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Neuropathological Studies of Creutzfeldt-Jakob Disease. Two Cases, One with and One without Prominent Senile Changes

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ABSTRACT. Neuropathological findings of two cases of Creutzfeldt-Jakob disease were described.

The cases were a 67-year-old woman and a 74-year-old woman, both of whom showed visual disturbance, mental confusion, rigidity of the extremities, myoclonic jerks, and periodic synchronous discharges on electroencephalograms. The former died after five months of the illness and the latter after three months.

Neuropathologically, marked nerve cell loss, protoplasmic astrocytosis and stromal spongiosis were observed in the cerebral cortex of both cases, especially in the occipital and temporal lobes. There were mild to moderate similar changes also in the basal ganglia, thalamus and cerebellum. In the first case, many typical senile plaques, neurofibrillary changes and Hirano bodies were found in the hippocampus, and primitive senile plaques in the cerebral cortex.

Electron microscopically, spongiosis in the stroma of both cases was observed as accumulations of vacuoles of various sizes, usually with single or double limiting membranes in the neuropil.

Although both cases might belong to the subacute spongiform encephalopathy type of Creutzfeldt-Jakob disease, the coexistence of prominent senile changes in the first case suggested a relation between this case and Alzheimer's disease.

Creutzfeldt-Jakob disease[1-4] is a rapidly progressive disorder of the presenile ages characterized by dementia associated with various neurological manifestations such as pyramidal and extrapyramidal symptoms and signs, and myoclonus. The essential neuropathological pictures consist of neuronal loss, astrocytosis and spongiosis, involving mainly the cerebral cortex. Formerly it was included within the category of presenile degenerative diseases, but nowadays it is regarded as a slow virus infection based on experimental transmissibility to primates[5-8].

In recent years, the possibility of transmissibility of Alzheimer's disease, which is a representative degenerative disease of presenile and senile dementia,

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has been discussed, especially in familial cases[9]. A possible relation between Creutzfeldt-Jakob disease and Alzheimer's disease has also become an issue.

Recently, we experienced an autopsy case of Creutzfeldt-Jakob disease with prominent senile changes reminiscent of Alzheimer's disease. It is the purpose of this paper to describe the neuropathological findings of this case, comparing them with those of another case of Creutzfeldt-Jakob disease with only mild senile changes, and to discuss the significance of senile changes in Creutzfeldt-Jakob disease.

CASE REPORT

Case 1

Clinical Course (B 5358) :

A 67-year-old woman was admitted to the Kawasaki Medical School Hospital on October 20, 1980, because of mental confusion and rigidity of the extremities.

The patient was well until July, 1980, when she began to complain of visual disturbance. Her family noticed that she had a tendency to say the same word repeatedly. Next month she began to experience myoclonic jerks in the extremities. In September she became confused, and rigidity of the extremities was noted.

She had delivered her fourth child by cesarean section. She had complained of sleep disturbance since the spring of this year. There was no family history of neurologic disease.

Physical examination on admission revealed an emaciated woman. Her temperature was 37.2°C, pulse 113 per minute with irregular rhythm, and respirations 12 per minute. The blood pressure was 126/76 mm Hg. An old operation scar was observed in the abdomen.

Neurologically, she was mutistic and reacted only to painful stimuli. The pupils were isocoric and reactive to light. The neck and extremities were moderately rigid. Occasionally myoclonic jerks were observed in the face and extremities. No pathological reflexes were obtained.

The cerebrospinal fluid was clear and colorless. It contained one lymphocytes per cubic millimeter, with 21 mg of protein and 83 mg of sugar per deciliter. An electrocardiogram demonstrated sinus tachycardia with frequent ventricular premature contractions. Computed tomography (CT) brain scan showed mild dilatation of the third and lateral ventricles. An electroencephalogram revealed periodic synchronous discharges with a periodicity of 0.7 to 1.2 seconds (Fig. 1).

After admission, the patient's condition became progressively worse. General convulsions were sometimes observed. She died on December 3, five months from the onset of the illness.

Autopsy Findings (A 80-143) :

The general autopsy findings included organized pneumonia, multiple gastric erosions, chronic cystitis and hypocellular bone marrow.

