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One Autopsy Proved Neocortical Lewy Body Disease Without the Involvement of the Olfactory Bulb and Brainstem

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ABSTRACT

Lewy bodies (LBs) and Lewy neurites (LNs) are pathological hallmarks of Parkinson's disease (PD) or dementia with LBs (DLB). Incidental Lewy body disease (iLBD) is defined when LBs and LNs are found in the brain of normal elderly individuals. A 65-year-old man presented with autopsy-proven Lewy body pathology (LBP). He had never complained of cognitive impairments or parkinsonian motor symptoms, and he had always maintained independence in activities of daily living. Hypopigmentations in the locus coeruleus and substantia nigra were discovered during the autopsy. The patient showed severe-to-extremely severe LBs in the neocortex and limbic areas, except in the nucleus basalis of Meynert, amygdala, and brainstem, according to microscopic findings. Hence, using several of the previously known staging systems, it was difficult to classify the patient's LBP type. Furthermore, these findings were unique because they had never been observed before in iLBD.

Keywords: Incidental Lewy Body Disease; Parkinson Disease; Lewy Body Dementia; Lewy Bodies; Lewy Neurites; Synucleinopathies

INTRODUCTION

Lewy body dementia (LBD) has been used as a generic or an umbrella term for Parkinson's disease (PD), Parkinson's disease with dementia (PDD), and dementia with Lewy body (DLB).[1-3] The pathological hallmarks of LBD are Lewy bodies (LBs) and Lewy neurites (LNs), which are the pathologic aggregations of α-synuclein (αSyn).[1,2,4-6]

Lewy body pathology (LBP) is found in the brain of elderly individuals with normal neurological function, and this is referred to as incidental Lewy body disease (iLBD).[7-13] iLBD might be a preclinical or presymptomatic PD, PDD, or DLB.[7,9,10]

The Braak staging system (Braak staging) and the DLB consensus criteria (McKeith criteria) are two major LBP staging systems.[2,3,14,15] In the Braak staging of PD, the first two (stages 1 and

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Chung EJ, Kim SJ. Data curation: Hur DY, Kim YS. Formal analysis: Lee KH. Investigation: Lee KH. Methodology: Cho HJ. Writing - original draft: Chung EJ, Cho HJ. Writing - review & editing: Hur DY, Kim YS, Lee KH, Kim SJ.

2) are presymptomatic stage, and they are correlated with iLBD.[11,14,15] In the DLB consensus criteria, the involvement of olfactory bulb alone and LBP predominantly in the amygdala regions indicate a low-likelihood for DLB, or they can be used to assess prodromal LBD.[3,15-18]

Here we report a patient with autopsy-proven LBP findings concentrated in the neocortex. The patient independently performed the activities of daily living until he died. Therefore, he was considered to have an iLBD.

CASE DESCRIPTION

Clinical history

A 65-year-old man died because of cardiac arrest. He had been receiving hemodialysis treatment due to chronic renal insufficiency (CRI). He could independently take prescribed drug doses until he died. He was completely independent in performing activities of daily living. His brain computed tomography only showed diffuse mild cortical atrophy but did not show any hemorrhage or cerebral infarction. In his medical records of regular clinic visits, there were no abnormal neurological symptoms and signs including parkinsonism and/or dementia. After his death, according to an interview with his brother, his global deterioration scale score was appraised as normal.

Neuropathological findings

Gross findings

Autopsy was performed within 12 hours of death. The weight of the whole brain was 1,446 g. Atherosclerotic plaques were observed in the basilar artery. However, there was no infarction or hemorrhage. Moreover, minimal to mild atrophy was observed in the frontal, temporal, and parietal cortex. The substantia nigra (SN) and locus coeruleus (LC) presented with mild hypopigmentation (**Fig. 1A and B**).

