Case report

Amyloid-beta pathology in a case with dementia with Lewy bodies with a rapidly progressive clinical course similar to Creutzfeldt–Jacob disease

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Abbreviations: Aβ, amyloid-beta; AD, Alzheimer's disease; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; DWI, diffusion-weighted imaging; EEG, electroencephalogram; MIBG, meta-iodobenzylguanidine; MRI, magnetic resonance imaging; NFTs, neurofibrillary tangles; PD, Parkinson's disease; PET, positron emission tomography; PSD, periodic synchronous discharges; RPD, rapidly progressive dementia; RT-QuIC, real-time quaking-induced conversion; SPECT, single photon emission computed tomography.

ABSTRACT

Most cases of dementia with Lewy bodies (DLB) follow a chronic course. However, some cases of rapidly progressive dementia (RPD) are difficult to distinguish from other diseases. Herein, we report how to differentiate DLB presenting with RPD from other diseases and its pathological features, with examples from our own experience. A 70-year-old male with RPD and psychiatric symptoms, including hallucinations and delusions, was transferred to our hospital. We suspected Creutzfeldt-Jakob disease (CJD), but disease-specific tests were all negative. The patient was treated with corticosteroids on the suspicion of an autoimmune condition; however, his symptoms did not improve. Based on the results of nuclear medicine and other tests, we suspected DLB and administered anti-Parkinsonian drugs; however, they were ineffective and the patient died. Brain autopsy revealed extensive deposits of Lewy bodies, which were pathologically diagnosed as DLB. Additionally, extensive deposition of senile plaques was observed; however, neurofibrillary tangles (NFTs) were not prominent. DLB generally presents as a chronic disease. However, some patients with DLB present with RPD; therefore, the differential diagnosis of other diseases, such as CJD, is very important. In addition, although this case was not diagnosed with Alzheimer's disease (AD) due to the lack of NFTs, extensive amyloid deposition was observed in the brain tissue. Previous reports have described cases of RPD with amyloid deposition alone, and in this case too, it is suggested that amyloid deposition may have had a strong influence on the clinical course of RPD.

Keywords: dementia with Lewy bodies, rapidly progressive dementia, Creutzfeldt–Jakob disease, Alzheimer's disease, Amyloid-beta

INTRODUCTION

Rapidly progressive dementia (RPD) is defined as cognitive dysfunction that progresses weekly, monthly, or daily. The causes of RPD are diverse and may include neurodegenerative diseases, infectious diseases, toxic and metabolic disorders, and autoimmune diseases, and diagnosis is often complicated.[1]

Dementia with Lewy bodies (DLB) is a neurodegenerative disease for which progressive cognitive decline, Parkinsonism, visual hallucinations, and extensive Lewy body deposits in the cerebral cortex are recognized as core symptoms. Most cases of DLB have a chronic course; However, some cases present with RPD, and in such cases, it may be difficult to differentiate from other diseases such as Creutzfeldt-Jakob disease (CJD). We experienced a case presenting with RPD and diagnosed with DLB as a result of autopsy, so we report on the clinical course and the pathological background that led to the presentation of RPD.

CASE PRESENTATION

A 70-year-old man was referred to our hospital due to RPD and psychiatric symptoms such as hallucinations and delusions. Before the onset of the symptoms, the patient performed activities of daily living independently and was able to perform personal activities without problems. Six months before his admission to our hospital, he complained of feeling unwell and headaches and had visited

several hospitals; however, no abnormalities were noted. At the same time, he also began to decrease his food intake. Three months before admission, he was admitted to another hospital because he was unable to eat. At the time of admission, he was able to ascend and descend stairs, but gradually began to show psychiatric symptoms such as hallucinations and delusions. The patient was subsequently transferred to the Department of Psychiatry 1 month after admission to our hospital. At this point, he required the assistance of several people to help him stand. Due to the rapid progression of cognitive dysfunction and psychiatric symptoms, the patient was transferred to our hospital for examination and treatment.

