\Box REVIEW ARTICLE \Box

Diffuse Lewy Body Disease

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Diffuse Lewy body disease (DLBD) has been studied from various viewpoints, and although clinical diagnostic criteria for DLBD have been proposed, the diagnosis remains difficult. It has been reported that DLBD is the second most frequent degenerative dementia among the elderly, following Alzheimer-type dementia. Many DLBD cases, however, are clinically misdiagnosed. Therefore, the search for diagnostic markers for DLBD must continue. Very recently, "dementia with Lewy bodies" (DLB) was proposed as a generic term including DLBD and similar disorders. Cortical Lewy bodies are the most important pathological marker for diagnosis of DLB. At this time, however, the mechanism of cortical Lewy body formation is yet to be disclosed. (Internal Medicine 37: 6–10, 1998)

Key words: Diffuse lewy body disease, lewy body, dementia

Introduction

Diffuse Lewy body disease (DLBD) has received much attention following a series of reports by Kosaka who was the first to describe in detail the characteristics and distribution of cortical Lewy bodies (1). He also proposed "diffuse Lewy body disease" as a designation for a particular type of Lewy body disease (2). DLBD is now categorized into two forms: a common form and a pure form (3). The common form of DLBD is distinguished from the pure form by the presence of senile plaques and neurofibrillary tangles of varying degree in the cerebral cortex. The common form typically affects the elderly, while the pure form can also sometimes occur at ages younger than 40 years. Similar terminology has been proposed by some researchers, such as Lewy body dementia [Gibb et al (4)], senile dementia of Lewy body type [SDLT, Perry et al (5)] and Lewy body variant of Alzheimer's disease [LBV, Hansen et al (6)]. Among them, the neuropathological criteria for the diagnosis of DLBD are the most strict and demand the presence of more than 5 or 10 cortical Lewy bodies in a ×100 visual field in H.E. or ubiquitin-immunostained preparations of their predilection sites, respectively (7). Less frequent cortical Lewy bodies are present in the cerebral cortex in SDLT. At least one cortical Lewy body seems to be necessary for the diagnosis of LBV. There is still some confusion regarding the disease states that these terms actually represent. Therefore, in the first International Workshop on Lewy Body Dementia held in Newcastle upon Tyne in October 1995, the generic term "Dementia with Lewy Bodies" (DLB) was proposed to include the disorders mentioned above. The results of this workshop were reported in detail in 1996 (8) and 9). In this article, I will review recent reports of DLBD or DLB.

Frequency of DLBD

Several American and English groups have recently demonstrated that DLB is the second most common form of dementia (12.0–24.7%), following Alzheimer-type dementia (ATD) in the elderly (10–12). Kosaka and Iseki (7) carried out a clinicopathological study of 79 elderly patients with dementia who had died in a geriatric hospital in Japan. They found that DLBD (15.4%) was the second most frequent degenerative dementia in the elderly, with the most frequent being the ATD (43.6%). Ince et al (13) also reported that 6 (8.5%) of 69 patients with dementia, who had been pathologically examined in Oslo, had SDLT, suggesting that DLB is as frequent among the elderly of Scandinavia as it is in Europe and USA.

Clinical Aspects

Kosaka et al (14) and McKeith et al (15) reviewed the clinical aspects of DLBD and SDLT, respectively. Recently, Louis et al (16) compared clinical features of 8 DLBD cases, which were pathologically diagnosed on the basis of Kosaka's criteria (3), with clinical features of 20 pathologically diagnosed cases of Parkinson's disease (PD). According to their results, DLBD patients had an earlier mean age at onset than PD patients (57 and 64 years, respectively). However, Kosaka (3) found in a review of 92 cases with the common form of DLBD that onset had occurred later with a mean of 66.7 years. Louis et al suggested that DLBD patients presenting with cognitive changes. In fact, in most patients with the pure form of DLBD, whose initial symptom was parkinsonism, the age of onset was younger than 40 years (3). The mean duration of

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disease (12–13 years) was almost identical for DLBDA and PD patients. This is longer than the duration (mean, 6 years) of the reviewed DLBD cases. Louis et al (16) explained this in terms of a later onset of cognitive changes in their DLBD cases. The male: female ratio is 1.7: 1 in DLBD.

