestimation.

Conclusion

Our findings suggest that the *APOE4* effect on disease risk is dependent on its effects on β-amyloid deposition; however, *APOE4* further interacts with typical LBD to induce worse general cognition and higher occipital β-amyloid deposition. This study highlights the possible interaction of β-amyloid and LBD pathologies converging in the occipital cortex. Future studies should elucidate the underlying mechanism and clinical significance of occipital β-amyloid deposition.

Abbreviations

AD = Alzheimer's disease; ADCI = Alzheimer's disease-related cognitive impairment; AD/DLB = Alzheimer's disease with dementia with Lewy bodies; CDR-SOB = Clinical Dementia Rating Sum of Boxes; DLBA = dementia with Lewy bodies with amyloid deposition; DWMH = deep white matter hyperintensities; FBB = ^{18}F-Florbetaben; FDG = ^{18}F-Fluorodeoxyglucose; FDR = false discovery rate; FP-CIT = ^{18}F-fluorinated N-3 fluoropropyl-2-beta-carboxy-methoxy-3-beta-(4-iodophenyl) nortropane; K-MMSE = Korean version of Mini-Mental State Examination; LBCI = Lewy body disease-related cognitive impairment; LBD = Lewy body disease; LBVAD = Lewy body variant of Alzheimer's disease; NC = normal cognition; OR = odds ratio; CI = confidence interval; PAD = pure Alzheimer's disease; PLBD = pure Lewy body disease; PWMH = periventricular white matter hyperintensities; SUVR = standardized uptake value ratios; UPDRS = Unified Parkinson's Disease Rating Scale.

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of the Yonsei University Medical Center. Since this was a retrospective study, the requirement for patient consent was waived.

Consent for publication: None

Availability of data and materials: For purposes of replicating procedures and results, any qualified investigator can request anonymized data after ethics clearance and approval by all authors.

Potential Conflicts of Interest: None.

