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Dementia-Parkinsonism Syndrome With Numerous Lewy Bodies and Senile Plaques in Cerebral Cortex

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Summary. Five cases of age range 62—72 years with progressive dementia and muscular rigidity are reported and discussed from the clinicopathologic point of view.

The neuropathology of these cases was characterized by the widespread occurrence of Lewy bodies (LB) in the CNS as well as the presence of senile changes. The presence of numerous LB in the cerebral cortex and basal ganglia was especially characteristic, although their distribution pattern in the diencephalon and brain stem was identical to that found in paralysis agitans. On the other hand, the presence of senile changes in the cerebral cortex was almost identical to the neuropathology of senile dementia or Alzheimer's disease.

Nosologically, the present cases may represent either a combination of atypical paralysis agitans with senile dementia and Alzheimer's disease, or a new disease.

Key words: Dementia-Parkinsonism syndrome – Lewy body – Senile changes.

Zusammenfassung. Fünf Fälle (3 Männer, 2 Frauen) von progressiver Demenz mit Muskelrigor im Alter von 62—72 Jahren werden beschrieben und mit ihren klinischen und neuropathologischen Befunden diskutiert.

Die Neuropathologie dieser Fälle ist charakterisiert durch zahlreiche Lewy-Körper in den Nervenzellen und senile Veränderungen im Zentralnervensystem. Typisch ist vor allem das Vorkommen vieler Lewy-Körper in der Hirnrinde (besonders Pyramidenzellen der 5. und 6. Rindenschichten) und den Stammganglien, während die Verteilung in Zwischenhirn und Hirnstamm dem Vorkommen bei der Paralysis agitans entspricht. Die senilen Veränderungen der Hirnrinde entsprechen etwa denen der senilen Demenz oder der Alzheimerschen Krankheit.

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Es bleibt offen, ob die Fälle nosologisch eine Kombination von atypischer Paralysis agitans mit seniler Demenz und Morbus Alzheimer oder eine neue Krankheit sind.

Schlüsselwörter: Demenz – Parkinson-Syndrom – Lewy-Körper – Senile Hirnveränderungen.

Introduction

We have previously reported three presenile or senile cases with progressive dementia and muscular rigidity, the neuropathology of which revealed the presence of numerous Lewy bodies (LB) in the cerebral cortex and brain stem and of senile plaques diffusely distributed in the cerebral cortex (Kosaka et al., 1976; Kosaka, 1978).

At the Max-Planck-Institute for Psychiatry (Munich) we studied 20 cases of paralysis agitans light-microscopically in detail and found two which resembled the ones previously reported. In this paper we described these two cases and discuss all five cases from the clinicopathologic viewpoint in comparison with another four cases reported elsewhere in the literature.

Case Reports

Cases 1, 2, and 3 were previously reported by one of us (Kosaka et al., 1976; Kosaka, 1978) (Tables 1 and 2).

Case 4 (MPI 226/75). The patient was a 72-year-old female, whose anamnesis and family history were not remarkable. At the age of 70, forgetfulness and disturbance of concentration were noticed and thereafter the memory disturbance progressed gradually. She was hospitalized at the age of 72 because of exacerbation of the complaints. The initial physical and psychiatric examination disclosed severe dementia, remarkable muscular rigidity of all extremities with mild hand tremor, and high fever. The laboratory examinations including routine blood tests, urine analysis, liquor tests, radiographs, and fundus oculi revealed no noticeable abnormalities except for leucocytosis (8025) and accelerated erythrocyte sedimentation rate (50/78 mm). About 2 months after admission she died of pulmonary abscess and right ventricular heart failure. Total duration of her illness was about 2 years.

Postmortem examination revealed pulmonary abscess and pulmonary infarction with emboli in the pulmonary arteries.

Neuropathologic Findings

Gross. The brain weighed 1120 g after 10% formalin fixation. There was moderate diffuse cerebral atrophy with accentuation in the frontal region. On coronal section of the brain there was no remarkable change except for moderate gyral atrophy with mild dilatation of the lateral ventricle.

