A Case of Diffuse Lewy Body and Alzheimer's Diseases with Periodic Synchronous Discharges

TORU YAMAMOTO, M.D. AND TERUKUNI IMAI, M.D.

Abstract. Periodic synchronous discharges were consistently observed in a 68-year-old man with a four-year history of progressive dementia. Pathological examination revealed diffuse atrophy of the brain with remarkable dilatation of the temporal horns. Histologically there were severe changes of Alzheimer's disease and diffuse Lewy bodies (LB), either typical or less distinctive ones without clear halos. Cerebellar LB were also observed in the cerebellum. Four types of abnormal intraneuronal filamentous structures were observed: neurofibrillary tangles, accumulated neurofilaments, thick linear structures studded with ribosome-like dense granules, and fuzzy, thin filaments similar to, but generally wider than, a neurofilament.

Key Words: Alzheimer's disease; Diffuse Lewy body disease; Lewy body, cerebellar; Neurofilament; Periodic synchronous discharge; Ribosome-associated thick filament.

INTRODUCTION

A recent study reported that Lewy body (LB) disease and Pick’s diseases are the two most frequent types of dementia, after Alzheimer’s disease (AD), among the various disorders designated primary degenerative dementia (1). The term LB disease, originally used by Forno and Alvord (2) has been stated by some authors (3) to encompass idiopathic Parkinson’s disease (PD) and the so-called diffuse LB disease. The latter was characterized clinically by progressive dementia with or without Parkinsonism and pathologically characterized by widespread LB or Lewy-like bodies throughout the cerebral cortex and subcortical structures. Cases of diffuse LB disease, however, were first noted by Okazaki et al (4) and some 30 cases have been reported so far, mostly from Japan (1, 3-13). Although diffuse LB disease may occur in a pure form (1, 3, 4, 7), it has frequently been associated with numerous cortical senile plaques. Several cases have been reported in which AD coincided with diffuse LB disease (3, 5, 6).

We report the case of a profoundly demented patient who showed periodic synchronous discharges suggestive of Creutzfeldt-Jakob's disease (CJD). On neuropathological examination special attention was devoted to the ultrastructure of the abnormal filamentous structures which characterize the neuronal inclusions in AD, PD and Pick's diseases as well as amyotrophic lateral sclerosis.

CASE REPORT

A self-employed retailer who began losing his way when delivering goods at the age of 64 years stopped work a year later. He had slowly progressive difficulty in performing routine daily tasks and frequently became disoriented at home and behaved inappropriately. When the patient was first seen two-and-a-half years after...
the onset of his symptoms, he was a talkative, pleasant, elderly man who could not carry on a meaningful conversation. He was not oriented to time, place, or persons, even his family members. Word registration was defective and his recent memory was severely impaired. Confrontation naming and repetition of a sentence were done, but writing, reading, calculations and visuospatial tasks were impaired. In a modified Japanese version of the mini-mental status examination (14) he scored a potential 7 of 30 points. The remainder of the neurological examination revealed no significant abnormalities other than the absence of ankle reflexes. No frontal release signs were detected. Routine laboratory tests of the blood, urine and cerebrospinal fluid were normal. Computed tomographic (CT) scans of the brain demonstrated marked enlargement of the temporal horns and mild diffuse cerebral atrophy. A few months later he became incontinent, acutely developed a gait disturbance and became bedridden. He was admitted to the Kitano Hospital.

Family history was not contributory. There were no previous medical problems except for occasional glycosuria.

On admission he was a slim, elderly man who was still sociable and smiling but slightly lethargic most of the time. There were no significant physical abnormalities other than a decubitus ulcer in the sacral region. The score of the mini-mental status examination was only one of 30 (sentence repetition). He was profoundly demented. The cranial nerves were intact except for a sluggish right pupillary light reflex. There was no definite weakness of the extremities, but muscle tone was rigid and paratonic. There was no tremor or myoclonus. Deep reflexes were diminished or absent. The plantar reflexes were extensor bilaterally. There were snout, Myerson's, palmomental and forced grasping reflexes. Evaluation of the sensory system was limited, but no definite abnormalities were demonstrated. He was unable to remain seated because of a tendency to fall backward. His neck was rigid but there was no dystonic nuchal posture.