Microscopic findings

The distinguishing features of the patient were significant neuronal loss, gliosis, and subtle microvascular proliferation (**Fig. 2A**) with transcortical vacuolation concentrating in cortical layers II and III, which is consistent with global ischemic injury (**Fig. 2B**). Transcortical

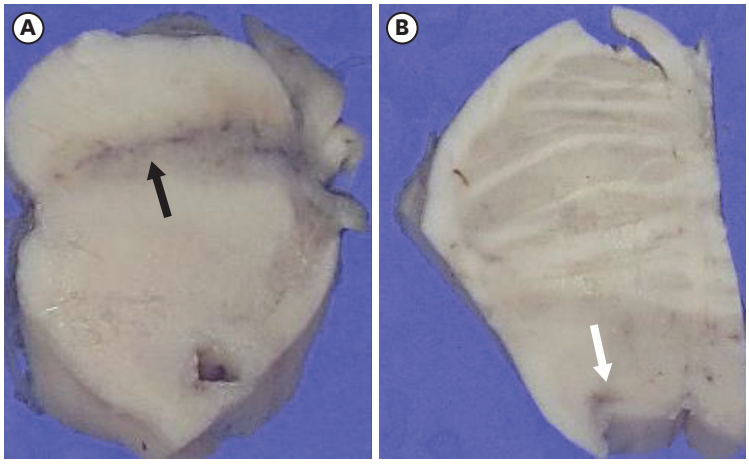

Fig. 1. Gross findings of the brian of the patient. The substantia nigra (black arrow) (**A**) and locus coeruleus (white arrow) (**B**) presented with mild hypopigmentation.

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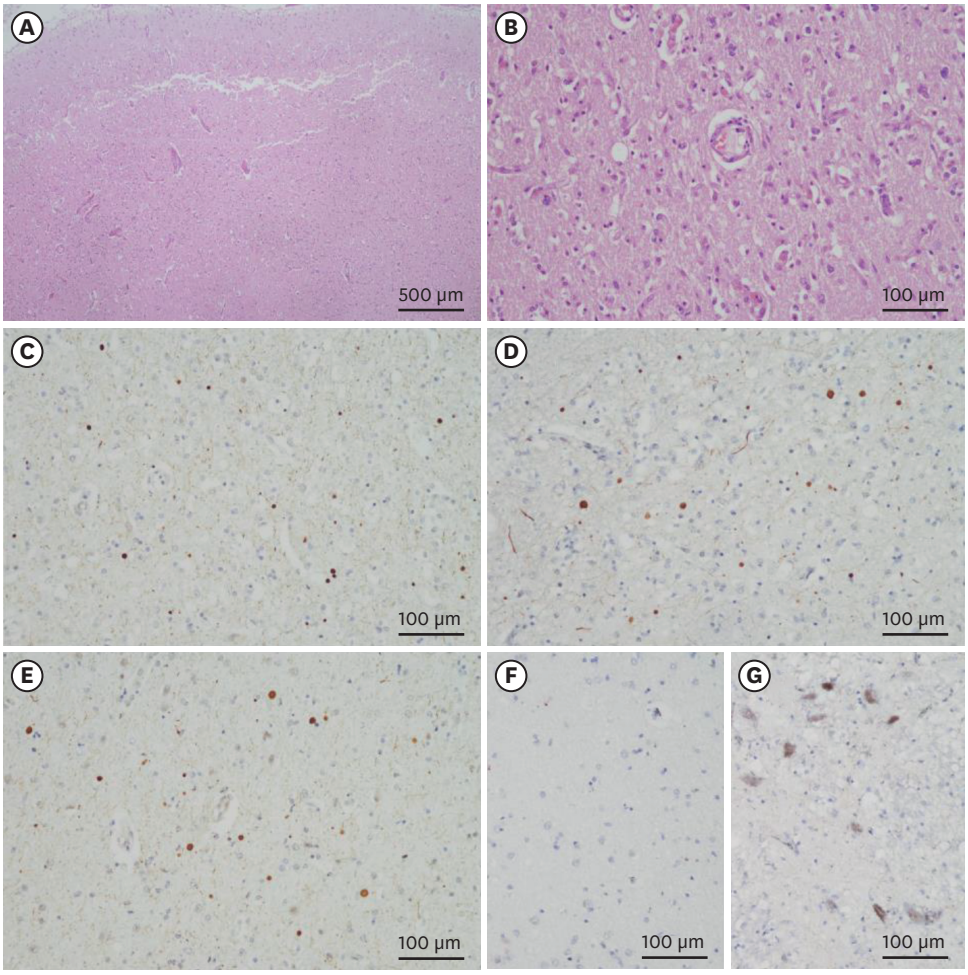