The main clinical symptoms of DLBD are progressive cortical dementia and parkinsonism, although the latter is absent in about 30% of common form DLBD patients (3). Cognitive impairment usually precedes parkinsonism. However, in some patients with the common form and in most younger patients with the pure form of DLBD, parkinsonism precedes dementia.

Although tremor is a rather uncommon feature of DLBD (3, 14), it was noted by Louis et al (16) in 57% of DLBD and 75% of PD patients. Rigidity is more frequent than tremor in DLBD. Bradykinesia is also common in DLBD. Visual hallucination and persecutive delusions are also frequently present.

Very recently, clinical diagnostic criteria for DLB have been proposed by the CDLB International Workshop group (Table 1)(8). Sahgal et al (17) investigated the differences in visuospatial memory between mildly demented SDAT (senile dementia of Alzheimer type) and DLB patients and suggested that the differences between these two groups of dementia patients were not due to a specific mnemonic impairment, but reflected a dysfunction in non-mnemonic processes mediated by the fronto-

Table 1. Consensus Criteria for the Clinical Diagnosis of Probable and Possible "Dementia with Lewy Bodies" (8)

- 1. The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.
- 2. Two of the following core features are essential for a diagnosis of probable DLB, and one is essential for possible DLB:
 - a. Fluctuating cognition with pronounced variations in attention and alertness
 - b. Recurrent visual hallucinations that are typically well formed and detailed
 - c. Spontaneous motor features of parkinsonism
- 3. Features supportive of the diagnosis are
 - a. Repeated falls
 - b. Syncope
 - c. Transient loss of consciousness
 - d. Neuroleptic sensitivity
 - e. Systematized delusions
 - f. Hallucinations in other modalities
- 4. A diagnosis of DLB is less likely in the presence of
 - a. Stroke disease, evident as focal neurologic signs or on brain imaging
 - b. Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

subcortical circuits, which are more severely damaged in DLB patients.

Neuropathology

The most characteristic neuropathological feature is the presence of numerous Lewy bodies in the cerebral cortex and amygdala as well as in the brain stem and diencephalon nuclei including the substantia nigra, locus ceruleus and basal nucleus of Meynert (1, 2). Therefore, Kosaka et al (2) proposed the term "Lewy body disease", and classified it into three types: a brain stem type, a transitional type and a diffuse type. The brain stem type of Lewy body disease is equal to PD, and the diffuse type is called DLBD.

Cortical Lewy bodies occur in small neurons of the deep cortical layers. Their predilection sites are the temporal, cingulate, insular and frontal cortices (1). The brain stem and diencephalon pathology is consistent with that of PD. Kosaka (1) was the first to describe the frequent appearance of Lewy bodies in the amygdala, and Iseki et al (18) provided a detailed description of their distribution in this structure, showing that they are preferentially present in the medial parts of the accessory basal nucleus and the basal nucleus.

As mentioned above, Kosaka (3) classified DLBD into two forms: a common form and a pure form. In the common form of DLBD there are senile plaques and neurofibrillary tangles of various degrees, while in the pure form no or few senile changes are found. Since Kosaka et al (19) reported the first case of combined DLBD and ATD in 1976 and Hansen et al (6) proposed the term LBV in 1990; the concurrence of DLB and ATD has been frequently found (20).

Neuropathological studies on the pathogenesis of DLB have been recently performed using immunohistochemical methods. Several studies have focused on the nature of Lewy bodies or Lewy body-containing neurons in DLB. Using double immunostaining with an antibody to ubiquitin and SmI32, an antibody directed against non-phosphorylated neurofilaments, Wakabayashi et al (21) showed that cortical Lewy-containing neurons were pyramidal cells. In addition, Smith et al (22) detected granular and fragmented pyramidal neurons in DLB with the antibody SmI32. Furthermore, Nishiyama et al (23) showed that Lewy bodies in PD are immunostained with an antibody against Cu/Zn superoxide dismutase.