Laboratory examination did not reveal any significant abnormalities except for mild hyperglycemia.

His hospital course was characterized by a progressive worsening of dementia, a decline in the state of consciousness and by general wasting and poor healing of the ulcer. He curled into a pelvicroural position and tube-feeding was begun five months after admission. The initial electroencephalograms (EEG) were mildly abnormal with an irregular slow background activity of 8 Hz alpha waves, intermingled with frequent diffuse theta and delta waves. Four months after admission periodic synchronous discharges (PSD) appeared occasionally, with a periodicity of from 1 to 1.5 seconds. These PSD, confirmed with various montages, became more obvious in several successive records until the patient died of bronchopneumonia nine months after admission. The periodicity of PSD had elongated slightly from 1.2 to 1.8 seconds in the later records (Fig. 1). The total course of the disease was about four years.

NEUROPATHOLOGY

A general autopsy was performed three hours after death. The unfixed brain weighed 1,120 grams, was bilaterally symmetrical and diffusely atrophic. The right cerebral hemisphere was frozen and submitted to neurochemical analysis. Part of the brain was inoculated into experimental animals at Kyushu University School of Medicine, but no disease transmission has been observed in nine months. Coronal sections of the left half of the brain revealed a markedly dilated temporal horn and prominent atrophy of the adjacent Ammon's horn and amygdala (Fig. 2). There was mild cerebral atherosclerosis, but no softening. The substantia nigra and locus cerule-
us were depigmented. The rest of the cerebrum, cerebellum, brainstem and spinal cord was unremarkable.

Histological examination revealed two major findings. One was that of AD with profuse neurofibrillary tangles and senile plaques in the cerebral cortex and Ammon's horn, and in selected areas of the diencephalon and brainstem (Fig. 3) (15). The most severely-involved areas were the amygdala and temporal lobe, where loss of neurons and fibrillary and hypertrophic astrocytosis were extensive (Fig. 4). Many senile plaques were of the primitive type without distinctive amyloid cores. Large neurons were reduced and associated with gliosis in the nucleus basalis of Meynert. In the nucleus raphe dorsalis, neurofibrillary tangles were abundant, but the reduction in the neuronal population of large neurons was not severe (16).

The second finding was even more impressive. In the cerebral cortex there were numerous so-called cortical-type LB (Fig. 5a) which were slightly eosinophilic in hematoxylin and eosin stains, cytoplasmic inclusions with occasional condensation in their core areas, some associated with halos. They were not as deeply eosinophilic, distinctive or concentric as the typical LB found in the pigmented cells of the substantia nigra and locus ceruleus (Fig. 5b). In the modified Bielschowsky method we employed (17) the cortical LB were impregnated less well than the usual brainstem LB, and they were far paler than neurofibrillary tangles. The largest number of cortical LB was in the amygdala and temporal isocortex, which were also the sites of severe AD changes. In contrast, LB were few in the Ammon's horn and subiculum. The frontal, parietal, occipital and insular cortices and the cingulate gyrus showed many cortical LB in their fifth and sixth layers and some in the third and fourth layers as well. The claustrum, nucleus basalis of Meynert (nbM) and hypothalamus also contained LB. Typical brainstem-type LB were found in the substantia nigra, locus ceruleus, nucleus raphe dorsalis and dorsal motor nucleus of the vagus, and in the anterior horn of the sacral spinal cord. No LB were observed in the dorsal root ganglia available for examination. Although there were none in the ordinary

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*Fig. 1.* Electroencephalogram one month before death showing periodic synchronous discharges with a periodicity of 1.2–1.8 seconds. Bar: 50 μV or 1 second.
sections, one LB was found in the molecular layer of an Epon-embedded section of
the cerebellar hemisphere (Fig. 6) (3, 11).

A small, old microscopic infarct was found in the occipital cortex. There was
minor spongy change only in the neighborhood of this infarct. Congo-red-stained
sections of the parietal and occipital cortex under polarized light revealed amyloid
angiopathy of many small blood vessels of the cortex and leptomeninges. In the
dentate nucleus of the cerebellum, a few neurons showed grumose degeneration in
their dendrites. There were several torpedoes in the granular layer and cerebellar
white matter. The cerebral subcortical white matter, as defined by the luxol fast blue
stain, was not abnormal except near the infarct. However, there may have been
slight myelin pallor in the areas where astrogliosis was observed, such as the temporal
and occipital lobes.