The patient had a history of surgery for lumbar disc herniation, but no other medical history or history of head surgery. The patient had no family history of neuromuscular disorders. The patient had no history of alcohol consumption, smoking, or allergies.

He was 168.0 cm tall and weighed 52.0 kg. Vital signs did not show abnormalities. He could say his name, but could not indicate his date of birth, current location, or today's date. He was also disoriented, refused treatment, and exhibited unusual behavior. He presented with visual hallucinations and delusions, which had appeared two months prior to his admission to our hospital. The muscle tone of the extremities was hypertonic. We suspected muscular rigidity but also considered the possibility of paratonia due to the inability to relax the muscles. The patient also presented with myoclonus of the left lower extremity but without obvious paralysis. The patient was unable to follow basic instructions;

86 therefore, it was difficult to assess sensory impairment or ataxia. The patient was unable to stand or
87 walk.

88 Peripheral blood tests revealed a mildly high C-reactive protein level (5.73 mg/dL) and an
89 erythrocyte sedimentation rate (67 mm/h). However, aspiration pneumonia due to food aspiration
90 associated with altered consciousness developed when the patient was transferred to the hospital and
91 improved following antibiotics administration. His blood count, blood sugar, electrolytes, liver
92 function, renal function, thyroid function, and ammonia levels were within the normal ranges. Vitamin
93 B1 levels were within the normal ranges. Antinuclear, anti-TPO, anti-Tg, anti-GAD, and anti-
94 neutrophil cytoplasmic antibodies were negative. Beta-D-glucan and tuberculosis-interferon gamma
95 release assays and common syphilis tests, such as rapid plasma reagin and *Treponema pallidum*
96 hemagglutination assays, were negative.

97 In the cerebrospinal fluid (CSF) test, the lumbar CSF opening pressure was 70 mmH_2O, the
98 number of cells was 6 /μL (lymphocytes, 6; neutrophils, 0), the protein level was 98.5 mg/dL, and the
99 glucose level was 61 mg/dL. CSF culture and cytological results were negative. The CSF
100 phosphorylated tau protein and amyloid-beta (Aβ) 40/42 ratio were not measured.

101 Magnetic resonance imaging (MRI) did not reveal any marked brain atrophy or ventricular
102 enlargement. Diffusion-weighted imaging (DWI) revealed no abnormal hyperintense areas, including
103 the gray matter or the basal ganglia (Fig. 1A). T2-weighted imaging and fluid-attenuated inversion

104 recovery revealed no lesions with abnormal signal intensity (Fig. 1B). Brain MRI was performed
105 several times during hospitalization; however, no abnormal findings were observed.
106 Electroencephalogram (EEG) showed generalized slow waves, but no epileptic waves or periodic
107 synchronous discharges (PSD). Whole-body computed tomography revealed no abnormalities.

108 We considered prion diseases, including CJD, as a potential cause of RPD. Although there were
109 no typical findings, such as a cortical hyperintensity signal on DWI of brain MRI or PSD on EEG, the
110 rapid progression of symptoms and clinical findings, such as myoclonus, were considered undeniable.
111 Tests for CSF total tau protein, 14-3-3 protein, and real-time quaking-induced conversion (RT-QuIC)
112 assays were performed, but all were negative. Analysis of the prion protein gene revealed no mutations.
113 Furthermore, we suspected autoimmune limbic encephalitis due to elevated levels of the CSF protein.
114 On day 4 of hospitalization, the patient was treated with methylprednisolone (1000 mg/day) for 3 days,
115 followed by oral prednisolone; however, his symptoms did not improve. On day 21, the prednisolone
116 treatment was discontinued.

117 Other differential diagnoses include neurodegenerative diseases such as Alzheimer's disease
118 (AD), Parkinson's disease (PD), and DLB. These diseases usually progress slowly but can cause
119 cognitive dysfunction; therefore, we performed various diagnostic tests. Significant hypointensity was
120 observed in bilateral striata on ^{123}I-ioflupane brain single photon emission computed tomography
121 (SPECT), Specific Binding Ratio: the right striatum was 1.21, and the left striatum was 1.12) (Fig.