Another neuropathological feature specific to DLBD is ubiquitin-positive neurites found in CA_{2-3} areas which were first described by Dickson et al (24). Kim et al (25) showed that these CA_{2-3} ubiquitin-positive neurites frequently coexist with cortical Lewy bodies. Kosaka and Iseki (7) observed the same ubiquitin-positive neurites not only in the CA_{2-3} areas but also in the parahippocampal cortex, amygdala and basal nucleus of Meynert. In addition, Iseki et al (18) found many ubiquitinpositive spheroids in the central amygdaloid nucleus of all DLBD cases studied.

Spongiform change in the entorhinal cortex is also usually present in DLB cases. This was first described by Hansen et al (26). Very recently, Iseki et al (27) pointed out that the vacuoles

derive from degeneration of terminal axons of the large pyramidal neurons of the transentorhinal cortex.

Kosaka et al (28) reported an interesting case of a new type of DLB which they referred to as a "cerebral type of Lewy body disease". Their patient presented with progressive cortical dementia without parkinsonism. The main neuropathological feature in this case was the presence of numerous cortical Lewy bodies in the cerebral cortex and amygdala with evidence of pathological aging. PD pathology was not present in the brain stem. Therefore, they added the cerebral type to the other three types of Lewy body disease. Thus, DLBD can be said to fall within the spectrum of Lewy body disease, but not within the spectrum of ATD (7).

Biochemistry

Perry et al (29), using autoradiography to examine highaffinity nicotine binding, detected the presence of CNS $\alpha_4 \beta_2$ nicotine receptor subunits in DLB brains. The high density of nicotine binding in the pars compacta of the substantia nigra and the dorsolateral tegmentum was significantly reduced in both DLB and PD. Binding in the granular layer of the hippocampus was decreased in DLB and ATD. The normally dense bands of bound receptor in the presubiculum and parahippocampal gyrus were diminished in ATD but not in DLB. In the temporal neocortex of ATD brains, there was reduced binding throughout the cortical layers, but in DLB brains, this was only noted in the lower cortical layers where Lewy bodies are concentrated. Mantle et al (30) used biochemical techniques to measure the levels of activity of the lysosomal proteases, cathepsins B, D, H and L, and dipeptidyl aminopeptidases I and II in the frontal cortex and white matter of control subjects and patients with ATD, DLB and PD. Although there were no significant differences in activity among the protease types in tissue from the controls or patients with ATD, DLB or PD, dipeptidyl aminopeptidase H activity was reduced in DLB and PD cases. Since this was not apparent in ATD, they suggested that this reduction may be related to the presence of Lewy bodies. According to a biochemical study by Scott et al (31) who examined the glutamate/aspartate uptake system in brain samples from ATD, DLBD and non-demented control patients, the density of D-[³H] aspartate binding sites was significantly lower in both dementia groups, but within each group differences were not significant.

Molecular Biology

Some recent investigations have revealed that the apolipoprotein E (ApoE)- ε 4 allele, which has been linked to ATD, is also overrepresented in LBV or DLBD. Lippa et al (32) examined the ApoE genotype in DLBD cases (4 with the pure form, 14 with the common form with pathological aging but not combined with ATD, and 22 with the common form with ATD). The apoE allele frequencies in the DLBD with pathological aging group were as follows: ε 2, 0.18; ε 3, 0.57 and ε 4, 0.25. Frequencies in the DLBD plus ATD group were 0.14, 0.64 and

0.22. It is noteworthy that three of the four pure DLBD cases were of the ApoE ϵ 3/3 genotype, while only one had the ApoE ϵ 3/4 genotype. The mean β -amyloid plaque density was lower in ApoE ϵ 3/3 cases than in the groups with the ApoE ϵ 2 or ApoE ϵ 4 allele, and CA₂₋₃ neuritic degeneration was greater in those with the ApoE ϵ 4 allele. These data are consistent with the hypothesis that the ApoE genotype may affect neuropathology in DLBD. In addition, the presence of ApoE genotype was not related to the density of Lewy bodies, suggesting that this genotype may not have a major direct effect on Lewy body formation. Kawanishi et al (33) also examined the ApoE genotype in 14 pathologically diagnosed DLBD cases, and reported similar results in the ApoE allele frequencies.

