Review

Lewy body disease and dementia with Lewy bodies

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Abstract: In 1976 we reported our first autopsied case with diffuse Lewy body disease (DLBD), the term of which we proposed in 1984. We also proposed the term “Lewy body disease” (LBD) in 1980. Subsequently, we classified LBD into three types according to the distribution pattern of Lewy bodies: a brain stem type, a transitional type and a diffuse type. Later, we added the cerebral type. As we have proposed since 1980, LBD has recently been used as a generic term to include Parkinson’s disease (PD), Parkinson’s disease with dementia (PDD) and dementia with Lewy bodies (DLB), which was proposed in 1996 on the basis of our reports of DLBD.

DLB is now known to be the second most frequent dementia following Alzheimer’s disease (AD).

In this paper we introduce our studies of DLBD and LBD.

Keywords: Lewy body disease (LBD), diffuse Lewy body disease (DLBD), dementia with Lewy bodies (DLB), Parkinson’s disease (PD), Parkinson’s disease with dementia (PDD)

1. Introduction

We1) proposed the term Lewy body disease (LBD) in 1980. LBD is now understood as a generic term that includes Parkinson’s disease (PD), Parkinson’s disease with dementia (PDD) and dementia with Lewy bodies (DLB).2)3) Many dementia specialists, however, misunderstand the relationship between LBD and DLB. Therefore, we propose to explain the concept of LBD and DLB from an historical point of view.

2. Proposal of DLBD and LBD

James Parkinson reported detailed clinical symptoms of paralysis agitans in 1817, and Charcot proposed the term of Parkinson’s disease in 1868. The neuropathology of PD, however, remained unknown, till Fritz Heinrich Lewy,4) who studied the neuropathology of PD at Munich University, described eosinophilic intracytoplasmic inclusions in the dorsal vagal nuclei and substantia innominata of PD brains in 1912. These inclusions were later called “Lewy bodies” by Tretiakoff5) in 1919, and he pointed out for the first time the importance of nigral degeneration in PD. From the 1920s to the 1950s, the differences between PD and postencephalitic parkinsonism were discussed not only clinically, but also neuropathologically. For example, Hassler6) reported the differences in distribution of neuronal cell loss in the substantia nigra between these two diseases in 1939. It was not, however, until 1953 that Greenfield and Bosanque7) revealed that Lewy bodies were always found in the brain stem nuclei in PD, while neurofibrillary tangles were present in postencephalitic parkinsonism. Bethlem and Den Haltog Jager8) (1960) reported the detailed distribution of Lewy bodies in both the central and autonomic nervous systems.

Thus, the neuropathological basis of PD was established in the 1950s. Since then, it has been widely believed that only rare Lewy bodies are found in the cerebral cortex.

In 1976 we9) reported an autopsied case with progressive dementia and parkinsonism, in which I myself was the physician in charge. At that time, I clinically diagnosed the case as atypical presenile Alzheimer’s disease with parkinsonism, and the autopsy was done on the patient. I found numerous intracytoplasmic eosinophilic inclusions in small neurons at the deeper cortical layers and typical
Lewy bodies in the brain stem nuclei (Fig. 1), in addition to the Alzheimer pathology. I also found similar pathological findings in another older patient with depression, persecutive delusions, mild dementia and mild parkinsonism. In 1978, we reported the features of cortical Lewy bodies in comparison with brain stem type of Lewy bodies in our three autopsied cases. In addition, we also found and reported two German autopsied cases, when I was at the Max-Planck Institute for Psychiatry in Munich. These were the first autopsied cases with DLBD in Europe. In 1980, we proposed the term “Lewy body disease (LBD)” based on our 20 autopsied cases. Subsequently, we classified LBD into three types: type A (brain stem type), type B (transitional type) and type C (diffuse type). The brain stem type of LBD is consistent with PD, and the diffuse type was later called “diffuse Lewy body disease (DLBD)”. In 1996, we added a cerebral type of LBD, in which Lewy pathology was widely present in the cerebral cortex, but rare in the brain stem. In this case, no Parkinsonian symptoms were detected in any of the clinical stages.