1C). On ^{123}I- meta-iodobenzylguanidine (MIBG) myocardial scintigraphy, the heart-to-mediastinum (H/M) ratio was low (early H/M ratio 1.47, and delayed H/M ratio, 1.26) and on ^{123}I-IMP SPECT, bilateral medial occipital lobe blood flow was decreased (Fig. 1D). Amyloid positron emission tomography (PET) was not performed. Based on the scintigraphy results, PD and DLB were suspected. We began treatment with 200 mg/day of oral L-dopa and 4.5 mg/day of rotigotine transdermal patches on day 21. Immediately after starting treatment, his psychiatric symptoms and cognitive dysfunction improved slightly. However, he gradually developed difficulty closing his mouth due to oromandibular dystonia and a dislocation of the temporomandibular joint was observed on day 29. We considered these to be extrapyramidal symptoms, so we gradually increased the dose of anti-Parkinson's drugs, eventually using 600 mg/day of L-dopa and 13.5 mg/day of rotigotine; however, the symptoms did not improve. Subsequently, he developed frequent dislocations of the temporomandibular joint, recurrent infections, such as aspiration pneumonia, and a gradually worsening state of consciousness. On day 51, the patient experienced tongue root subsidence and temporary respiratory arrest shortly after dislocation of the temporomandibular joint, which improved with repositioning of the dislocation. Considering the possibility of drug-induced dystonia, the anti-Parkinson's drugs were tapered, but there was no improvement in his oromandibular dystonia or consciousness. He repeatedly stopped breathing and died from suffocation due to tongue root subsidence on day 77.

Diagnostic criteria for DLB include progressive cognitive decline and the presence of at least two

core clinical features, one core clinical feature, and at least one indicative biomarker.[2] The patient had two core clinical features (fluctuating cognition and Parkinsonism) and two indicative biomarkers (reduced dopamine transporter uptake in the basal ganglia, as shown by ^{123}I-ioflupane brain SPECT and low-uptake ^{123}I-MIBG myocardial scintigraphy), indicating probable DLB. However, DLB generally follows a chronic progressive course with an average disease duration of approximately 8.8 years.[3] The patient died approximately eight months after disease onset, which is an atypical course of DLB. Therefore, we performed an autopsy after obtaining the family's consent.

PATHOLOGICAL FINDINGS

On autopsy, the brain weighed 1,040 g. Macroscopic examination revealed cerebral atrophy and depigmentation of the substantia nigra and locus coeruleus (Fig. 2A–D). There were no neoplastic lesions, edema, or congestion on the cerebral surface and no vascular lesions in the main trunk arteries. Hematoxylin and eosin staining revealed neuronal loss and marked Lewy bodies in the brainstem (substantia nigra, locus coeruleus, and dorsal motor nucleus of the vagus nerve), limbic system (transentorhinal cortex and anterior cingulate gyrus), and neocortex (middle frontal and supramarginal gyrus) (Fig. 2E–H). Anti-phosphorylated alpha-synuclein immunohistochemistry revealed intracytoplasmic bodies, neurites, and dots in the raphe nucleus, reticular formation, periaqueductal gray matter, and interbrain (caudate nucleus, putamen, piriform cortex, and insular gyrus), in addition

158 to the above areas (Fig. 2I–K). The Braak Stage was at least 5,[4] while the BBAR Stage was 5.[5]
159 Numerous senile plaques were observed in the substantia nigra, neocortex, entorhinal cortex,
160 hippocampus, insular gyrus, putamen, and caudate nucleus (Fig. 2L–M), but not in the cerebellum.
161 Immunostaining with anti-Aβ antibody showed many diffuse and cored plaques.[6 7 8] Gallyas staining
162 and immunostaining with anti-phosphorylated tau antibody (AT8) immunostaining revealed numerous
163 neurofibrillary tangles (NFTs), pre-tangles, and neuropil threads in the transentorhinal and entorhinal
164 cortices. In the hippocampus, NFTs and threads were not conspicuous, except for CA2[6] (Fig. 2N–O).
165 The ABC score for AD neuropathologic change was A3B1C3, which is "low," indicating that there
166 were no complications from AD pathology.[9] No pathological findings suggestive of CJD were
167 observed.
168 The neuropathological diagnosis was DLB and a neocortical form consistent with the clinical
169 diagnosis. Numerous senile plaque deposits were observed in the brainstem, limbic system, and
170 neocortex; however, AD was not diagnosed.
171
172 **DISCUSSION**
173 Dementia generally progresses chronically from months to years. However, some cases classified
174 as RPD show a much more acute progression. Although there is no clearly written definition of "rapid"
175 and exact definitions vary in practice, it has been stated that RPD progresses monthly, weekly, or daily,