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Tables

Table 1. Demographic characteristics of the study participants

	NC	PAD	LBVAD	AD/DLB	DLBA	PLBD	p^1	p^2
Number	126	57	32	42	21	56		
Age (years)	68.5 ± 8.3[c,d,f]	71.7 ± 7.7	73.3 ± 8.1[a]	75.1 ± 7.2[a]	73.13 ± 7.0	75.02 ± 7.3[a]	<0.001	0.114
Sex, female	91 (72.2)[c,e]	39 (68.4)	16 (50.0)[a]	26 (61.9)	8 (38.1)[a]	33 (58.9)	0.017	0.132
Education (years)	10.7 ± 4.5	10.6 ± 4.5	9.4 ± 5.5	8.9 ± 5.9	11.4 ± 5.8	9.3 ± 5.1	0.152	0.281
Vascular risk factors, n (%)								
Hypertension	65 (51.6)	25 (43.9)	16 (50.0)	24 (57.1)	9 (42.9)	35 (62.5)	0.396	0.272
Diabetes mellitus	25 (19.8)[f]	10 (17.5)[f]	6 (18.8)	7 (16.7)[f]	6 (28.6)	22 (39.3)[a,b,d]	0.037	0.035
Dyslipidemia	48 (38.1)	26 (56.6)	14 (43.8)	13 (31.0)	7 (33.3)	18 (32.1)	0.591	0.448
Cognitive status							NA	0.009
Non-demented	NA	38 (66.7)[d,e]	19 (59.4)[d]	14 (33.4)[b,c,f]	8 (38.1)[b]	30 (55.4)[d]		
Dementia	NA	19 (33.3)[d,e]	13 (40.6)[d]	28 (66.7)[b,c,f]	13 (61.9)[b]	25 (44.6)[d]		
K-MMSE	27.7 ± 2.0[b,c,d,e,f]	23.4 ± 3.3[a,d]	22.5 ± 3.1[a,d]	19.8 ± 4.8[a,b,c,f]	21.5 ± 6.1[a]	22.4 ± 4.5[a,d]	<0.001	0.002
CDR-SOB	0[b,c,d,e,f]	2.5 ± 1.5[a,d,e,f]	3.1 ± 2.1[a,d,e]	4.7 ± 3.2[a,b,c]	5.2 ± 3.7[a,b,c]	3.67± 2.8[a,b]	<0.001	<0.001
Vascular MRI markers								
Number of lacunes	0.9 ± 2.00	1.0 ± 1.7	1.6 ± 2.3	1.8 ± 2.9	1.8 ± 2.8	1.5 ± 2.5	0.189	0.563
PWMH	1.4 ± 0.6[d]	1.5 ± 0.7	1.7 ±0.7	1.8 ± 0.7[a]	1.5 ± 0.7	1.7 ± 0.7	0.009	0.248
DWMH	1.3 ± 0.6	1.4 ± 0.7	1.4 ± 0.6	1.5 ± 0.6	1.3 ± 0.5	1.3 ± 0.5	0.713	0.681
FBB-PET[3]								
Global FBB SUVR	1.2 ± 0.1[b,c,d,e]	1.9 ± 0.2[a,f]	2.0 ± 0.3[a,f]	1.9 ± 0.3[a,f]	1.9 ± 0.4[a,f]	1.3 ± 0.9[b,c,d,e]	<0.001	<0.001
Frontal SUVR	1.2 ± 0.1[b,c,d,e]	2.0 ± 0.3[a,f]	2.0 ± 0.4[a,f]	2.0 ± 0.3[a,f]	1.9 ± 0.4[a,f]	1.3 ± 0.1[b,c,d,e]	<0.001	<0.001
Parietal SUVR	1.2 ± 0.1[b,c,d,e]	1.9 ± 0.2[a,f]	2.0 ± 0.3[a,f]	1.9 ± 0.3[a,f]	1.9 ± 0.4[a,f]	1.3 ± 0.1[b,c,d,e]	<0.001	<0.001
Temporal SUVR	1.2 ± 0.1[b,c,d,e]	1.9 ± 0.3 [a,f]	1.9 ± 0.3[a,f]	1.9 ± 0.3[a,f]	1.9 ± 0.3[a,f]	1.3 ± 0.1[b,c,d,e]	<0.001	<0.001
Occipital SUVR	1.3 ± 0.1[b,c,d,e]	1.7 ± 0.2[a,f]	1.8 ± 0.3[a,f]	1.8 ± 0.3[a,f]	1.9 ± 0.3[a,f]	1.4 ± 0.1[b,c,d,e]	<0.001	<0.001
APOE genotyping, n (%)								
APOE4 carrier	22 (17.5)[b,c,d,e]	42 (73.7)[a,f]	17 (53.1)[a,f]	25 (59.5)[a,f]	10 (47.6)[a,f]	11 (19.6)[b,c,d,e]	<0.001	<0.001

APOE4 homozygote	0 (0)[b,c]	4 (7.0)[a]	5 (15.6)[a,f]	1 (2.4)	0 (0)	1 (1.8)[c]	<0.001	0.056
APOE2 carrier	22 (17.5)[b,d]	0[a,c,f]	4 (12.5)[b]	1 (2.4)[a,f]	2 (9.5)	9 (16.1)[b,d]	0.001	0.003

Abbreviations: *APOE* = *Apolipoprotein E*; AD = Alzheimer's disease; PAD = pure Alzheimer's disease; AD/DLB = Alzheimer's disease with dementia with Lewy bodies; DLBA = dementia with Lewy bodies with amyloid deposition; PLBD = pure Lewy body disease; NC = normal cognition; FBB = Florbetaben; PET = positron emission tomography; DWMH = deep white matter hyperintensity; PWMH = periventricular white matter hyperintensities; K-MMSE = Korean version of the Mini-Mental State Examination; CDR-SOB = Clinical Dementia Rating Sum of Boxes; MRI = magnetic resonance imaging; SUVR = standardized uptake value ratio.

[1] P values are results of comparisons among all six study groups.

[2] P values are the results of comparisons among the five disease groups.

[3] A total of 11 of 126 (8.3%) NC participants and all patients with cognitive impairment underwent FBB-PET scans. Global FBB SUVR was not calculated because of issues with imaging quality in three, two, two, one, and two patients with PAD, LBVAD, AD/DLB, DLBA, and PLBD, respectively.