LBD is now defined as follows: “LBD is a chronic progressive neuropsychiatric disorder, which is clinically characterized by Parkinson symptoms of presenile or senile, or sometimes younger onset, often followed by dementia at the later stages. Case by case, progressive dementia or various kinds of psychiatric symptoms including characteristic visual hallucination and delusions are the chief symptoms, frequently followed by Parkinson symptoms. It is neuropathologically characterized by numerous Lewy bodies and neurites (Lewy pathology), and neuronal cell loss in the central and autonomic nervous systems”. Yoshimura, one of my colleagues, reconfirmed our study of LBD, when he was in Vienna, and proposed the term DLBD in 1983. Based on 11 autopsied cases with the diffuse type of LBD, we also proposed the term “diffuse Lewy body disease (DLBD)” in 1984.

DLBD was defined as follows: “DLBD is characterized clinically by progressive dementia and Parkinson symptoms of presenile or senile, or sometimes younger onset, and neuropathologically by numerous Lewy bodies and neuronal cell loss in the central and autonomic nervous systems, frequently followed by various degrees of Alzheimer pathology”.

3. Proposal of DLB

Since we emphasized in our paper of 1984 that DLBD had been overlooked in European and American countries, many autopsied cases with DLBD were also reported in those countries. Furthermore, in 1990 I indicated in my review of 36 autopsied DLBD cases reported in Japan that
DLBD could be classified into two forms: a common form and a pure form, and that the clinical features differed in the two forms. In the common form, the onset was usually older than 65 years (presenile or senile onset), and the chief symptom was cognitive impairment, followed by parkinsonism in 70% of the cases, while no parkinsonism was detected in 30% of the cases. On the other hand, in the pure form, the onset was usually younger and the initial symptom was usually parkinsonism followed by dementia. Thereafter, when I was invited to the 150th Annual Meeting of the German Psychiatry Association, on the basis of a comparative study between Japanese and European-American autopsied cases with DLBD, I reported that no apparent differences of the clinical features in the common form were present between the two groups, but that in the pure form the Japanese cases had much younger onset and parkinsonism preceded dementia, while most European-American cases were of presenile or senile onset and dementia preceded parkinsonism. Perry et al. (1990) proposed “senile dementia of the Lewy body type”, and Hansen et al. (1990) proposed the term “Lewy body variant of Alzheimer’s disease”. In 1995, the first International Workshop on DLB was held in New Castle upon Tyne in England. The title of my lecture was “Diffuse Lewy body disease within the spectrum of Lewy body disease”. In this international workshop the term “dementia with Lewy bodies (DLB)” was proposed. The results of the Workshop were reported in Neurology in 1996. At that time, the clinical and pathological guidelines for DLB (CDLB guidelines) were published, and the clinical diagnosis of DLB became possible. Thereafter, clinical studies of DLB have been developed further.

4. Recent advances of DLB studies

The Second International Workshop on DLB was held in Amsterdam in 1998, and the results of the workshop were published in 1999. The Third Workshop was again held in New Castle upon Tyne in 2003, and the CDLB guidelines-Revised were published in 2005. A symposium of “A cross-road at DLB and PDD” was held in Washington in 2005, and the results were published in 2007. In 2006, the fourth International Workshop on DLB and PDD were held in Yokohama, Japan. Since 2007, I have held the Japan DLB Research Meeting in Yokohama every November. In the Second Japan Annual Meeting, I organized the DLB Family Association in Japan. In the USA, the LBD Organization was established mainly for DLB families in 2005. In 2012 we published the “Front Line of DLB Research in Japan”,