176 with the majority progressing from independence to complete dependence within 1–2 years.[10] The
177 causes of RPD are varied and include neurodegenerative diseases (e.g., DLB, CJD, AD), infectious
178 diseases (e.g., herpes simplex encephalitis, neurosyphilis, progressive multifocal
179 leukoencephalopathy), toxic and metabolic disorders (e.g., uremia, hepatic encephalopathy vitamin
180 B1 deficiency), autoimmune diseases (e.g., autoimmune limbic encephalitis, Hashimoto's
181 encephalopathy, lupus cerebritis), endocrine disorders (e.g., adrenal insufficiency, thyroid disturbances,
182 parathyroid abnormalities), and tumor-related diseases (metastatic brain tumors, intravascular
183 lymphoma, lymphomatoid granulomatosis etc.). Immediate history-taking, examination, and
184 diagnostic treatment are sometimes necessary; however, a definitive diagnosis is difficult to make.[1]
185 Most cases of DLB have a chronic course, but a study reported that in 83 cases with diffuse Lewy
186 body deposits in brain tissue, six patients died within 15 months of onset.[11] Mean age at disease onset
187 was 72.5 years, and mean disease duration was nine months. Onset consisted of delirium in three
188 patients and cognitive decline in the other three. All cases presented visual hallucinations and
189 delusions, cognitive symptoms were fluctuating in two, parkinsonism occurred in four, and myoclonus
190 in three. Compared to this report, this case also followed a similar course. These symptoms make it
191 difficult to clinically distinguish them from CJD. In fact, three of the six patients were clinically
192 diagnosed with CJD, making it difficult to make a differential diagnosis based only on clinical
193 symptoms. In recent years, several studies have reported that t-Tau and 14-3-3 proteins have high

194 specificity in the discrimination of CJD from neurodegenerative diseases such as AD and DLB,[12 13 14]

195 while RT-QuIC has also been shown to be very useful in the detection of CJD, with a sensitivity of

196 90.3% and specificity of 98.5%.[15]

197 In recent years, the concept of prodromal DLB (a condition in which symptoms suggestive of the

198 onset of DLB, such as psychiatric symptoms and sleep disorders, are observed before dementia

199 appears) has been proposed as a means of diagnosing atypical DLB at an early stage [16 17]. Prodromal

200 DLB is classified into three clinical subtypes: mild cognitive impairment, delirium-onset, and

201 psychiatric-onset. This case may match the delirium-onset prodromal DLB. Although it is difficult to

202 distinguish prodromal DLB from other neurodegenerative diseases based on only prodromal

203 symptoms, one of the characteristics of delirium-onset prodromal DLB is that the delirium is

204 prolonged and resistant to treatment [18]. Therefore, as in this case, if symptoms of delirium persist for

205 a long time, it may be better to have a nuclear medicine examination even if cognitive function are

206 maintained to some extent before the onset of the disease.

207 The specific triggers of RPD in DLB are unclear. However, several studies have reported that

208 RPD is often observed in patients with AD pathology, in addition to Lewy body deposition. David

209 reported that the time interval from the onset of motor symptoms to dementia and disease duration

210 (the time interval from the onset to death) was significantly shorter in patients with AD pathology[19 20].