Saitoh et al (34) studied 44 cases of LBV to determine the incidence of the cytochrome P450 CYP2D6 (debrisoquine 4-hydroxylase) mutant B allele which is a susceptibility gene for PD. As a result, they reported a higher representation of this allele in LBV than in pure ATD or in non-ATD without Lewy bodies. Therefore, it is likely that the CYP2D6B allele is a risk factor for both PD and LBV, but not for ATD.

Cytochrome oxidase (complex IV) is the terminal complex of the mitochondrial respiratory chain which generates ATP by oxidative phosphorylation. Some recent reports have documented reduced cytochrome oxidase activity in ATD brains. Chagnon et al (35) measured cytochrome oxidase activity in ATD, DLB with SDAT, and PD brains. A significant reduction in activity was found in the frontal and parietal cortex of SDAT cases, but no statistically significant differences could be observed in AD, DLB with SDAT, or PD patients, although DLB patients exhibited a small reduction in cytochrome oxidase activity in the frontal and parietal cortex. In the substantia nigra, no significant differences could be measured between PD, ATD and DLB. No correlation was noted between cytochrome oxidase activity and the number of senile plaques or neurofibrillary tangles.

GAP-43 is a growth-associated calmodulin-binding phosphoprotein and substrate for protein kinase C. According to a study by de la Monte et al (36), end-stage ATD brains exhibited reduced neuronal expression but increased glial cell levels of GAP-43mRNA and protein. Similar neuronal abnormalities were also found in DLBD, Pick's disease and PD. These findings suggest that common mechanisms exist in their respective cascades of neurodegeneration.

Very recently, Iwatsubo et al (37) succeeded in the purification of Lewy bodies from 10 DLBD brains, and found that the LB112, an antibody against the purified Lewy bodies, recognized poly-ubiquitin chains specifically. This suggested that Lewy bodies contain poly-ubiquitin chains. In addition, it was reported by Spillantini et al (38) that α -synuclein is an important component of Lewy bodies.

Treatment

Supersensitivity to conventional neuroleptics is common in DLB patients which makes treatment of behavioral and psychotic symptoms problematic. Allen et al (39) reported that low

doses of risperidone produced useful antipsychotic effects in three patients with clinically diagnosed DLB, without imposing substantial side effects. On the other hand, McKeith et al (40) described neuroleptic sensitivity to risperidone in three patients with DLB. Since risperidone is a strong D₂ receptor antagonist and might be expected to provoke neuroleptic sensitivity reactions in DLB patients, they recommend drugs with a lower degree of D₂ antagonism for DLB patients. It was recently reported by Perry et al (41) that neuronal damage in the nucleus basalis of Meynert and reduction in neocortical choline acetyltransferase activity are more severe in SLDT patients than in patients with pure ATD. Furthermore, it was shown in a preliminary report by Levy et al (42) that tacrine has a more marked effect on LBV patients than on those with pure ATD. Therefore, Liberini et al (43) hypothesized that the subgroups of ATD patients who respond positively to the administration of tacrine are patients affected by DLB irrespective of their ATD diagnosis.

