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LETTER TO THE EDITOR

An Autopsy-Proven Case of Lewy Body Disease Presenting with Severe Dysphagia

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Dear Editor,

Lewy body dementia (LBD) is the second most common neurodegenerative dementia after Alzheimer's disease (AD).[1] LBD includes dementia with Lewy bodies (DLB) and Parkinson's disease (PD) with dementia (PDD), which share clinical features. DLB and PDD are classified according to the timing of the onset of dementia in relation to that of motor symptoms. PDD and DLB show similar neuropathological changes, such as cortical and brainstem Lewy bodies accompanied by varying degrees of AD pathology.

Dysphagia is not uncommon in PD, LBD, or other dementias; it is equally common in patients with PDD and PD and occurs more frequently in patients with DLB than in patients with AD.[2] Severe dysphagia often occurs in patients with advanced PD. The early presentation of dysphagia suggests atypical parkinsonism, e.g., progressive supranuclear palsy (PSP), multiple system atrophy, or corticobasal degeneration.[3] We report a patient with autopsy-proven LBD presenting with severe dysphagia in the early stage of LBD associated with prominent Lewy pathology in the dorsal motor nucleus of the vagus (DMV).

A 58-year-old schoolteacher presented with severe dysphagia and gait disturbance. He was healthy until a year prior, when he developed dysphagia and dragging of the left leg while walking; subsequently, he noted clumsiness of the left hand. Over the course of the year, he lost approximately 12 kg body weight owing to the severe dysphagia. On a functional inquiry, the patient reported constipation and sexual dysfunction but no urinary symptoms, orthostatic dizziness, or sleep dysfunction. The past medical and family histories were unremarkable. During the neurological examination, he was alert and oriented to time, place and person. The Mini-Mental State Examination (MMSE) score was 29. A cranial nerve examination showed mild saccadic slowing, hypomimia and hypophonia. The gag reflex was absent with no other abnormal findings in the soft palate and tongue. The jaw jerk was normal. There were mild bradykinesia and subtle rigidity in the neck and arms; tremors were absent. The finger-to-nose and heel-to-shin test results and postural balance were all normal. He walked with a mild dragging of the left foot without gait freezing. In the levodopa test, the patient showed a modest response to 200 mg levodopa; the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) scores were 21 and 12 in the off and on states, respectively. The coin rotation test showed 14.7 half-turns/10 sec for the right hand and 7.0 half-turns/10 sec for the left hand (data are the means of 3 trials). A videofluoroscopic swallowing examination revealed dysfunction in the oral and pharyngeal phases of swallowing with food material not moving into the esophagus. [^{18}F]FP-CIT PET showed a profound loss of dopamine transporters in the striatum. [^{18}F]FDG PET revealed significant hypometabolism in the frontal cortices without significant asymmetry and no significant changes in the striatum, thalamus, or occipital cortex (Supplementary Figure 1 in the online-only Data Supplement).

Two months later, the patient was hospitalized again due to worsening dysphagia and received a percutaneous endoscopic gastrostomy. In addition to dysphagia, he showed mild cognitive decline, compulsive behavior and visual hallucinations. The MMSE score was 26. The neuropsychological test battery showed impaired verbal fluency and short-term memory with retrieval

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deficits. The visuospatial function was spared. His behavioral symptoms did not improve after the reduction of levodopa/carbidopa/entacapone from 1,000 mg/day to 300 mg/day, which was the only antiparkinsonian drug he was taking. He developed mild vertical gaze palsy with limitations in up- and downgaze.

Two years after the referral, he showed further cognitive decline with an MMSE score 17. Three years after the referral, he died of aspiration pneumonia at the age of 61 years. The final clinical diagnosis was variant PSP.

A general autopsy was performed 2.5 hours after death. The brain weighed 1,250 g before fixation and showed mild frontal and temporal lobe atrophy. There was depigmentation in the substantia nigra and locus coeruleus (Figure 1A). The hippocampus appeared relatively normal. Microscopic examination showed severe neuronal loss and gliosis with extracellular and phagocytosed neuromelanin pigment in the substantia nigra; moderate neuronal loss in the frontal cortex and amygdala; mild neuronal loss in the temporal cortex, hippocampus, caudate nucleus, putamen, globus pallidus, pons, and medulla; and no significant neuronal loss in the parietal and occipital cortices or the thalamus.