211 The ABC score was used to grade AD pathology. This score is based on the extent and degree of

deposition of Aβ plaques, NFTs, and neuritic plaques and is classified as “not,” “low,” “intermediate,” or “high.” The diagnosis of AD can be pathologically established when the score is “intermediate” or “high.”[9] The present case showed extensive deposition of Aβ plaques and neuritic plaques, but no noticeable deposition of NFTs, and therefore this patient was classified as “low” on the ABC score. This case could not be histologically diagnosed as AD, which differs from the findings of previous reports. However, some case reports of rapidly progressive DLB have reported extensive deposition of senile plaques, but only mild deposition of NFTs.[11, 21] Moreover, compared to DLB with a general course, DLB with RPD was reported to show predominant deposition of soluble Aβ40 and Aβ42 in brain tissue.[21] It suggests that amyloid deposition alone caused rapidly worsening the symptoms of DLB, even if it is not diagnosed as AD or pathology. This case showed extensive amyloid deposition in brain tissue, which could have been the cause of RPD. Among the reports of autopsies on DLB patients who presented with RPD, there are few reports of cases that show abundant amyloid deposition in the brain tissue but lack AD pathology, and this case is considered to be worth reporting.

In addition, although not performed in this case, there are some reports of amyloid PET performed in patients that show a correlation between amyloid deposition and the rate of progression of brain atrophy and cognitive dysfunction[22, 23]. In the future, quantitative evaluation of amyloid levels using imaging and CSF testing could predict the rate of progression of cognitive dysfunction before death. Furthermore, only a high load and the neocortical distribution of alpha-synuclein pathology have been

reported to be involved in disease progression,[24] so further case accumulation is necessary to determine this trend.

In conclusion, DLB presents mainly with a chronic course; however, some patients present with RPD, and therefore this condition should be considered as part of the differential diagnosis. As a differential diagnosis for DLB with RPD, prion diseases, including CJD, are particularly important, and imaging tests such as brain MRI and CSF biomarker tests such as RT-QuIC are useful. DLB patients with AD pathology are more likely to develop RPD, but this case did not fulfill the pathological diagnostic criteria for AD. However, in this case, extensive amyloid deposition was observed in the brain tissue, and in past reports, there have been cases of RPD presenting with only amyloid deposition, so it is possible that amyloid pathology is involved in the progression of cognitive impairment. The possibility that CSF Aβ and amyloid PET are useful for predicting prognosis is also being investigated, therefore, more case studies should be conducted.

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ETHICS STATEMENT:

Informed consent for autopsy including the use of tissues for research purposes was obtained from the patients' families.

Approval of the research protocol: not applicable.

Registry and the Registration No. of the study/trial: not applicable.

Animal Studies: not applicable.

Research involving recombinant DNA: not applicable.