Fig. 2. Histopathological findings of the brain. (**A**) The frontal lobe presented with laminar necrosis and transcortical vacuolation in layers II and III. (**B**) Cortical vacuolation and neuronal dropout were observed at high magnification (**A** and **B**: hematoxylin and eosin staining, original magnification, ×40 and ×200, respectively). IHC of αSyn revealed a worse number of LBs and LNs in the temporal cortex (**C**), cingulate gyrus (**D**), and entorhinal cortex (**E**). However, LBs were not observed in the amygdala (**F**) or midbrain (**G**) (**C-G**, αSyn IHC, original magnification, ×200).
LB = Lewy body, LN = Lewy neurity, IHC = immunohistochemistry, αSyn = α-synuclein.

vacuolation was moderate to severely widespread in the neocortex, but it was mild in the limbic regions (amygdala and transentorhinal/entorhinal) (**Table 1**). However, the disappearance of Purkinje neurons and mild Bergmann gliosis were observed in the cerebellum. Multiple microinfarcts were identified in the frontal cortex, temporal cortex, and midbrain.

Hematoxylin and eosin (H&E) staining did not identify any LBs. However, αSyn immunohistochemistry (αSyn-IHC) revealed very severe LBs and LNs in the temporal (**Fig. 2C**, **Table 1**) and parietal cortex, severe LBs in the frontal cortex, precentral and cingulate gyrus (**Fig. 2D**), and transentorhinal and entorhinal cortex (**Fig. 2E**), and moderate LBs in the hippocampus. However, there were no LBs in the basal forebrain, amygdala (**Fig. 2F**), and brainstem including the SN (**Fig. 2G**) and LC. The definite pathological diagnosis of the patient was LBD, neocortical stage (diffuse LBD), by the DLB consensus criteria.[2,3]

Neurofibrillary tangles were localized sparsely in the entorhinal cortex based on tau immunohistochemistry. β-amyloidopathy was not identified on β-amyloid

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Table 1. Microscopic and immunohistochemical findings of the patient's brain

Locations	Transcortical vacuolation	Neuronal loss and gliosis	Lewy bodies on hematoxylin and eosin staining	α-Synuclein-positive Lewy bodies	Tau-positive neurofibrillary tangles
Frontal cortex	+++	++	0	+++	0
Temporal cortex	+++	++	0	++++	NA
Parietal cortex	+++	++	0	++++	NA
Occipital cortex	++	++	0	NA	NA
Precentral gyrus	+++	++	0	+++	NA
Cingulate gyrus	+++	++	0	+++	NA
Amygdala	+	++	0	0	NA
Hippocampus	0	+	0	++	0
Entorhinal cortex	+	+	0	+++	+
Transentorhinal cortex	+	+	0	+++	++
Ventral striatum	0	+	0	0	NA
Globus pallidus	0	+	0	0	NA
Nucleus basalis of Meynert	0	0	0	0	NA
Thalamus	0	+	0	0	NA
Cerebellum	0	+	0	NA	NA
Substantia nigra	0	+	0	0	NA
Locus coeruleus	0	0	0	0	NA
Medulla oblongata	0	0	0	0	NA
Olfactory bulb	0	+	0	0	NA

0 = not identified, + = mild, ++ = moderate, +++ = severe, ++++ = very severe, NA = not applicable.

immunohistochemistry, which is consistent with definite primary age-related tauopathy (PART).[19] The Alzheimer's disease (AD) neuropathologic changes according to the National Institute on Aging-Alzheimer's Association (NIA-AA) guideline was A0 B1 C0.[19,20] Additional staining of TDP-43 in the hippocampus, entorhinal cortex, and amygdala was performed, and analysis yielded negative results.

Ethics statement

This work was approved by the appropriate Institutional Ethics Committee or Review Board (IRB No. BPIRB 2021-06-023). All procedures during the brain autopsy were performed using the established protocol of the Korean Brain Bank Network under Korea Brain Research Institute (http://www.kbri.re.kr/new/pages_eng/main/) and the proposal guidelines for standardized operative procedures.[21] Autopsy was performed at Inje University Busan Paik Hospital Brain Bank after the families of the patient provided written informed consent.

DISCUSSION

Two types of LBs in LBD are the classical brainstem and cortical LBs.[22] Classical LBs are intraneuronal cytoplasmic inclusion bodies with an eosinophilic core surrounded by a narrow pale stained halo.[6,22,23] Cortical LBs present with eosinophilic and various morphologies without the peripheral halo.[22,23] Generally, H&E staining is adequate for the detection of classical LBs, but not for cortical LBs.[2,6,23,24] Despite many LBs in the neocortex detected by the αSyn-IHC, the H&E staining could not detect LBs in our patient.