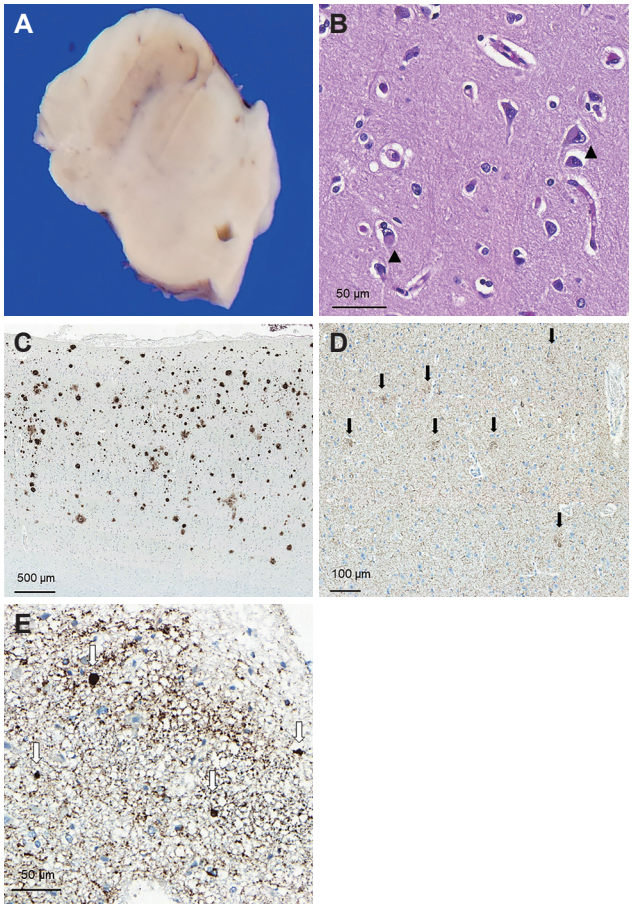

Figure 1. Autopsy findings. A: The macroscopic findings in the midbrain show depigmentation in the substantia nigra. B: The hematoxylin staining in the middle frontal gyrus shows moderate Lewy bodies. C: The immunohistochemical staining of amyloid-β in the parietal cortex shows several amyloid-β plaques. D: The immunohistochemical staining of pTau in the parietal cortex shows moderate to severe neuritic plaques. E: The immunohistochemical staining of α-synuclein in the dorsal motor nucleus of the vagus shows moderate to severe Lewy bodies or Lewy neurites. The black arrowheads indicate the Lewy bodies, the black arrows indicate the neuritic plaques, and the white arrows indicate the Lewy bodies and Lewy neurites.

Immunohistochemistry was performed using antibodies against α-synuclein (CG1656, Cell Applications, San Diego, CA, USA), amyloid-β (4G8, BioLegend, San Diego, CA, USA), pTau (AT8, Thermo Fisher, Waltham, MA, USA), and pTDP-43 (TIP-PTD-M01, Cosmo Bio, Tokyo, Japan). There were widespread Lewy bodies in the neocortical, limbic, basal forebrain, and brainstem regions (Figure 1B). The Lewy body scores, as recommended by the DLB consortium, were 2–3, 3–4, and 1–2 in the neocortical, basal forebrain/limbic, and brainstem regions, respectively. There were several amyloid-β plaques in the cerebral cortex with a few plaques in the cerebellum (Thal stage 5) (Figure 1C) and moderate to severe neurofibrillary tangles and neuritic plaques in the cerebral cortex, including the occipital cortex (Braak stage VI) (Figure 1D). There was a moderate to severe presence of α-synuclein-immunoreactive Lewy bodies and Lewy neurites in the DMV (Figure 1E). TAR DNA binding protein 43 (TDP-43) was not observed in the brain. The neuropathological diagnosis was diffuse neocortical Lewy body disease with Alzheimer neuropathology.