Over the last 18 years, many important reports on DLB have been published. For example, DLB has been reported to be the second most frequent dementia following AD. Some biological markers for the diagnosis of DLB have also been developed, such as brain SPECT/PET, dopamine transporter imaging (FP-CIT SPECT or DaT scan), and MIBG myocardial scintigraphy. Alpha-synuclein gene mutations were found in familial PD and DLB from 1997 to 2004. Alpha-synuclein was found to be the main component of Lewy bodies in 1997. Alpha-synuclein is a 140 amino acid protein encoded by the SNCA gene, rich in nuclei and presynaptic areas, but its function has not yet been understood. In 2000, the real alpha-synuclein-positive inclusions were first identified in transgenic animals. Braak et al. hypothesized that Lewy pathology initiated in the brain stem and propagated upward to the cerebral cortex in PD. However, the cerebral type of LBD, in which numerous Lewy bodies were found in the cerebral cortex despite there being only a few in the brain stem nuclei, suggests the possibility that Lewy pathology occurs in the cerebral cortex and propagates downward to the brain stem. Lewy pathology may also start from Auerbach’s plexus of the lower esophagus or the olfactory bulb. Recently, the possibility that aggregation of alpha-synuclein could spread trans-cellulary throughout the brain in a prion-like way has been discussed.

Some therapeutic trials on galantamine and donepezil in DLB patients have been reported. Recently, PD, PDD and DLB have usually been called Lewy body disease, the term we have been using since 1980.

We expect that the mechanism of alpha-synuclein aggregation will be elucidated, and that an effective therapy for LBD will be developed in the near future.

References

1) Kosaka, K., Matsushita, M., Oyanagi, S. and Mehraein, F. (1980) Clinicopathological study of Lewy body disease. Psychiat. Neurol. Jap. 82, 292–311 (in Japanese).

2) McKeith, I.G., Dickson, D.W., Lowe, J., Emre, M., O’Brien, J.T., Feldman, H., Cummings, J., Duda, J.E., Lippa, C., Perry, E.K., Aarsland, D., Arai, H., Ballard, C.G., Boeve, B., Burn, D.J., Costa, D., Del Ser, T., Dubois, B., Galasko, D., Gauthier, S., Goetz, C.G., Gomez-Tortosa, E., Halliday, G.,
1) Kosaka, K., Yoshimura, M., Ikeda, K. and Budka, H.
2) Kosaka, K., Iseki, E., Odawara, T. and Yamamoto, T.
3) Lippa, C.F., Duda, J.E., Grossman, M., Hurtig, H.I.,
   Duda, J.E., Grossman, M., Hurtig, H.I.,
   Lippa, C.F., Duda, J.E., Grossman, M., Hurtig, H.I.,
4) Bethlem, J. and Den Haltog Jager, W.A. (1960) The
5) Tretiako
6) Hassler, R. (1938) Zur Pathologie der Paralysis
7) Green
8) Kosaka, K., Oyanagi, S., Matsushita, M. and Hori,
9) Kosaka, K., Mehaein, P. (1979) Dementia-
10) Kosaka, K. (1978) Lewy bodies in cerebral cortex;
11) Kosaka, K., Iseki, E., Odawara, T. and Yamamoto, T.
12) Kosaka, K., Lee, V.M.Y., Lees, A., Litvan, I.,
13) Kosaka, K., Yoshimura, M., Kalaria, R.N.,
14) Yoshimura, M. (1983) Cortical changes in the
15) Kosaka, K. (1990) Diagnosing and managing of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65, 1863–1872.
16) Kosaka, K. (1992) Differential diagnosis, treatment, molecular pathology, and biomarkers. Neurology 68, 812–819.
17) Kosaka, K. (1996) Diffuse Lewy body disease within the spectrum of Lewy body disease. In Dementia with Lewy bodies. Clinical, Pathological and Treatment Issues (eds. Perry, R., McKeith, I. and Perry, E.). Cambridge University Press, Cambridge.
18) Perry, R., McKeith, I. and Perry, E. (1990) Clinical and pathological entity. Neurology 40, 1–8.
19) Hansen, L., Salmon, D., Galasko, D., Masliah, E.,
20) Perry, R.H., Irving, D., Blessed, G., Blessed, G.,
21) McKeith, I.G., Galasko, D., Kosaka, K., Perry, E.K.,
22) Kosaka, K. and Iseki, E. (1996) Diffuse Lewy body disease within the spectrum of Lewy body disease. In Dementia with Lewy bodies. Clinical, Pathological and Treatment Issues (eds. Perry, R., McKeith, I. and Perry, E.). Cambridge University Press, Cambridge.
23) Japan DLB Research Association (2012) The
24) Aarsland, D., Rongve, A., Piepenstock Nore, S.,
25) Walker, Z., Jaros, E., Walker, R.W.H., Lee, L.,
26) Hansen, L.A., Hardy, J., Iwuatsubo, T., Kalaria, R.N.,
27) Kosaka, K. (1978) Lewy bodies in cerebral cortex;
28) Kosaka, K., Iseki, E., Odawara, T. and Yamamoto, T.
29) Kosaka, K., Lee, V.M.Y., Lees, A., Litvan, I.,
30) Hansen, L., Salmon, D., Galasko, D., Masliah, E.,
31) Kosaka, K., Oyanagi, S., Matsushita, M. and Hori,
26) Yoshita, M., Taki, J. and Yamada, M. (2001) A clinical role for [123I]MIBG myocardial scintigraphy in the distinction between dementia of the Alzheimer’s type and dementia with Lewy bodies. J. Neurol. Neurosurg. Psychiatr. 71, 583–588.