References

- Kosaka K. Lewy bodies in cerebral cortex. Report of three cases. Acta Neuropathol (Berl) 42: 127, 1978.
- Kosaka K, Yoshimura M, Ikeda K, Budka H. Diffuse type of Lewy body disease. Progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree – a new disease? Clin Neuropathol 3: 185, 1984.
- 3) Kosaka K. Diffuse Lewy body disease in Japan. J Neurol 237: 197, 1990.
- Gibb WRG, Esiri MM, Lees AJ. Clinical and pathological features of diffuse cortical Lewy body disease (Lewy body dementia). Brain 110: 1131, 1987.
- 5) Perry RH, Irving D, Blessed G, et al. Senile dementia of Lewy body type. A clinically and neuropathologically distinct type of Lewy body dementia in the elderly. J Neurol Sci **95:** 119, 1990.
- Hansen L, Salmon D, Galasko D, et al. The Lewy body variant of Alzheimer's disease: A clinical and pathological entity. Neurology 40: 1, 1990.
- Kosaka K, Iseki E. Diffuse Lewy body disease within the spectrum of Lewy body disease. in: Dementia with Lewy bodies, Perry R, McKeith I, Perry E, Eds. Cambridge University Press, Cambridge, 1996, p. 238.
- McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. Neurology 47: 1113, 1996.
- Perry R, McKeith IG, Perry E. Dementia with Lewy Bodies. Clinical, Pathological, Treatment Issues. Cambridge University Press, Cambridge, 1996.
- Dickson DW, Crystal H, Mattiace LA, et al. Diffuse Lewy body disease: light and electron microscopic immunocytochemistry of senile plaques. Acta Neuropathol (Berl) 78: 572, 1989.
- Burns A, Luthert P, Levy R, et al. Accuracy of clinical diagnosis of Alzheimer's disease. Brit Med J 301: 1026, 1990.
- Galasko D, Hansen LA, Katzman R, et al. Clinical-neuropathological correlations in Alzheimer's disease and related dementias. Arch Neurol 51: 888, 1994.
- 13) Ince PG, McArthur FK, Bjertness E, et al. Neuropathological diagnoses in elderly patients in Oslo: Alzheimer's disease, Lewy body disease, vascular lesions. Dementia 6: 162, 1995.
- 14) Kosaka K, Mark MH, Sage JI. Diffuse Lewy body disease. in: Practical Neurology of the Elderly. Sage JI and Mark MH, Eds. Marcel Dekker, New York, Basel, Hong Kong, 1996, p. 697.
- McKeith IG, Galasko D, Wilcock GK, et al. Lewy body dementia. Diagnosis and treatment. Brit J Psychiatry 167: 709, 1995.

