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Re: Comments on "Neuropsychological Comparison of Patients With Alzheimer's Disease and Dementia With Lewy Bodies": Author Response

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Dear Editor,

We are grateful for the response to our published paper.[1] We agree that the copathology of Parkinson's disease (PD) should be considered in patients with Alzheimer's disease (AD) and parkinsonism. However, we respectfully disagree on a few of the comments made and provide some reasons here.

Motor examinations based on the Unified Parkinson's Disease Rating Scale (UPDRS) have not often been performed on all patients with cognitive impairment in previous studies. Most previous studies involving patients with AD excluded those who exhibited significant motor parkinsonism or clinical symptoms suggestive of Lewy body disease (LBD). Previous literature on parkinsonism in patients with AD is therefore biased because of the concerns of the researchers in including patients with dementia with Lewy bodies (DLB) or PD. One of the purposes of our recent study was to describe the features (including motor parkinsonism and cognitive dysfunction) of patients with AD with parkinsonism (which could be a symptom of LBD) based on the conjecture that there could be frequent mixed pathologies of AD and LBD, and so we did not exclude patients with moderate-to-severe motor parkinsonism. Moreover, while a significant portion of our patients with AD had concomitant physical conditions that caused gait disturbance, including general weakness, arthritis, lumbar stenosis, or renal/cardiac problems, we did not ignore them. This clinical approach is helpful in sensitively detecting the progression of motor parkinsonism in the elderly during follow-up. Based on our experience as dementia specialists and as neurologists in performing UPDRS motor examinations on all patients with cognitive impairment, patients or their caregivers usually complain of motor parkinsonism symptoms such as gait or motion slowing when their UPDRS motor score is >20. Most importantly, the proportion of patients with motor parkinsonism is similar to that with concomitant Lewy body pathologies among patients with pathologically confirmed AD.[2,3]

In the paper[4] referenced in the comment that presented UPDRS scores of 7 as being indicative of mild parkinsonism, the abbreviated version of the motor portion of the UPDRS was applied when examining parkinsonian symptoms (ranging from 0 [no parkinsonism] to 40 [maximum]), and scores were not assigned for limb bradykinesia or gait. Standardized UPDRS motor examinations were performed on all of the patients in our study (ranging from 0 [no parkinsonism] to 108 [maximum]), which resulted in motor-severity criteria that differed from those in the previous study.[4]

We think that a high proportion of patients with AD^{P+} have concomitant AD and LBD pathologies. The idea that AD and LBD must be strictly differentiated makes the clinical diagnosis of mixed pathology more difficult. Several patients with AD^{P+} underwent dopamine transporter (DAT) positron emission tomography (PET) and there were various pat-

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terns of DAT uptake including typical posteriorly affected pattern (just as in patients with PD), diffusely affected pattern, and more anteriorly affected pattern. However, we did not exclude the patients with AD^{P+} and PD-like DAT uptake pattern, since all patients with AD presented typical patterns of cognitive decline and satisfied the strict diagnostic criteria for AD based on amyloid and neurodegeneration biomarkers. Excluding such patients due to their DAT uptake pattern could introduce severe selection bias that occurs very frequently in the field of degenerative research. The main objective of our study was to describe the clinical features of patients with AD^{P+} while considering the possibility of concomitant LBD (including PD).

Regarding disease duration, the onset of both cognitive dysfunction and motor parkinsonism need to be considered. However, since some patients with AD do not complain of motor parkinsonism, and likewise some patients with DLB do not complain of memory problem, strict comparison and description is not feasible due to the high proportion of missing values.

Among the 86 patients with AD^{P+}, 50 underwent FDG PET, 3 underwent FP-CIP PET, and 33 underwent both investigations. The 83 patients with AD^{P+} who underwent FDG PET presented a PD-related pattern (PDRP), with increased metabolic activity in the posterior putamen on the FDG PET scans. Among the 36 patients with AD^{P+} who underwent DAT PET, 7 presented moderate DAT depletion in the striatum, while 29 presented suspected DAT depletion in the striatum with prominent PDRP and increased perfusion in the posterior putamen. Patients with PD whose motor symptoms precede cognitive impairment generally had a large decreasing gradient in the anterior and posterior striatum, which could be detected sensitively using a visual rating. However, in AD^{P+} where cognitive decline is prominent from the beginning, it is not easy to diagnose using a visual rating because the anterior-to-posterior gradient is often reversed or absent. We performed single-subject automatic quantitative DAT PET imaging analysis to overcome this problem. Below we present examples of quantitative analyses of patients with AD^{P+} and diffusely or anteriorly decreased DAT uptake but with normal visual-rating results (Fig. 1).

These patients with AD would not be diagnosed with concomitant PD elsewhere. More seriously, they are usually excluded from research not only on AD but also on PD/DLB.