Regions with αSyn-positive LBP generally coincide with the areas of neuronal loss and gliosis.[13] However, according to some studies, LBP and neuronal loss are not always linked in a causal chain.[13,25] Incidentally found LBP and neuronal loss in the brainstem of elderly individuals do not usually show abnormal neurological symptoms or signs.[13,26,27] Similarly, our patient showed severe extended transcortical vacuolation, neuronal loss, gliosis, and

αSyn-positive LBP but no abnormal neurological symptoms and signs. CRI and hemodialysis might have masked his neurological deficits. Hemodialysis is one of the risk factors of small-vessel cerebrovascular disease; however, no supporting evidence by multicenter or autopsy-based studies has sufficiently verified this.[28] Therefore, we thought that the hemodialysis-induced vacuolation in our patient was not sufficiently confirmed.

Generally, LBP in PD is restricted to the brainstem and limbic areas, whereas LBP in DLB and PDD is extended to the cerebral cortex.[2,3,5,14,29] In our patient, LBs were intensively observed in the neocortical areas, precentral and cingulate gyri, entorhinal and transentorhinal cortexes, and hippocampus, but none of the LBs were in the globus pallidus, nucleus basalis of Meynert, thalamus, brainstem, amygdala, and olfactory bulb. These patterns of LBP in our patient were closer to those in DLB.

For definitive pathological diagnosis, we used the Braak staging[14] and McKeith criteria.[2,3] They have been using the semi-quantitative scoring of the LBP.[2,3,14] In the Braak staging, LBP initiating in the olfactory bulb and dorsal medulla oblongata progressed to the SN and sequentially to the neocortex via the basal forebrain/limbic areas.[14] The important point was that the inclusion of the basal forebrain and mesocortex before the neocortical involvement of LBP was a prerequisite.[14]

The McKeith criteria added the olfactory bulb only and amygdala-predominant LBP stages to the existing brainstem, limbic, and diffuse neocortex types.[3,17,18] Upon applying the Braak staging and McKeith criteria,[2,3,14] LBP of our patient could still be theoretically categorized as a diffuse neocortical type; however, it was not entirely appropriate because there was no LBP in the lower brain regions. In a previous study,[30] 17% (13 brains) of 76 brains had Lewy body pathologies in a higher region which was absent in a lower region. These fall into two broad groups.[30] First, among those with cortical pathology (limbic, neocortical, or both) but absent α-synuclein (αSyn) in the midbrain or medulla (7 brains, 9%), there were 6 showing predominant neocortical pathology (8%) with very limited involvement (occasional pale bodies, isolated LB, or a few LN) of the amygdala or substantia nigra.[30] Secondly, there was a group of 6 brains (8%) in which LBs were not demonstrable in the limbic areas despite their presence both in a neocortical area and in a brainstem/midbrain area.[30]

Approximately 3.8–23% of elderly individuals with normal neurological function present with LBP, and this is referred to as iLBD.[7-9,12,13,31] Some cases of iLBD have been regarded as preclinical PD suitable for the Braak ascending scheme, and others have been considered preclinical DLB with a remarkable cortical involvement of LBP.[9,10] However, in our patient, it was difficult to determine the LBP type or predict its progression using the previous criteria.[2,3,14]

The most frequently affected regions by LBP in the iLBD were the olfactory bulb, brainstem, and amygdala[7,11,12,18]; the olfactory bulb and medulla were the most common sites of iLBD, followed by the amygdala and pons.[18] Therefore, most iLBDs were classified as brainstem-predominant stage IIa, and several patients were also classified to have limbic-predominant stage IIb.[18] The tentative order within the LB spectrum in a previous study was iLBD, PD-not demented, PDD, DLB, and DLB with AD.[29] Moreover, individuals with iLBD had intermediated nigrostriatal pathological features between pathologically normal individuals and typical PD.[9]

Although only 30% of patients with iLBD progressed to neurodegenerative disorders,[27] LBP had not been always correlated with neurological deficits and was not the definitive maker of neuronal dysfunctions.[32] If pathological aggregations of αSyn extend to the axons and dendrites,

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abnormal neurological deficits can occur ultimately.[13] Therefore, the neocortex, entorhinal/transentorhinal cortex, and cingulate in our patient have not yet been completely destroyed to cause neurological deficits. However, long-term clinical follow-up and neuropathological studies in the elderly are needed because iLBD-related studies are too limited.

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