ELECTRON MICROSCOPIC EXAMINATION

For electron microscopy, small pieces of brain tissue were fixed in 2% glutaral-
dehyde and were processed in the usual fashion, except for sections taken from the
formalin-fixed brainstem. The cortical LB were composed of clusters of randomly-
arranged thick linear structures, about 40 nm in diameter, studded with ribosome-
Fig. 3. Numerous neurofibrillary tangles and senile plaques of the primitive type in the temporal isocortex. A round, less argyrophilic cortical-type LB (arrow) is also seen. Modified Bielschowsky. ×190.

Fig. 4. Cortical type LB (arrows) and hypertrophic astrocytosis in the amygdala. H&E. ×290.

like dense granules and a smaller amount of thin, fuzzy, straight filaments, ranging from 10 to 15 nm in diameter. These filaments were similar to, but generally wider than, the neurofilaments in nearby axons (Fig. 7a). Typical LB in the pigmented neurons of the brainstem were composed of filamentous structures essentially identical to the cortical LB, although they tended to be radially-oriented around the
condensed core and the amount of thinner filaments exceeded that of thicker ones (Fig. 7b).

In the periphery of the typical LB of a locus ceruleus neuron, the presence of the paired helical filaments (PHF) of the neurofibrillary tangle was confirmed (Fig. 8a). In the neurofibrillar tangle of a parahippocampal neuron, there was a small LB (Fig. 8b).

In a neuromelanin-containing neuron of the substantia nigra, there was a large accumulation of whorled neurofilaments among which were islands of organelles such as mitochondria and dense vesicles (Fig. 9). This structure was not identified in slides of the substantia nigra processed for light microscopy.

NEUROCHEMISTRY

The choline acetyltransferase activity of the frozen right cerebral hemisphere was approximately half that of non-demented elderly persons (age 83.7 ± 1.1, mean ± SEM) in the frontal and temporal cortex (5.54 vs 9.62 ± 1.34; 4.21 vs 9.55 ± 1.19; and 7.98 vs 13.15 ± 1.21 nmol ACh/min/100 mg protein, mean ± SEM, in Brodmann’s areas 4, 10 and 22, respectively). The values were higher in the parietal and calcarine cortices (11.75 vs 7.27 ± 0.78 and 8.64 vs 5.83 ± 0.58 in areas 7 and 17, respectively) (18).

DISCUSSION

Clinically the patient’s illness was characterized initially by memory and visuospatial disturbances followed by aphasia, apraxia, agnosia, constructional disturbance, and inappropriate behavior. The last year of his life was complicated by prominent motor disturbances and clouded consciousness. It is not uncommon for patients with AD to show extrapyramidal signs (19), yet these were never outstanding during the entire course of this patient’s illness. Diffuse LB disease, on the other hand, frequently fails to show any evidence of Parkinsonism (1, 3, 10).

Periodic synchronous discharges (PSD) in the EEG are considered important findings in several neurological diseases, such as CJD, subacute sclerosing panenceph-
alitis (SSPE), and in various other conditions such as anoxic and hepatic encephalopathies (20). The pathogenetic mechanism of PSD is still unclear, but it is generally regarded as an indication of severe organic or functional disturbances of the cortex and subcortical white and gray matter (20, 21). Unlike CJD and SSPE, PSD have been observed rarely in AD. When seen, they have been rather irregular with a periodicity of one to two seconds, in contrast to a shorter periodicity in CJD and a longer one in SSPE (6, 22–25). Compared to the PSD reported in AD, those of our patient were distinguished by their constant presence and well-defined periodicity. The diffuse nature of the pathologic alterations demonstrated in our patient supports the current concept of the pathogenesis of PSD.

A case similar to our patient was reported by Kuroda and his colleagues (6), with an association of AD and diffuse LB disease in conjunction with PSD. The PSD may not be unusual in some primary degenerative dementias if they are studied more carefully. It remains to be determined whether there is any difference in PSD as to wave form, periodicity, or progression with time between CJD, AD and diffuse LB disease, since recognition of its different causes is obviously important in the assessment and care of patients with PSD.