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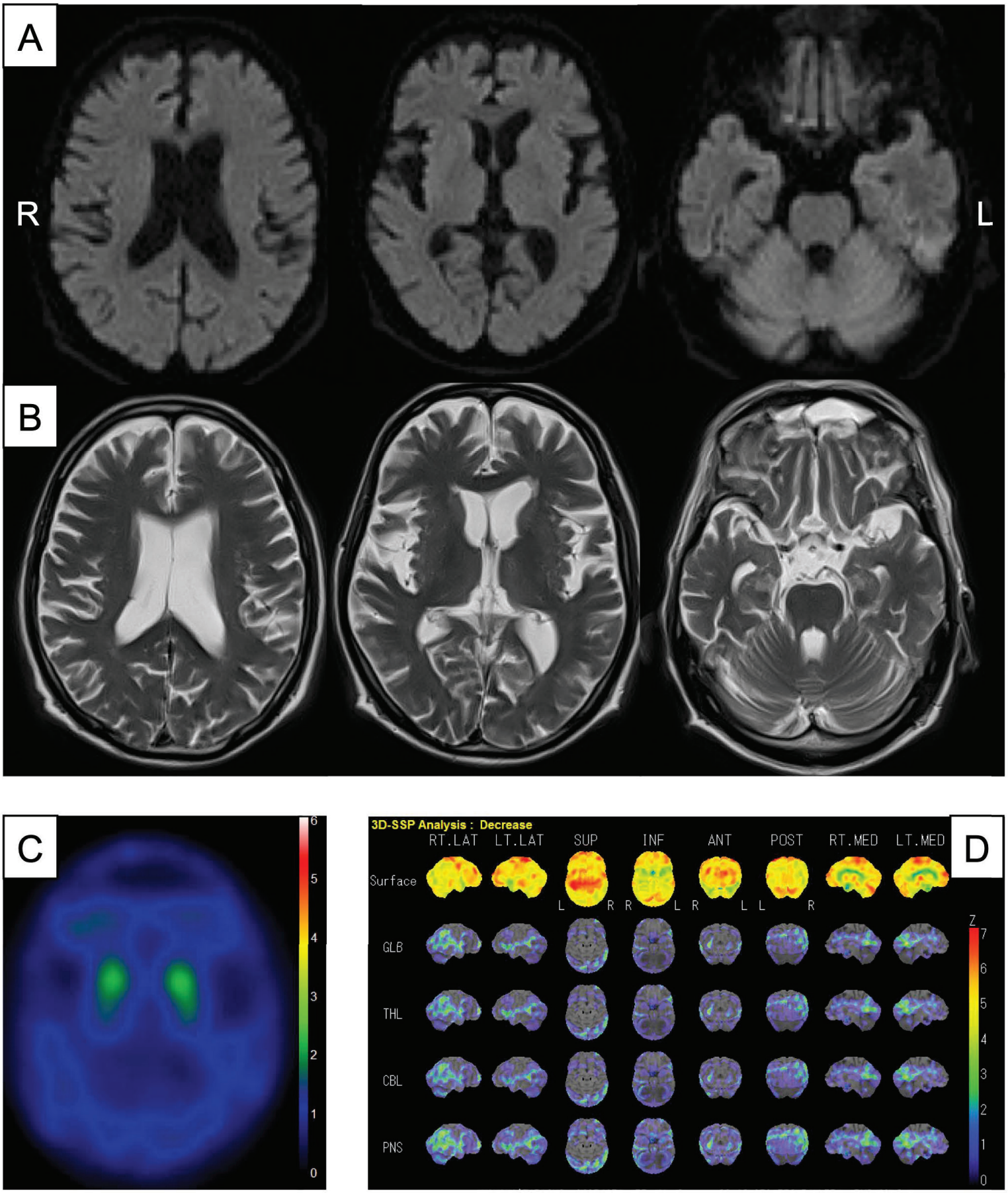
Dr. Shinya Tanaka is an Editorial Board member of Journal of General and Family Medicine and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

FIGURE LEGENDS

Figure 1. A: MRI diffusion-weighted imaging did not reveal any abnormal hyperintensity areas. B: MRI T2-weighted imaging did not reveal any marked brain atrophy, ventricular enlargement, or abnormal hyperintensity areas. C: ^{123}I-ioflupane brain SPECT revealed significant hypointensity in the bilateral striatum (Specific Binding Ratio: the right striatum was 1.21, and the left striatum was 1.12). D: On ^{123}I-IMP SPECT, bilateral medial occipital lobe blood flow decreased.

