

## LETTERS TO THE EDITOR

## CASE REPORT

## Association between clinical symptoms and post-mortem neuropathology in dementia with Lewy bodies

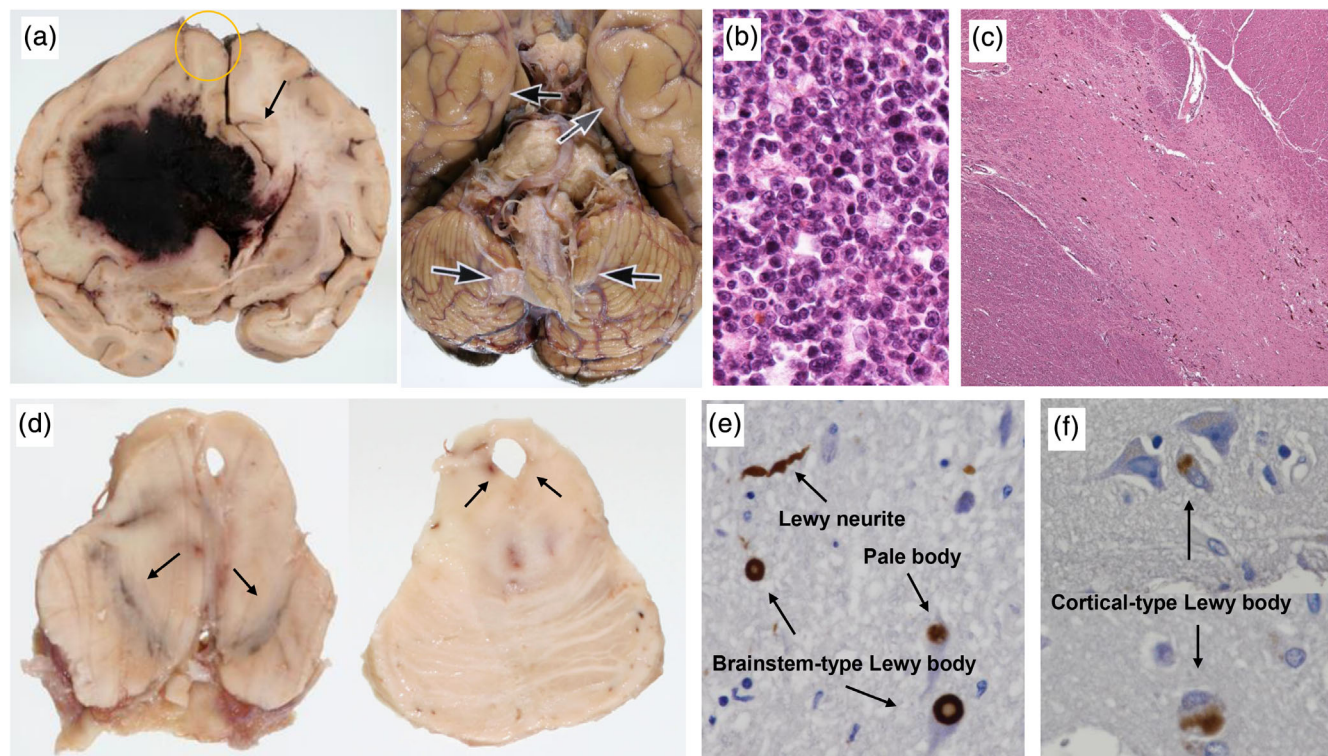
Dear Editor,

The association between clinical symptoms and neuropathological changes in dementia with Lewy bodies (DLB) patients has not been elucidated to date.

We report a case of an 87-year-old man, clinically diagnosed as probable DLB and confirmed as definite DLB on autopsy. Approximately 5 years before his death, his wife noticed that he talked loudly and flapped his upper/lower limbs during his sleep, leading to a diagnosis of rapid eye movement behavior disorder (RBD). Approximately 3 years previously, the patient had noticed forgetfulness, and 1.5 years previously, he recognized occasional visual hallucinations, such as seeing insects on the ceiling, and his Mini-Mental State Examination

score was 26. Neurological examination showed no parkinsonism, including muscle rigidity, tremor, limb paralysis and dysautonomia, such as orthostatic hypotension. Brain perfusion single-photon emission computed tomography showed significant hypoperfusion in the bilateral temporoparietal/medial occipital lobes. There were no cerebral infarctions or hippocampal atrophy on magnetic resonance imaging. (123I)-metaiodobenzylguanidine scintigraphy showed a significant reduction in the heart.