Light Microscopy. Two groups of outstanding findings were identified. The first was the presence of LB in the cerebral cortex and basal ganglia as well as in the brain stem and diencephalon. The LB in the cerebral cortex ('cerebral type of LB'), which had ill-defined contours without clear halos and central cores in

Table 1. Clinical data of our five and another similar cases

	Age	Sex	Duration of illness (years)	Initial symptoms	Dementia[a]	Rigidity[a]	Tremor[a]	Miscellaneous
Case 1	65	F.	9	Memory disorder involuntary movement of neck	+3	+2	0	Clinical diagnosis: unclassified presenile dementia
Case 2	62	M.	5	Memory disorder	+3	+3	0	Quadriparesis in flexion and akinetic mutism at the terminal stage
Case 3	70	M.	2¼	Depressive-paranoic state	+1	+1	+1–0	Sudden death in acute renal insufficiency
Case 4	72	F.	2	Memory disorder	+3	+3	+1	
Case 5	65	M.	>12	Psychotic state	+1?	+3	—	Clinical diagnosis: schizophrenia and paralysis agitans
Okazaki et al. (1961)	69	M.	7	Memory disorder	+2	+3	0	The rigidity was regarded as quadriparesis in flexion
	70	M.	—	Memory disorder	+2	+3	0	The rigidity was regarded as quadriparesis in flexion
Kono et al. (1976)	68	F.	13	Hand tremor bradykinesia dizziness	+3	+2	+2	Clinical diagnosis: paralysis agitans with idiopathic orthostatic hypotension
Ikeda et al. (1978)	38	M.	8	Gait disturbance bradykinesia	0	+3	0	Clinical diagnosis: paralysis agitans

[a] +3–severe; +2–moderate; +1–mild; 0–none; —–not described

Table 2. Neuropathologic findings of our five and another similar cases

	Lewy bodies[c]		Senile plaques[c]	Neuro-fibrillary tangles[c]	Miscellaneous[d]
	in C.C.[a]	in B.S.[b]			
Case 1	+3	+3	+3	+3	B.W. 1130 g, localized atrophy in the hypocampal region
Case 2	+3	+3	+3	+2	B.W. 1200 g, small cystic cavitation in the basal ganglia and cerebral white matter
Case 3	+2	+2	+1	+1	B.W. ?
Case 4	+2	+3	+2	+1	B.W. 1120 g
Case 5	+2	+3	+1	+1	B.W. 1340 g
Okazaki et al. (1961)	+3	+3	+1	0	B.W. 1098 g
	+3	+3	+1	0	B.W. 1342 g
Kono et al. (1976)	+1	+1–2	+3	0	B.W. 1175 g, numerous Lewy bodies in the sympathetic ganglia
Ikeda et al. (1978)	+3	+3	0	0	B.W. 1320 g

[a] C.C.–cerebral cortex; [b] B.S.–brain stem; [c] +3–severe; +2–moderate; +1–mild; 0–none; [d] B.W.–brain weight

contrast to the typical LB in the brain stem ('brain stem type of LB'), were found in small or medium-sized pyramidal neurons in the fifth and sixth layers throughout the cortex (Fig. 1A—C) and quite rarely in the second and third layers. They were numerous in the insular cortex as well as in the medial part of the temporal cortex, while only a few were seen in the parietal and occipital cortex. Furthermore, numerous 'cerebral type of LB' were also found in the amygdaloid nucleus and a few in the claustrum. The neurons containing the LB showed degeneration as described previously (Kosaka, 1978). However, nerve cell loss and astrocytic proliferation were not severe in the deep cerebral layers where cerebral type of LB were mainly localized, although some were found throughout the cortical layer. On the other hand, in the brain stem and diencephalic nuclei most of the LB were typically round and homogeneously eosinophilic with pale halos (Fig. 1D) and, occasionally, strongly eosinophilic central cores. A few had dark halos. 'Intraneuritic LB' (Kosaka, 1978) were also frequently found. In the substantia nigra and dorsal vagal nucleus moderate nerve cell loss and depigmentation of melanin with corresponding astrocytosis were present and in the locus ceruleus they were more marked.