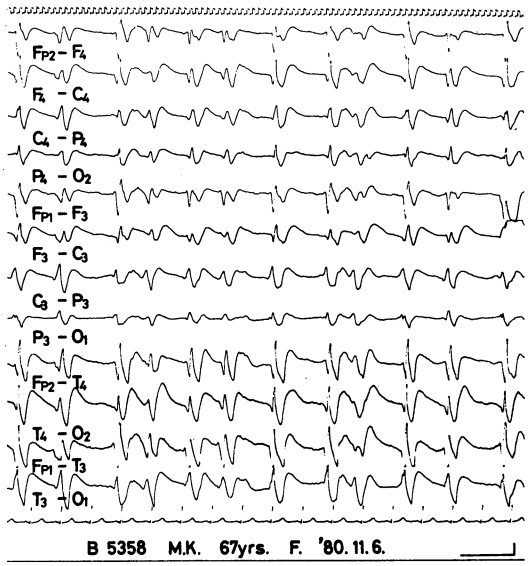

Fig. 1. Electroencephalogram of case 1 recorded four months after onset of the illness and one month before death showing periodic synchronous discharges with a periodicity of 0.7 to 1.2 seconds.

The weight of the brain was 1,100 g. The leptomeninges were slightly thickened and turbid, and their blood vessels were congested. The gyri of the cerebral hemispheres were diffusely narrowed, while the sulci were widened. The arteries at the base of the brain showed mild atherosclerosis. On coronal sections, the cerebral cortex was narrow in width and brownly pigmented, especially in the temporal and occipital lobes. The cerebellar cortex was also slightly atrophic. The cerebral and cerebellar white matter were well preserved. The lateral and third ventricles were moderately dilated.

Microscopically, the nerve cells of the cerebral cortex were markedly reduced in number and shrunken, while the protoplasmic astrocytes showed diffuse proliferation. In addition, small vacuoles of 10 to 20 microns in diameter, were scattered in the stroma of the cerebral cortex. These changes were most prominent in the occipital and temporal lobes. In the temporal lobe, the vacuoles were larger, 30 to 60 microns in diameter, and had a tendency to form groups and fuse with each other. Furthermore, Bodian's silver stainings demonstrated many round foci, 30 to 40 microns in diameter, containing fine rods or amorphous materials suggestive of primitive senile plaques, particularly in the temporal lobe. Alzheimer's neurofibrillary changes were observed mainly in the parahippocampal gyrus. The cerebral white matter was unremarkable except for mild proliferation of protoplasmic astrocytes in the subcortical area.

In the hippocampus, neuronal loss, astrocytic gliosis and spongy appearance of the stroma were not apparent. In Bodian's silver stainings, however, there were numerous distinct senile plaques, 50 to 60 microns in diameter, composed of