[a] Significantly different compared to the NC group.

[b] Significantly different compared to the PAD group.

[c] Significantly different compared to the LBVAD group.

[d] Significantly different compared to the AD/DLB group.

[e] Significantly different compared to the DLBA group.

[f] Significantly different compared to the PLBD group.

Table 2. Effect of *apolipoprotein E* on the risk of cognitive impairment in specific disease groups

	APOE4		*APOE2*	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1 (control + each disease group)				
PAD	14.71 (6.54-33.10)	<0.001	NA	NA
LBVAD	7.73 (2.85-21.02)	<0.001	1.01 (0.28-3.57)	0.994
AD/DLB	9.07 (3.52-23.37)	<0.001	0.21 (0.26-1.78)	0.153
DLBA	5.52 (1.68-18.13)	0.005	0.71 (0.14-3.67)	0.680
PLBD	1.37 (0.54-3.47)	0.511	1.15 (0.42-3.16)	0.786
Model 1 (control + combined disease groups)				
ADCI (PAD + LBVAD + AD/DLB + DLBA)	8.90 (4.78-16.56)	<0.001	0.29 (0.11-0.73)	0.009
LBCI (LBVAD + AD/DLB + DLBA + PLBD)	4.06 (2.13-7.74)	<0.001	0.69 (0.31-1.52)	0.359
Typical AD (PAD + LBVAD + AD/DLB)	9.39 (4.98-17.71)	<0.001	0.24 (0.09-0.70)	0.009
Typical LBD (AD/DLB + DLBA + PLBD)	3.58 (1.80-7.10)	<0.001	0.62 (0.26-1.47)	0.277
Model 2 (all participants)				
ADCI	8.41 (4.81-14.71)	<0.001	0.20 (0.08-0.50)	0.001
LBCI	0.71 (0.40-1.27)	0.251	1.75 (0.77-3.98)	0.180
Model 3 (all participants)				
Typical AD	7.01 (4.18-11.76)	<0.001	0.21 (0.08-0.56)	0.002
Typical LBD	1.34 (0.76-2.34)	0.310	0.86 (0.38-1.94)	0.712

Abbreviations: *APOE* = *Apolipoprotein E*; AD = Alzheimer's disease; LBD = Lewy body disease; ADCI = Alzheimer's disease-related cognitive impairment; LBCI = Lewy body disease-related cognitive impairment; PAD = pure Alzheimer's disease; LBVAD = Lewy body variant of Alzheimer's disease; AD/DLB = Alzheimer's disease with dementia with Lewy bodies; DLBA = dementia with Lewy bodies with amyloid deposition; PLBD = pure Lewy body disease; OR = odds ratio; CI = confidence interval; DWMH = deep white matter hyperintensities; PWMH = periventricular white matter hyperintensities.

Model 1 involved logistic regression analyses for the presence of each disease performed using all of the study participants with the *APOE* genotype as a predictor. Model 2 involved logistic regression analyses for the presence of ADCI or LBCI while Model 3 involved logistic regression analyses for the presence of typical AD or typical LBD in all study participants. Covariates included age, sex, education, hypertension, diabetes mellitus, dyslipidemia, DWMH, PWMH, and the lacune number. Model 2 analyses for ADCI and LBCI were further controlled for LBCI and ADCI presence, respectively. Model 3 analyses for typical AD and typical LBD were further controlled for the presence of typical LBD and typical AD, respectively.

Table 3. Effects of *apolipoprotein E4*, Alzheimer's disease, and Lewy body disease on the regional ^{18}F-Florbetaben standardized uptake value ratio