The second outstanding finding was the presence of various types of 'senile change.' Numerous senile plaques were diffusely distributed in the cerebral cortex. Neurofibrillary tangles were scattered in the hippocampal region and, though less in number, in the hypothalamic nuclei, substantia nigra, central

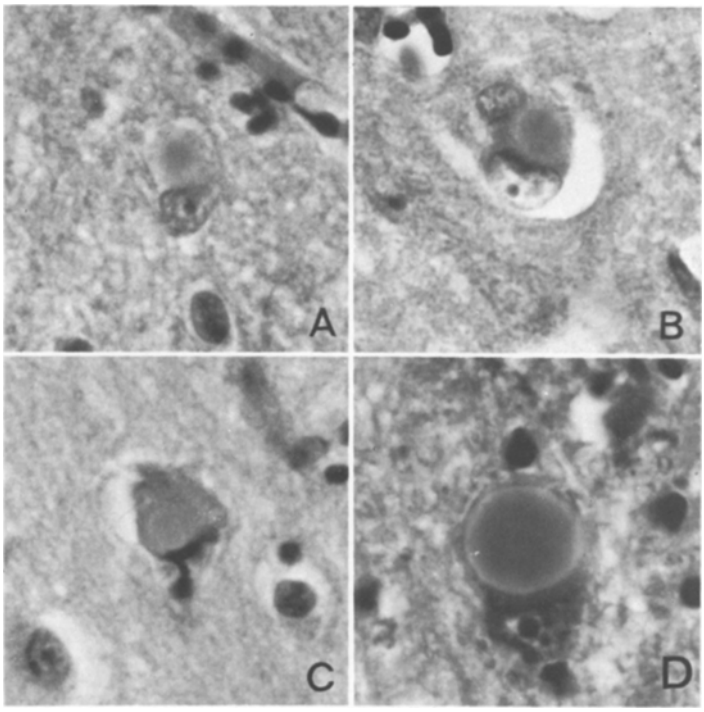

Fig. 1A–D. Lewy bodies. **A–C:** 'Cerebral type of Lewy bodies,' showing various stages of degeneration of nerve cells in the cerebral cortex (H.E., ×508). **D:** 'Brain stem type of Lewy body' in the substantia nigra (H.E., ×680)

tegmental nucleus, and locus ceruleus. Numerous nerve cells showing granulovacuolar degeneration and a few Hirano bodies were found in the Ammon's horn. In addition, a few swollen nerve cells with basophilic intracytoplasmic bodies similar to Pick bodies were seen in the cerebral cortex. Most of neurons in the CNS contained excess lipofuscin granules. Also, a few intranuclear eosinophilic inclusions in glial cells (perhaps in oligodendroglia) were encountered in the hypothalamic nuclei and cerebral cortex.

Other pathologic findings were firstly pigment atrophy of nerve cells with moderate gliosis in the dentate nucleus and inferior olive and secondly mild cerebral arteriosclerosis.

Case 5 (MPI 337/75). The patient was a 65-year-old male. At the age of 15 he was operated for gastric ulcer. From age 45 for 13 years he was in a mental hospital because of psychotic disorder. At the age of 53 muscular rigidity and bradykinesis appeared and thereafter progressed gradually. He was diagnosed as having paralysis agitans. From the age of 53 he was bedridden due to a severe hypertonic-hypokinetic state. One month before death the patient was hospitalized with jaundice and hepato-splenomegaly. Severe muscular rigidity of all extremities as well as memory disturbance were noticed on that occasion. His general condition was worsening and he died of hepatic failure. Little was known concerning the onset and the degree of mental disturbance in this case, since only limited historical information was available.