27) Polymeropoulos, M.H., Lavedan, C., Leroy, E., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E.S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Di Iorio, G., Golbe, L.I. and Nussbaum, R.L. (1997) Mutation in the \( \alpha \)-synuclein gene identified in families with Parkinson’s disease. Science 276, 2045–2047.

28) Singleton, A.B., Farrer, M., Johnson, J., Singleton, A., Hague, S., Kachergus, J., Hulihan, M., Maraganore, D., Adler, C., Cookson, M.R., Muerer, M., Baptista, M., Miller, D., Blancato, J., Hardy, J. and Gwinn-Hardy, K. (2003) \( \alpha \)-synuclein locus triplication causes Parkinson’s disease. Science 302, 841.

29) Farrer, M., Kachergus, J., Forno, L., Lincoln, S., Wang, D.-S., Hulihan, M., Maraganore, D., Gwinn-Hardy, K., Wszolek, Z., Dickson, D. and Langston, J.W. (2004) Comparison of kindreds with Parkinsonism and \( \alpha \)-synuclein genomic multiplication. Ann. Neurol. 55, 174–179.

30) Spillantini, M.G., Schmidt, M.L., Lee, V.M.Y., Trojanowski, J.Q., Jakes, R. and Goedert, M. (1997) \( \alpha \)-synuclein in Lewy bodies. Nature 388, 839–840.

31) Feany, M.B. and Bender, W.W. (2000) A dorsophila model of Parkinson’s disease. Nature 404, 394–398.

32) Masliah, E., Rockenstein, E., Weinbergs, I., Mallory, M., Hashimoto, M., Takeda, A., Sagara, Y., Sisk, A. and Mucke, L. (2000) Dopaminergic loss and inclusion body formation in \( \alpha \)-synuclein mice implications for neurodegenerative disorders. Science 287, 1265–1269.

33) Braak, H. and Del Tredici, K. (2008) Nervous system pathology in sporadic Parkinson disease. Neurology 70, 1916–1925.

34) Wakabayashi, K., Takahashi, H., Takeda, S., Ohama, E. and Ikuta, F. (1988) Parkinson’s disease: the presence of Lewy bodies in Auerbach’s and Meissner’s plexuses. Acta Neuropathol. 76, 217–221.