Predictors	Global SUVR		Frontal SUVR		Temporal SUVR		Parietal SUVR		Occipital SUVR	
	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value
Model 1										
APOE4	0.09 (0.04)	0.057	0.10 (0.05)	0.038	0.06 (0.04)	0.211	0.08 (0.04)	0.082	0.02 (0.04)	0.596
Typical AD	0.52 (0.05)	< 0.001	0.52 (0.06)	< 0.001	0.47 (0.05)	< 0.001	0.52 (0.05)	< 0.001[a]	0.33 (0.05)	< 0.001[a]
Typical LBD	0.05 (0.05)	0.351	0.03 (0.05)	0.630	0.06 (0.05)	0.249	0.06 (0.05)	0.245	0.10 (0.05)	0.037
Model 2										
APOE4 * Typical AD	-0.10 (0.09)	0.261	-0.07 (0.09)	0.438	-0.10 (0.09)	0.255	-0.12 (0.09)	0.177	-0.11 (0.08)	0.202
APOE4 * Typical LBD	0.09 (0.09)	0.284	0.08 (0.09)	0.399	0.08 (0.09)	0.336	0.10 (0.09)	0.244	0.21 (0.08)	0.010
Typical AD * Typical LBD	-0.22 (0.12)	0.060	-0.21 (0.12)	0.096	-0.20 (0.12)	0.091	-0.25 (0.12)	0.032	-0.17 (0.11)	0.105
Model 3										
APOE4	0.09 (0.04)	0.057	0.10 (0.05)	0.038	0.06 (0.04)	0.211	0.08 (0.04)	0.072	-0.09 (0.06)	0.132
Typical AD	0.52 (0.05)	< 0.001	0.52 (0.06)	< 0.001	0.47 (0.05)	< 0.001	0.71 (0.10)	< 0.001[a]	0.31 (0.05)	< 0.001
Typical LBD	0.05 (0.05)	0.351	0.03 (0.05)	0.630	0.06 (0.05)	0.249	0.26 (0.11)	0.015	-0.02 (0.06)	0.797
APOE4 * Typical LBD									0.21 (0.08)	0.010
Typical AD * Typical LBD							-0.25 (0.12)	0.032		

Abbreviations: *APOE4* = *apolipoprotein E4*; AD = Alzheimer's disease; LBD = Lewy body disease; FBB = ^{18}F-Florbetaben; SUVR = standardized uptake value ratio; SE = standard error; DWMH = deep white matter hyperintensities; PWMH = periventricular white matter hyperintensities.

Data are the results of general linear models for the global or mean lobar FBB SUVR after controlling for age, sex, education, hypertension, diabetes mellitus type 2, dyslipidemia, DWMH, PWMH, and the lacune number. Model 1 used *APOE4*, typical LBD, and typical AD as predictors. Model 2 tested the significance of the interaction terms (*APOE4* * Typical AD, *APOE4* * Typical LBD, or Typical AD * Typical LBD) by adding one of the three interaction terms as a predictor to Model 1. Model 3 used *APOE4*, typical LBD, typical AD, and the significant interaction terms in Model 2 as predictors.

Table 4. Effects of *apolipoprotein E4*, typical Alzheimer's disease, and typical Lewy body disease on neuropsychological test scores

Predictor	*APOE4*		Typical AD		Typical LBD		Typical AD * Typical LBD		*APOE4* * Typical LBD		*APOE4* * Typical AD	
Cognitive domain	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	P value
Model 1												
Attention	0.16 (0.15)	0.272	-0.57 (0.18)	0.002	-0.99 (0.18)	<0.001	0.47 (0.28)	0.096				
Language	0.01 (0.16)	0.938	-1.36 (0.20)	<0.001	-1.65 (0.20)	<0.001	1.22 (0.31)	<0.001				
Visuospatial	-0.06 (0.33)	0.856	-1.27 (0.33)	<0.001	-2.86 (0.34)	<0.001	1.12 (0.53)	0.035				
Memory	0.14 (0.5)	0.351	-1.71 (0.13)	<0.001	-1.75 (0.12)	<0.001	1.73 (0.18)	<0.001				
Executive	0.05 (0.12)	0.664	-1.16 (0.12)	<0.001	-1.58 (0.12)	<0.001	1.10 (0.19)	<0.001				
K-MMSE	-0.40 (0.42)	0.339	-4.10 (0.52)	<0.001[a]	-4.99 (0.52)	<0.001[a]	2.19 (0.80)	0.007				
CDR-SOB	0.89 (0.26)	0.001	1.76 (0.32)	<0.001	3.46 (0.32)	<0.001	-1.47 (0.50)	0.003				
Model 2												
Attention									0.39 (0.30)	0.200	-0.47 (0.30)	0.115
Language									-0.28 (0.33)	0.400	0.05 (0.32)	0.870
Visuospatial									0.54 (0.53)	0.306	-0.72 (0.52)	0.164
Memory									0.02 (0.18)	0.932	-0.52 (0.18)	0.003
Executive									-0.06 (0.19)	0.767	-0.25 (0.18)	0.169
K-MMSE									-0.97 (0.86)	0.262	-1.62 (0.84)	0.055
CDR-SOB									1.46 (0.53)	0.006	0.48 (0.52)	0.359
Model 3												
Memory	0.11 (0.12)	0.345	-1.71 (0.13)	<0.001	-1.76 (0.11)	<0.001	1.71 (0.17)	<0.001			-0.52 (0.18)	0.003
CDR-SOB	0.30 (0.33)	0.363	2.04 (0.33)	<0.001	3.12 (0.34)	<0.001	-2.03 (0.53)	<0.001	1.46 (0.53)	0.006		