Patients with drug-induced and vascular parkinsonism were excluded from this study. As mentioned in the exclusion criteria in the Methods section of our paper, we excluded patients with drug-induced cognitive impairment. The patients who used antipsychotics were consequently excluded in this study. In the future our study group will investigate vascular parkinsonism with a focus on the striatal metabolic, dopaminergic, and structural changes. Based on our experiences of simultaneously performing FDG PET and DAT PET, vascular parkinsonism is characterized by the simultaneous decrease in striatal metabolism and DAT uptake in the vascular lesion location (including in lacunes). We also excluded patients with brain lesions such as symptomatic cerebral infarction, severe subcortical ischemic changes, and normal-pressure hydrocephalus.

Distinguishing AD and DLB solely based on visual rating of DAT PET scans is very hazardous. Patients cannot be diagnosed with PD if the typical anterior-to-posterior gradient is not observed. A large proportion of patients with DLB and the visual rating of "normal finding" presented diffusely decreased DAT uptake in individual quantitative analyses. It is therefore suggested that dopaminergic imaging is useful for detecting patients with LBD features, although special caution

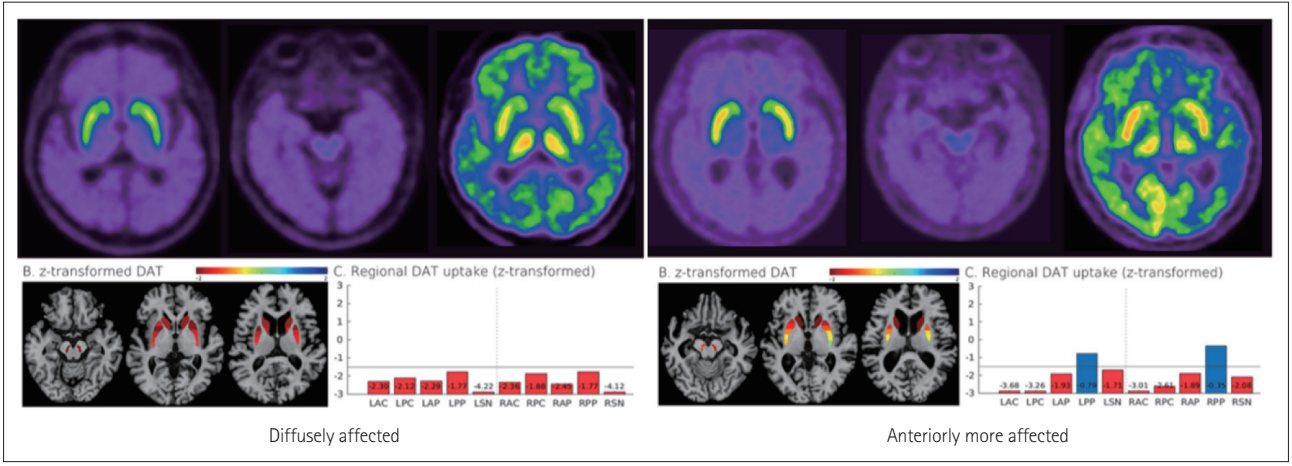

Fig. 1. Individual quantitative analysis of DAT uptake. DAT, dopamine transporter; LAC, left anterior caudate, LAP; left anterior putamen; LPC, left posterior caudate; LPP, left posterior putamen; LSN, left substantia nigra; RAC, right anterior caudate; RAP, right anterior putamen; RPC, right posterior caudate; RPP, right posterior putamen; RSN, right substantia nigra.

is needed to not rule them out solely based on visual ratings. Our recent study demonstrated that the pattern of DAT uptake decrease itself is affected by the concomitant AD or amyloid deposition.[5] Increased amyloid deposition is associated with increased DAT depletion in the caudate and ventral striatum.

Regarding the question about the handling of patients with cognitive impairment, parkinsonism, and DAT depletion but without cognitive fluctuation nor visual hallucination, if the patients presented with progressive memory impairment as the chief complaint and with biomarker evidence of amyloid deposition and AD related-neuronal injury, they were regarded as having AD^{P+} and included in our study. Otherwise (i.e., if they did not have AD), they were excluded from the current study. Our study focused on AD without LBD features (AD^{P-}) and AD with mild LBD features (AD^{P+}). Patients with DLB were included as a positive control group. Although the 2017 McKeith criteria permissively regarded patients with dementia and RBD or motor parkinsonism to have DLB solely based on DAT depletion, this might result in misdiagnosing patients with AD having very-early-stage LBD (just having RBD) as DLB. Since our study included patients with CDR of 0.5, we also wanted to increase the inclusion of patients with DLB (LB pathologies in the limbic or cortical regions) and to decrease the inclusion of patients with PD (LB pathologies in the brainstem). Furthermore, we did not include patients with PDD who clearly had preceding motor parkinsonism for more than 1 year before the dementia onset.

Ethics Statement

This study was approved by the Institutional Review Board of the Yonsei University Medical Center (IRB No. 4-2021-0759). Informed consent was waived because this study based on retrospective chart review.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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