35) Sengoku, R., Saito, Y., Bemura, M., Hatsuta, H., Sakiyama, Y., Kanemaru, K., Araiz, T., Sawabe, M., Tanaka, N., Mochizuki, H., Inone, K. and Murayama, S. (2008) Incidence and extent of Lewy body-related alpha-synuclein in aging human olfactory bulb. J. Neuropathol. Exp. Neurol. 67, 1072–1083.

36) Visanji, N.P., Brooks, P.L., Hazrati, L.N. and Lang, A.E. (2013) The prion hypothesis in Parkinson’s disease: Braak to the future. Acta Neuropathol. Commun. 1, 2.

37) Luk, K.C., Kehm, V.M., Zhang, B., O’Brien, P., Trojanowski, J.Q. and Lee, V.M.Y. (2012) Intracerebral inoculation of pathological \( \alpha \)-synuclein initiates a rapidly progressive neurodegenerative \( \alpha \)-synucleinopathy in mice. J. Exp. Med. 209, 975–986.

38) Masuda-Suzukake, M., Nonaka, T., Hosokawa, M., Oikawa, T., Arai, T., Akiyama, H., Mann, D.M.A. and Hasegawa, M. (2013) Prion-like spreading of pathological \( \alpha \)-synuclein in mice. Brain 136, 1128–1138.

39) McKeith, I., Del Ser, T., Spano, P., Emre, M., Wesnes, K., Anand, R., Ciecin-Suin, A., Ferrara, R. and Spiegel, R. (2000) Efficacy of rivastigmine in dementia with Lewy bodies: a randomized, double-blind, placebo- controlled international study. Lancet 356, 2031–2036.

40) Mori, E., Ikeda, K. and Kosaka, K. (2012) Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. Ann. Neurol. 72, 41–52.

41) Ikeda, M., Mori, E., Kosaka, K., Iseki, E., Hashimoto, M., Matsukawa, N., Matsuo, K., Nakagawa, M. on behalf of the Donepezil-DLB Study Investigators (2013) Long-term safety and efficacy of donepezil in patients with dementia with Lewy bodies: Results from a 52-week, open-label, multi-center extension study. Dement. Geriatr. Cogn. Disord. 36, 229–241.

42) Kosaka, K. (2000) Diffuse Lewy body disease. Neuropathology 20 (Suppl.), 73–78.

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Profile

Kenji Kosaka graduated from Kanazawa University School of Medicine in 1965. When he belonged to Nagoya University Department of Psychiatry, he began his clinical and neuropathological researches in dementing illnesses. In 1976, when he was in Tokyo Research Institute of Psychiatry, he reported the first autopsied case with dementia with Lewy bodies (DLB). In 1978 he also reported “Lewy bodies in cerebral cortex”, based on his three autopsied cases. In 1979, when he was in Max Planck Institute of Psychiatry (Munich), he reported two German autopsied cases with DLB, which were the first autopsied cases of DLB in Europe. In 1980 after he returned to Tokyo Research Institute, he proposed the concept of Lewy body disease, which contained Parkinson disease (PD) and DLB. Furthermore, he proposed the term “diffuse Lewy body disease (DLBD)” in 1984. Then, he insisted that DLBD had been missed in European and American countries. Furthermore, he reported the paper “Diffuse Lewy body disease in Japan”. Then, he classified the common form and the pure form of DLBD. Since then, DLBD have been paid attention in European countries. In 1995 the first International Workshop on DLB was held in England. He held the fourth International Workshop on DLB and PDD. Since then, he has continued active enlightenments on DLB in Japan. Otherwise, he also proposed two other dementias: diffuse neurofibrillary tangles with calcification (DNNT) in 1987 and “Limbic neurofibrillary tangle dementia” (LNTD) in 1984.

He is now the Emeritus Professor in Yokohama City University. On behalf of the discovery of DLB he was given “Asahi Prize” in 2013.