Abbreviations: *APOE4* = *apolipoprotein E4*; AD = Alzheimer's disease; LBD = Lewy body disease; DWMH = deep white matter hyperintensities; PWMH = periventricular white matter hyperintensities.

Data are the results of general linear models for neuropsychological test scores after controlling for age, sex, education, hypertension, diabetes mellitus type 2, hyperlipidemia, DWMH, PWMH, and the lacune number. Model 1 used *APOE4*, typical LBD, typical AD, and typical AD * typical LBD as predictors. Model 2 tested the significance of *APOE4* * typical AD and *APOE4* * typical LBD by adding one of the two interaction terms as a predictor to Model 1. Model 3 used *APOE4*, typical LBD, typical AD, and the significant interaction terms from Model 2 as predictors.

Figures

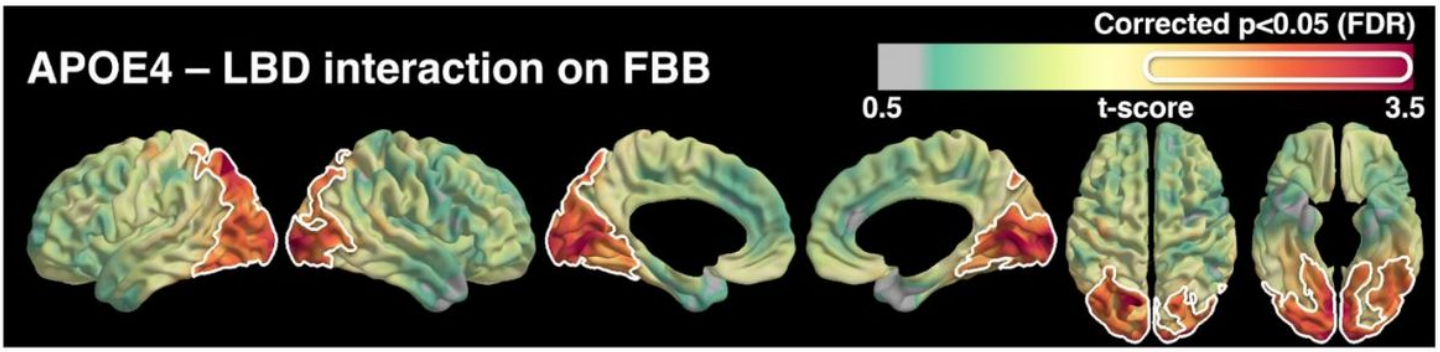

Figure 1

Statistical map of cortical regions with a significant interaction effect of APOE4 and typical Lewy body disease on cortical amyloid deposition. The results are based on the general linear model. Covariates include age, sex, education, hypertension, diabetes mellitus type 2, dyslipidemia, number of lacunes, and deep and periventricular white matter hyperintensities. The color scale represents t-values with areas bordered by the white line indicating statistically significant regions (corrected p<0.05, false discovery rate). Abbreviations: APOE4, apolipoprotein E4; LBD, Lewy body disease; FBB, 18F-Florbetaben; FDR, false discovery rate.