We diagnosed the patient's condition as probable DLB according to the consortium on DLB international workshop criteria,<sup>1</sup> and started donepezil treatment 1.5 years before his death. His visual hallucinations disappeared after donepezil



**Figure 1** Pathological findings of dementia with Lewy bodies on autopsy. (a) Left: Cingulate herniation owing to right frontal lobe tumor hemorrhage and intraventricular perforation was observed (arrow). The area enclosed by a circle was confirmed to be diffuse large B-cell lymphoma; right: uncus and tonsillar herniation owing to right frontal lobe tumor hemorrhage and intraventricular perforation was observed (arrows). (b) Hematoxylin–eosin staining of the area enclosed by a circle in (a) showing diffuse growth of large atypical lymphocytes. (c) Hematoxylin–eosin staining of the substantia nigra showing a mild decrease in the number of pigmented neurons in the low-magnified image. (d) Left: Mild-to-moderate depigmentation in the midbrain substantia nigra was observed (arrow); right: moderate-to-high depigmentation in the pons locus coeruleus was observed. (arrow). (e)  $\alpha$ -Synuclein immunohistochemistry demonstrating Lewy neurites, pale bodies, and brainstem-type Lewy bodies in the vagal nerve dorsal nucleus (arrows). (f)  $\alpha$ -Synuclein immunohistochemistry showing cortical-type Lewy bodies in the superior frontal gyrus (arrows).

administration and never appeared again. His RBD disappeared after starting treatment with a small amount of clonazepam. He did not show significant progression of cognitive decline nor any parkinsonism during the follow-up period.

Three years before his death, the patient was diagnosed with systemic diffuse large B-cell lymphoma by biopsy analysis of his inguinal lymph nodes. Despite repetitive relapse and remission, his condition entered complete remission after chemotherapy. However, he eventually presented left upper/lower limb hemiparesis and was admitted to Tokyo Medical University Hospital, Tokyo, Japan. Magnetic resonance imaging showed diffuse large B-cell lymphoma lesions in the central nervous system 2 months before his death, and he died of tumor hemorrhage and tonsillar herniation.

Autopsy showed a macroscopically large hemorrhagic lesion in the right frontal lobe, extending into the intraventricular space (Fig. 1a). Microscopically, invasion of diffuse large B-cell lymphoma cells was observed (Fig. 1b), but not in the non-central nervous system areas, including the lymph nodes. Regarding Parkinson's disease-associated pathology, mild-to-moderate depigmentation in the midbrain substantia nigra and moderate-to-high depigmentation in the pons locus coeruleus were observed (Fig. 1c,d). Lewy bodies (LB) were observed mainly in the vagal nerve dorsal nucleus (Fig. 1e), locus coeruleus, substantia nigra and limbic cortex, including the mammillary body and parahippocampal gyrus, whereas there were just two LB in the superior frontal gyrus of the neocortex (Fig. 1f). According to pathological diagnostic criteria for DLB,<sup>1</sup> semiquantitative evaluation scores were as follows: amygdala, vagus nerve dorsal nucleus, 2–3; locus coeruleus, substantia nigra, entorhinal cortex, 2; nucleus basalis of Meynert, 0–1; and anterior cingulate cortex, middle temporal gyrus cortex, middle frontal gyrus cortex and inferior parietal cortex, 0. Furthermore, few  $\alpha$ -synuclein deposits in the cardiac sympathetic nerve and ileocecum parasympathetic nerve, and substantially decreased expression of tyrosine hydroxylase were observed. Regarding Alzheimer disease pathology, we observed neurofibrillary tangles (Braak stages III–IV) and amyloid (Braak stage B), in accordance with the National Institute on Aging-Reagan diagnostic criteria.<sup>2</sup>

We considered that the lack of significant progression of the patient's cognitive decline was associated with the transition of his condition from brainstem-predominant to marginal-type DLB. This is also probably why he did not show any parkinsonism, although the mild-to-moderate depigmentation in the substantia nigra might be associated with compensatory mechanisms, such as increased dopamine turnover in the striatum and hypersensitivity of dopamine receptors.<sup>3</sup> Although orthostatic hypotension is a clinical feature of cardiovascular autonomic dysfunction,<sup>4</sup> the reason he did not show orthostatic hypotension might be associated with the few  $\alpha$ -synuclein deposits in the cardiac sympathetic nerve. RBD was reported to be associated with LB formation in the pons and medulla oblongata, which controls rapid eye movement sleep.<sup>5</sup> We believe the patient's RBD was associated with LB in the vagus nerve dorsal nucleus and locus coeruleus. RBD was recently shown to be associated with reduced myocardial (123)I-metaiodobenzylguanidine uptake, which is consistent with the present findings.<sup>6,7</sup> Visual hallucinations were reported to be associated with LB pathology, not in the primary visual area, but in the pulvinar nucleus of the thalamus and lateral geniculate nucleus.<sup>8,9</sup> We did not observe any LB in those areas, but his visual hallucinations might be associated with cholinergic deficits, because administration of donepezil had a significant effect. Finally, as an association between DLB and lymphoma has never been reported, we believe his comorbidities occurred coincidentally.


Our present case shows the importance of understanding the clinicopathological heterogeneity of DLB for considering appropriate treatment and care.

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## Disclosure statement

The authors declare no conflict of interest.

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