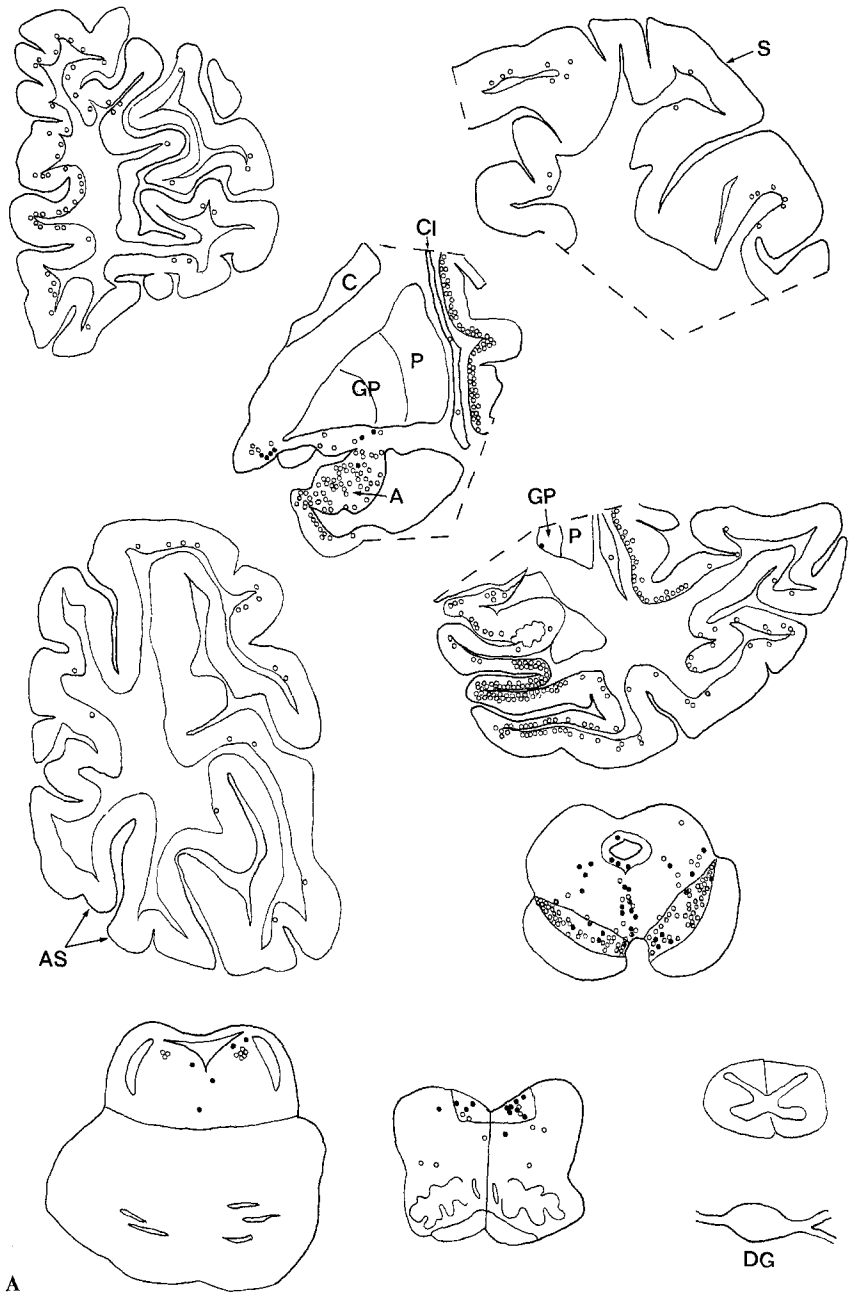

Fig. 2A and B. Distribution of Lewy bodies in two cases. **A:** Case 4. **B:** Case 5. o . . . one intracytoplasmic Lewy body, ● . . . one intraneuritic Lewy body. *C:* Caudatus, *P:* Putamen, *GP:* Globus pallidus, *Cl:* Claustrum, *A:* Amygdala, *T:* Thalamus, *MB:* Mammillary body, *M:* Motor cortex, *S:* Sensory cortex, *AS:* Area striata