Figure 2. A–D: Macroscopic findings of the brain. Generalized cerebral atrophy can be observed (A-C). In the brainstem, depigmentation of the substantia nigra can be seen (D). E–O: Microscopic findings of the brain autopsy specimen. On hematoxylin & eosin staining (E–H), neuronal loss and many Lewy bodies are observed in the brainstem, limbic system, and cerebral cortex (E, F: substantia nigra, G: locus coeruleus, H: middle frontal gyrus). Anti-phosphorylated alpha-synuclein immunohistochemistry (I–K) revealed intracytoplasmic bodies, neurites, and dots in many regions (I: substantia nigra, J: locus coeruleus, K: middle frontal gyrus). Immunostaining with anti-Aβ antibody (L, M) shows many diffuse plaques and cored plaques (L: substantia nigra, M: occipital lobe). Gallyas–Braak staining showed neurofibrillary tangles in the entorhinal cortex (N), but few in the hippocampus (O).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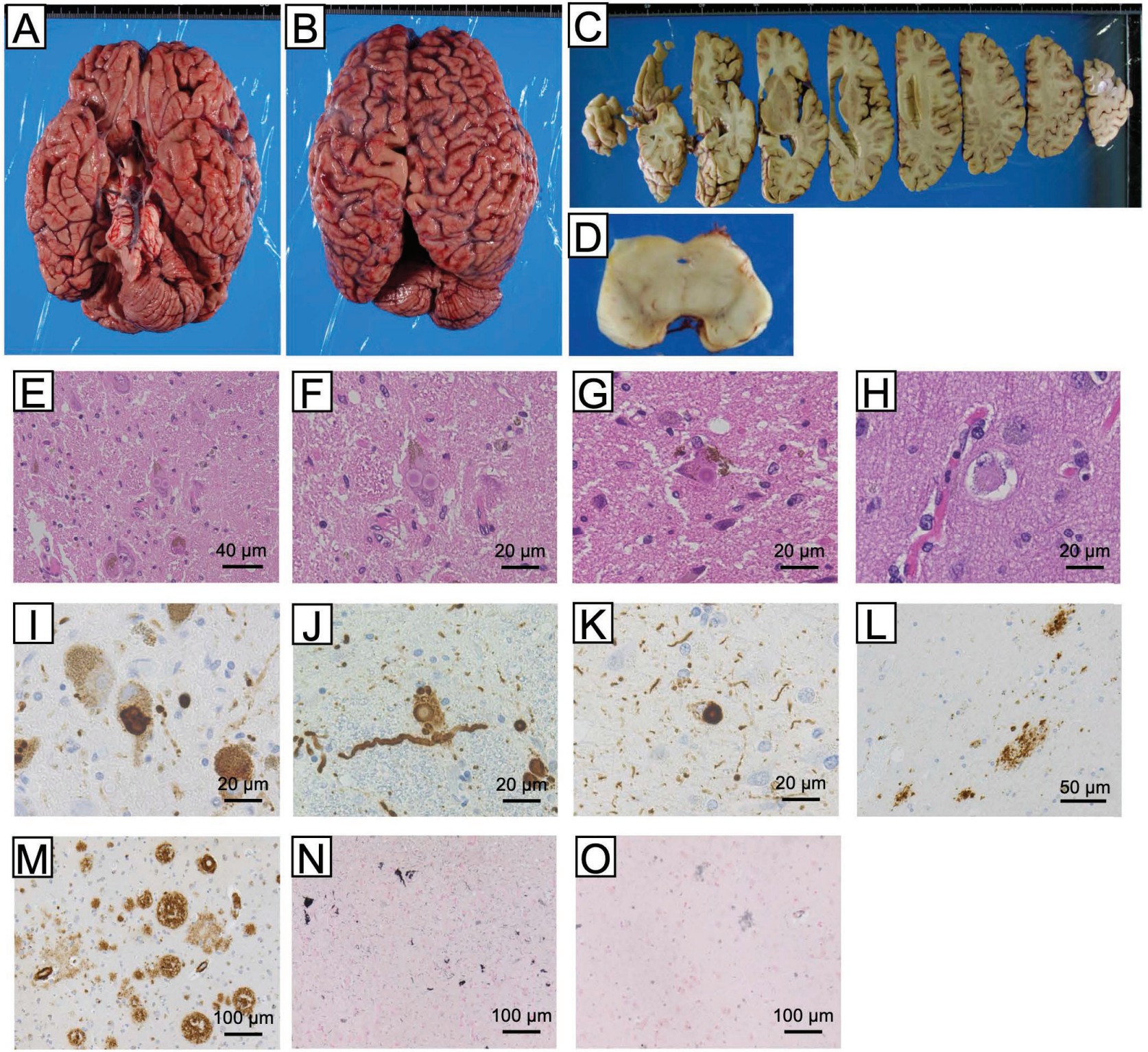
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