Ultrastructural studies of LB have described thin filaments with a dimension similar to that of the neurofilament, thicker filaments of variable diameters, electron-dense granular structures, circular profiles and crystalloids (5, 8–10, 26). The cortical-type LB was similar to, although light-microscopically different from, the typical brainstem-type, except for the loose and haphazardly-arranged filamentous structure in the former (5). We observed two kinds of filaments in LB: thin and thick. The thinner, fuzzy straight filaments 10–15 nm in diameter appeared the same as previously reported in LB (26) and were sometimes indistinguishable from, but generally wider than, neurofilaments. The thicker filaments studded with ribosome-like gran-
Fig. 7. Lewy bodies in the temporal isocortex (A) and locus ceruleus (B), consisting of thin, fuzzy, straight filaments 10–15 nm in diameter (arrowheads) and thick linear structures studded with ribosome-like dense granules (arrows). A, B, ×80,000.

ules in our patient’s LB resembled those in the Pick bodies in the so-called generalized variant of Pick’s disease (27, 28). These structures have also been described in several types of amyotrophic lateral sclerosis (ALS) (29–32), LB (8) and in other disorders (33). Munoz-Garcia and Ludwin noted that the amphophilic inclusions in the generalized variant of Pick disease may be similar to the cortical LB (27, 28). Although the correlation between these two filaments was obscured by their fuzzy surfaces, the thinner filament of LB might be the naked portion of the thicker one, since only
Fig. 8. In the periphery of a typical LB in the locus ceruleus the regularly-constricted form of neurofibrillary tangle with a periodicity of about 80 nm (arrowheads) can be seen. ×80,000. Inset: Neurofibrillary tangles and two LB in a neuron of the nucleus raphe dorsalis. Modified Bielschowsky. ×710. (B) Within the dense neurofibrillary tangles of a parahippocampal neuron there is a small LB (arrows). ×29,000.

the former constituted the LB when dense granules were scanty, e.g. in the cerebellar LB.

Immunocytochemical studies of the LB have shown the presence of phosphorylated and non-phosphorylated neurofilament antigens with somewhat different patterns between the brainstem and cortex (10, 34, 35). The usual neurofilaments were
Fig. 9. (A) Dense accumulation of neurofilaments in a neuromelanin-containing neuron from the substantia nigra. N: nucleus. ×3,500. (B) Higher magnification of its periphery demonstrates neurofilaments with side arms. ×80,000.

difficult to find in the LB in this study, presumably because of the complicated mixture of filamentous and granulovesicular structures. The thinner filaments might be neurofilaments, modified somehow by fine granular substances. On the other hand, immunostaining of LB with an antibody to the PHF of the neurofibrillary tangle has been demonstrated in an unusual case of a demented young adult with neurofibrillary changes and LB (13).

The massive accumulation of neurofilaments is one of the morphological features
of ALS referred to as spheroids (29). A similar structure has been identified in some of the chromatolytic neurons in the spinal anterior horn (29, 36). The accumulated neurofilaments in the pigmented neurons of the substantia nigra in our patient indicate that such a change can also occur in disorders other than ALS. However, the spheroids in ALS are characterized by an interwoven pattern of neurofilamentous skeins, in contrast to the randomly crisscrossed individual neurofilaments that we observed (29). A similar structure was previously reported as an intracytoplasmic inclusion of the Pick type in a patient with AD, Pick's disease and LB changes (5).

The concomitant presence of LB and PHF in a neuronal cytoplasm has been reported very rarely in the brainstem (13, 37–39). Our observation may be the first of such a coexistence in a cerebral cortical neuron. It was not possible, however, to detect a direct connection or transformation between filaments of the tangles and LB. Further studies, particularly combined immunocytochemical and electron microscopic investigation, are necessary to elucidate the relationship between these abnormal filamentous structures in apparently unrelated disorders.

Neurochemical evidence of a cortical cholinergic deficit, along with a loss of nbM neurons, is consistent with previous studies of three patients with diffuse LB disease without AD (10) and a similar neuronal loss in nbM has also been reported earlier in diffuse LB disease (12).

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