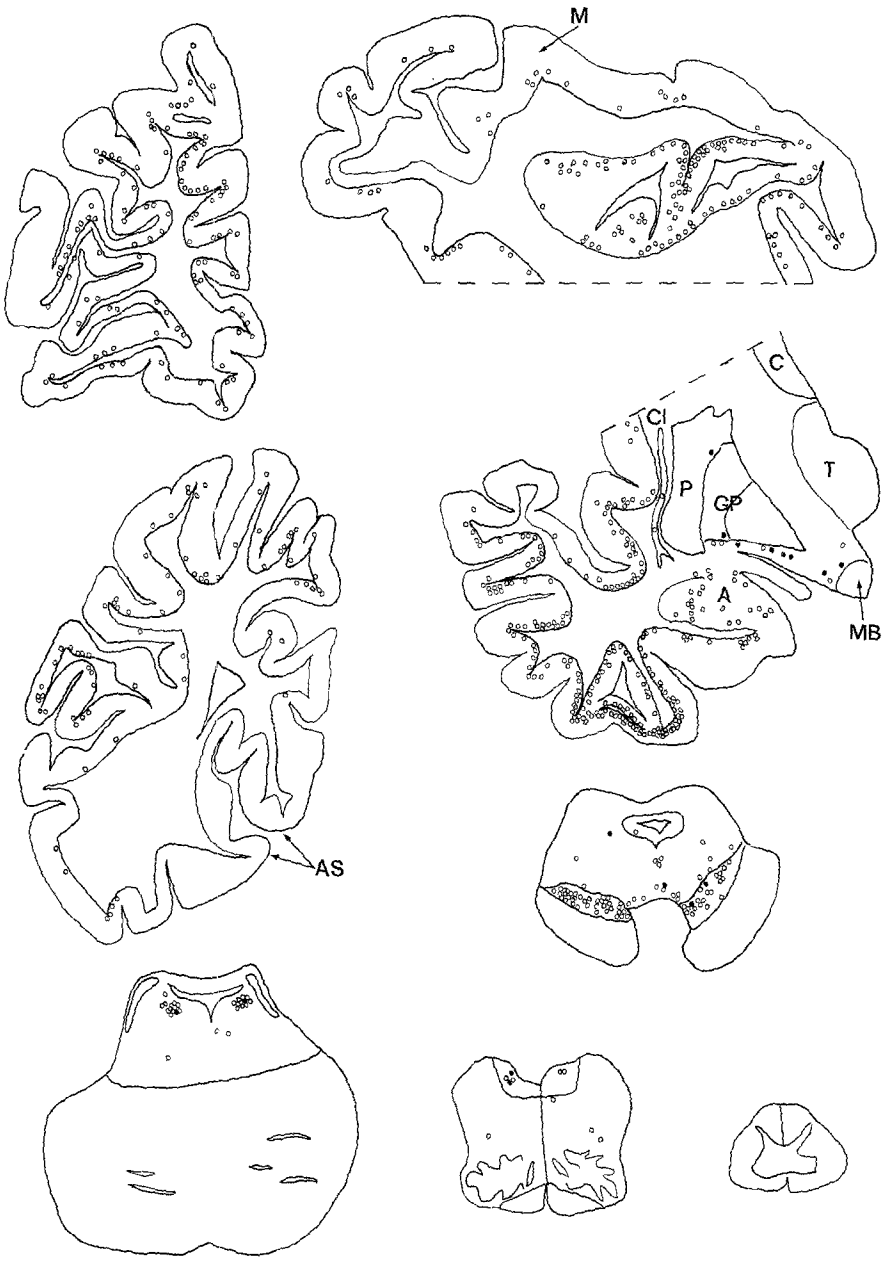

Fig. 2B

Neuropathologic Findings

Gross. The brain weighed 1340 g after 10% formalin fixation. There was mild cerebral atrophy in the frontoparietal regions and moderate depigmentation in the substantia nigra.

The light microscopic findings of this case were similar to those of case 4, but showed some noteworthy differences. In case 5 senile changes were not so remarkable as in case 4: senile plaques were scattered in the cerebral cortex and amygdaloid nucleus and only a few neurofibrillary tangles were found in the hippocampal formation. In addition, nerve cell loss was more severe in the dorsal vagal nucleus than in the substantia nigra and locus coeruleus. No intranuclear eosinophilic inclusion of glia cells was found.

The topographic distribution of the LB in both cases is illustrated in Figure 2.

Discussion

The present five cases were characterized by clinical features of progressive dementia and Parkinson syndrome, the neuropathologic features of which were the presence of numerous LB, not only in the brain stem and diencephalon but also in the cerebral cortex and basal ganglia, as well as of more or less severe senile changes. As far as we know, only four similar cases had been previously reported (Okazaki et al., 1961; Kono et al., 1976; Ikeda et al., 1978). The chief clinical and neuropathologic findings of all these nine cases are summarized in Tables 1 and 2.