- 16) Louis ED, Goldman JE, Powers JM, et al. Parkinsonian features of eight pathologically diagnosed cases of diffuse Lewy body disease. Mov Disord 10: 188, 1995.
- 17) Sahgal A, McKeith IG, Galloway PH, et al. Do differences in visuospatial ability between senile dementia of the Alzheimer and Lewy body types reflect differences solely in mnemonic function? J Clin Exp Neuropsychol 17: 35, 1995.
- 18) Iseki E, Odawara T, Suzuki K, et al. A pathological study of Lewy bodies and senile changes in the amygdala in diffuse Lewy body disease. Neuropathology 15: 112, 1995.
- Kosaka K, Oyanagi S, Matsushita M, et al. Presenile dementia with Alzheimer-, Pick- and Lewy-body changes. Acta Neuropathol (Berl) 36: 221, 1976.
- 20) Odawara T, Iseki E, Kosaka K, et al. Incidence and distribution of senile plaques and neurofibrillary tangles in late-onset diffuse Lewy body disease. Neuropathology 14: 7, 1994.
- Wakabayashi K, Hansen LA, Masliah E. Cortical Lewy body-containing neurons are pyramidal cells: laser confocal imaging of doubleimmunolabeled sections with anti-ubiquitin and SMI32. Acta Neuropathol (Berl) 89: 404, 1995.
- 22) Smith MC, Mallory M, Hansen LA, et al. Fragmentation of the neuronal cytoskeleton in the Lewy body variant of Alzheimer's disease. Neuroreport 6: 673, 1995.
- 23) Nishiyama K, Murayama S, Shimizu J, et al. Cu/Zn superoxide dismutaselike immunoreactivity is present in Lewy bodies from Parkinson disease: a light and electron microscopic immunocytochemical study. Acta Neuropathol (Berl) 89: 471, 1995.
- 24) Dickson DW, Ruan D, Crystal H, et al. Hippocampal degeneration differentiates diffuse Lewy body disease (DLBD) from Alzheimer's disease: light and electron microscopic immunocytochemistry of CA₂₋₃ neurites specific to DLBD. Neurology **41:** 1402, 1991.
- 25) Kim H, Gearing M, Mirra SS. Ubiquitin-positive CA2/3 neurites in hippocampus coexist with cortical Lewy bodies. Neurology 45: 1768, 1995.
- 26) Hansen L, Masliah E, Terry RD, et al. A neuropathological subunit of Alzheimer's disease with concomitant Lewy body disease and spongiform change. Acta Neuropathol (Berl) 78: 194, 1989.
- 27) Iseki E, Li F, Kosaka K. Close relationship between spongiform change and ubiquitin-positive granular structures in diffuse Lewy body disease. J Neurol Sci 146: 53, 1997.
- 28) Kosaka K, Iseki E, Odawara T, et al. "Cerebral type of Lewy body disease" – A case report. Neuropathology 16: 72, 1996.
- 29) Perry EK, Morris CM, Court JA, et al. Alteration in nicotine binding sites in Parkinson's disease, Lewy body dementia and Alzheimer's disease: possible index of early neuropathology. Neuroscience 64: 385, 1995.
- 30) Mantle D, Falkous G, Ishiura S, et al. Comparison of cathepsin protease activities in brain tissue from normal cases and with Alzheimer's disease, Lewy body dementia, Parkinson's disease and Huntington's disease. J Neurol Sci 131: 65, 1995.
- Scott HL, Tannenberg AE, Dodd PR. Variant forms of neuronal glutamate transporter sites in Alzheimer's disease cerebral cortex. J Neurochem 64: 2193, 1995.
- Lippa CF, Smith TW, Saunders AM, et al. Apolipoprotein Egenotype and Lewy body disease. Neurology 45: 97, 1995.
- 33) Kawanishi C, Suzuki K, Odawara T, et al. Neuropathological evaluation and apolipoprotein E gene polymorphism analysis in diffuse Lewy body disease. J Neurol Sci 136: 140, 1996.
- 34) Saitoh T, Xia Y, Chen X, et al. The CYP2D6B mutant allele is overrepresented in the Lewy body variant of Alzheimer's disease. Ann Neurol 37: 110, 1995.
- 35) Chagnon P, Betard C, Robitaille Y, et al. Distribution of brain cytochrome oxidase activity in various neurodegenerative diseases. Neuroreport 6: 711, 1995.
- 36) de la Monte SM, Ng SC, Hsu DW. Aberrant GAP-43 gene expression in Alzheimer's disease. Am J Pathol 147: 934, 1995.
- 37) Iwatsubo T, Yamaguchi H, Fujimuro M, et al. Purification and characterization of Lewy bodies from the brains of patients with diffuse Lewy body

disease. Am J Pathol 148: 1517, 1996.

- 38) Spillantini MG, Schmidt ML, Lee VML, et al. α-synuclein in Lewy bodies. Nature 388: 839, 1997.
- 39) Allen RL, Walker Z, O'Ath PJ, et al. Risperidone for psychotic and behavioural symptoms in Lewy body dementia. Lancet 346: 185, 1995 (letter).
- 40) McKeith IG, Ballard CG, Harrison RW. Neuroleptic sensitivity to risperidone in Lewy body dementia. Lancet **346**: 699, 1995 (letter).
- Perry EK, Haroutunian V, Davis KL, et al. Neocortical cholinergic activities differentiate Lewy body dementia from classical Alzheimer's disease. Neuroreport 5: 747, 1994.
- 42) Levy R, Eagger S, Griffiths M, et al. Lewy bodies and response to tacrine in Alzheimer's disease. Lancet **343:** 176, 1994 (letter).
- 43) Liberini P, Memo M, Spano P. Lewy body pathology and heterogeneity of Alzheimer's disease. JAMA **274**: 1199, 1995 (letter).