The main finding of this case is that an initial presentation of severe dysphagia preceded definite parkinsonism and dementia. Although the DMV is spared in some cases of Lewy body disease, α-synuclein pathology was evident in this case, suggesting a serious impact of α-synuclein on swallowing.[4] Dysphagia in LBD is attributed to pharyngeal dysfunction mediated by the glossopharyngeal and vagus nuclei.[3] Considering the absence of the gag reflex in this case, the dysphagia might be related to the α-synuclein pathology in the vagus nucleus. A correlation between dysphagia and Lewy body pathologies in the DMV was demonstrated in previous studies; Lewy body pathologies were limited to the brainstem, including the DMV,[5] or were found predominantly in the brainstem.[6] Although AD pathologies were not described in an earlier study,[6] these cases underscore the importance of Lewy body pathologies in the DMV in the development of dysphagia. Because an impaired cortical compensation mechanism was shown to be related to the development of dysphagia in PD, cortical pathology as well as brainstem pathology might have contributed to the development of dysphagia in this case.[7] Further research to investigate the correlation between dysphagia and α-synuclein deposition in the vagal nucleus is required. In summary, an early manifestation of dysphagia with lower brainstem pathology followed by parkinsonism and cognitive decline may represent a topographical

progression of α-synuclein pathology consistent with the Braak staging of Lewy body disease.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.20039.

Conflicts of Interest

The authors have no financial conflicts of interest.

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None

Author Contributions

Conceptualization: Sungyang Jo, Jae-Hong Lee, Chong Sik Lee. Data curation: Sungyang Jo, Soo Jeong Nam. Formal analysis: Sungyang Jo, Soo Jeong Nam, Kye Won Park. Investigation: Sungyang Jo, Soo Jeong Nam, Kye Won Park. Methodology: Chong Sik Lee, Sungyang Jo, Soo Jeong Nam, Kye Won Park. Project administration: Chong Sik Lee. Supervision: Chong Sik Lee, Jae-Hong Lee. Visualization: Soo Jeong Nam. Writing—original draft: Sungyang Jo, Chong Sik Lee. Writing—review & editing: Sungyang Jo, Chong Sik Lee.

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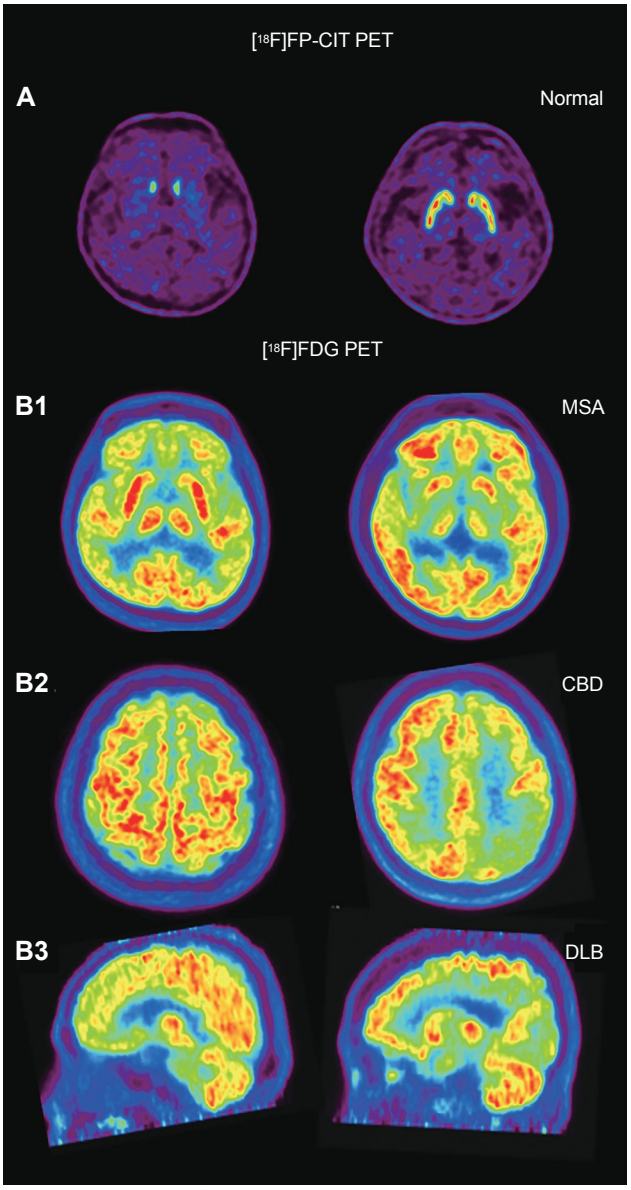

Supplementary Figure 1. [^{18}F] FP-CIT PET and [^{18}F]FDG PET findings of the case compared with healthy control or other atypical parkinsonian disorders. MSA: multiple system atrophy, CBD: corticobasal degeneration, DLB: dementia with Lewy body.