In five cases this disease began in the presenium or early senium with memory disturbance in three cases and psychotic symptoms in two. Constant and predominant symptoms were progressive dementia and muscular rigidity of all extremities. They were mild in case 3, which was regarded as being at the early stage of this disease because of milder clinical and neuropathologic findings. Only in case 2 was quadriparesis in flexion noticed at the terminal stage of the disease as in the two cases reported by Okazaki et al. Their two cases differed neuropathologically from ours in that LB were found in every layer of the cerebral cortex and senile changes were quite sparse. Okazaki et al. regarded the flexion contracture in their cases as quadriparesis in flexion and LB scattered throughout the cerebral cortical layers were held responsible for the quadriparesis as well as the dementia. On the other hand, in the case of Kono et al. Parkinson symptoms and orthostatic hypotension preceded dementia and it was clinically diagnosed as having paralysis agitans with idiopathic orthostatic hypotension. In this case LB were found more frequently in the sympathetic ganglia (in our cases the sympathetic ganglia were not available for histopathologic examination) and less in the cerebral cortex than in the brain stem nuclei. The distribution pattern of LB in the nervous system may play some role in the appearance and the degree of clinical symptoms. It is also interesting that only three of nine cases were clinically diagnosed as paralysis agitans and that, apart from the case of Kono et al., eight had no outstanding tremor, although all showed the neuropathologic findings of paralysis agitans.

The presence of numerous LB localized mainly in the deep cerebral layers might not alone bring about severe dementia. The case reported by Ikeda et al. seems to support this hypothesis. In this case, in which the distribution of LB in the cerebral cortex was the same as in ours, and that of Kono et al. dementia was not clinically evident and no senile changes in the CNS were found neuropathologically. It should be noted that the patient died at the age of 38: this might explain the absence of senile changes and perhaps also of dementia. Progressive dementia in our and Kono et al.' cases might be associated more with the presence of senile changes in the cerebral cortex than with the presence of numerous cerebral type of LB. In our cases the degree of dementia appeared to parallel that of senile changes in the cerebral cortex.

Nosologically, all the above-mentioned cases might belong to the same disease. Also, it might be said that Ikeda et al.'s case represents the pure form of the disease and that our case 1 with concomitant massive senile changes in the cerebral cortex shows the extreme form of it. As mentioned above, the findings in the diencephalon and brain stem of all cases are identical to the neuropathology of paralysis agitans. However, it is generally accepted that LB are only rarely found in the cerebral cortex of cases with paralysis agitans. Thus, all these cases might belong to atypical paralysis agitans. On the other hand, the presence of senile changes is almost identical to the neuropathology of senile dementia or Alzheimer's disease. Accordingly, it might be said that our five cases represent a combination of atypical paralysis agitans and senile dementia or Alzheimer's disease. But the presence of numerous LB in the cerebral cortex as well as in the basal ganglia, especially in the amygdaloid nucleus, of our cases was specific, since it has not been seen in the cases of paralysis agitans. In addition, as we had previously described (Kosaka, 1978), the distribution of cerebral type of LB in our cases was not in accordance with that of monoamine nerve terminals in the cerebral cortex, although we obtained as close a relationship between LB and monoamine neurons in the brain stem as Ohama and Ikuta (1976) had indicated. Based on this study, they advanced a hypothesis that paralysis agitans is a system degeneration of monoamine neuron systems. The distribution of cerebral type of LB and poor relationship between it and monoamine in our cases also suggest another possibility, namely, that our cases represent a defined entity. Our cases differ from 'arteriosklerotische Muskelstarre' (Foerster, 1909) and 'senile Muskelstarre' (Jakob, 1923) in that they had neither severe vascular nor parenchymatous changes in the striatum and pallidum also (Freund and Rotter, 1928) and also from Parkinsonism-dementia complex on Guam (Hirano et al., 1961) in that not neurofibrillary changes but LB played an important role in them. We will discuss this nosologic problem again in our next work in which the detailed distribution of LB in cases of paralysis agitans will be dealt with.

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