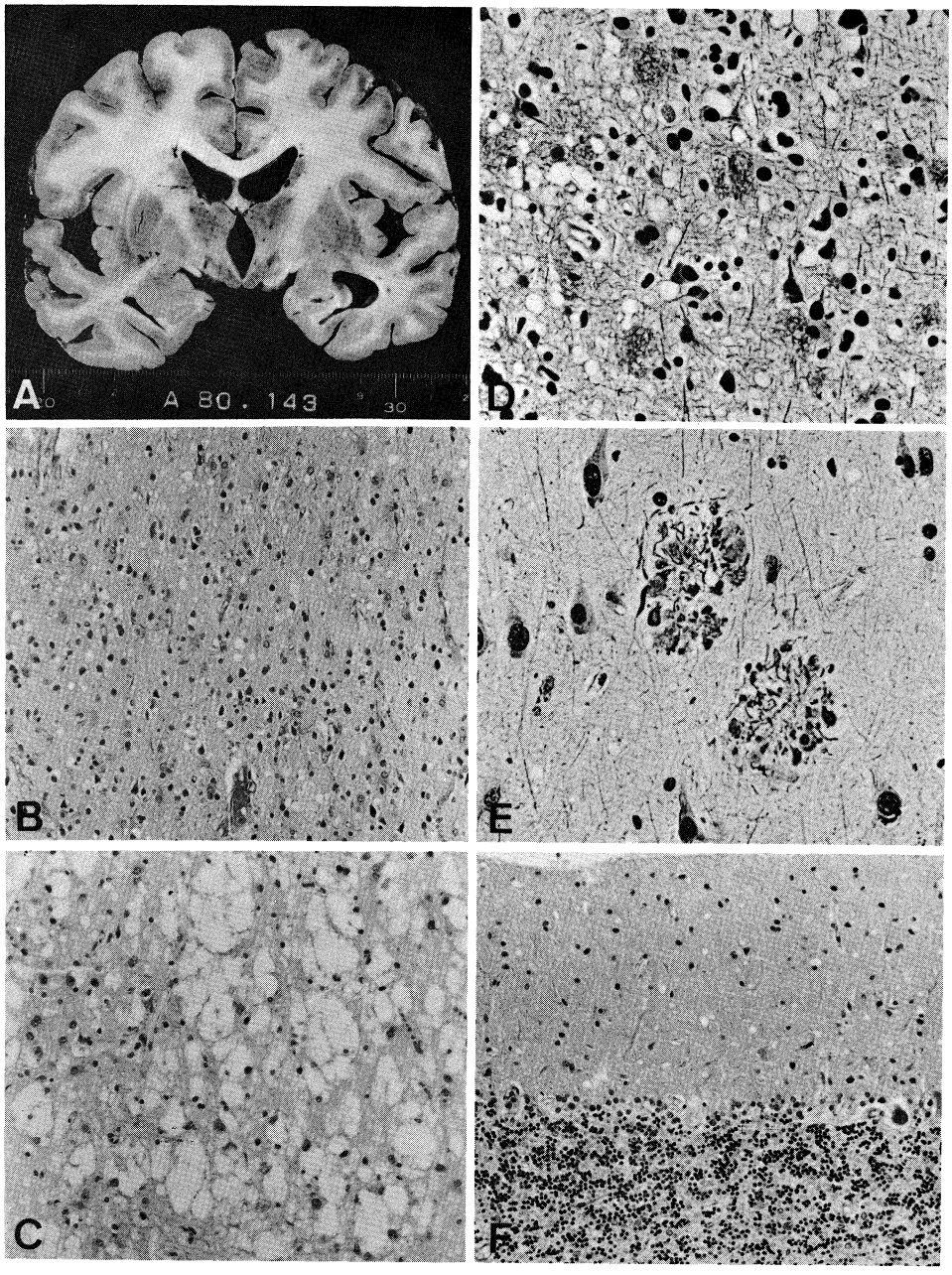

Fig. 2. Photograph and photomicrographs of case 1. A. Coronal section of the cerebral hemispheres through mammillary bodies. In this section cortical atrophy is minimal, whereas insular cisterns, and lateral and third ventricles are moderately dilated. B. Occipital cortex showing marked nerve cell loss, astrocytic gliosis and stromal spongiosis. HE, ×100. C. Temporal cortex showing conspicuous spongiosis with a tendency to form groups. HE, × 100. D. Temporal cortex demonstrating round foci

suggestive of primitive senile plaques. Bodian, × 200. E. Hippocampus showing numerous distinct senile plaques. Bodian, × 200. F. Cerebellar cortex. Purkinje cells and granule cells are decreased in number, while Bergmann glia are proliferated in the Purkinje cell layer, HE, × 100.

rods of various sizes and Alzheimer's neurofibrillary changes. Many eosinophilic rod-like structures (Hirano bodies) and some granulovacuolar degenerations were also observed in hematoxylin and eosin stainings.

Mild to moderate nerve cell loss, astrocytosis and stromal spongiosis were found also in the basal ganglia and thalamus.

In the cerebellum, the molecular layer was loose and spongy, and Purkinje cells and granule cells were moderately decreased in number. The Bergmann glia were proliferated in the Purkinje cell layer. The white matter of the cerebellum and the dentate nuclei were well preserved.

The changes of the brainstem were minimal except for mild pallor of the pyramidal tracts in the medulla oblongata.

Small specimens of the brain were fixed in glutaraldehyde at autopsy, which was carried out one and a half hours after the patient's death, and examined electron microscopically. Spongiosis in the stroma was observed as accumulations of vacuoles of various sizes, usually with single or double limiting membranes in the neuropil. Some vacuoles contained synaptic vesicles within them, and some were situated adjacent to the cytoplasmic membrane or even in the cytoplasm of nerve cells. At times vacuoles were surrounded by thin myelin lamellae. Senile plaques in the hippocampus were composed of twisted tubules, lamellated or amorphous dense bodies, membranous or filamentous bodies, a small amount of amyloid filaments and some other bodies. Neurofibrillary changes were constituted of twisted tubules, and Hirano bodies were found as parallel filamentous bodies or lattice like structures. Virus like particles were not detected anywhere.

Case 2

Clinical Course (B 23015) :

A 74-year-old woman was admitted to the Kawasaki Medical School Hospital on August 31, 1981, for mental deterioration and involuntary movements.

The patient was well until early in July, when she began to complain of visual disturbance. Late in the same month she became irritable and anxious. Memory disturbance and decreased ability to recognize people developed. Muscle tone became increased. In August choreic or athetoid involuntary movements and myoclonic jerks were observed.

She had suffered a myocardial infarction six months previously. There was no family history of neurologic disease.

On admission, the temperature was 37.0°C, and blood pressure 120/80 mm Hg. The patient was mutistic, and responded only to painful stimuli. The pupils were isocoric and reacted to light. The muscle tone had increased. There were choreiform movements and myoclonic jerks in the extremities. No

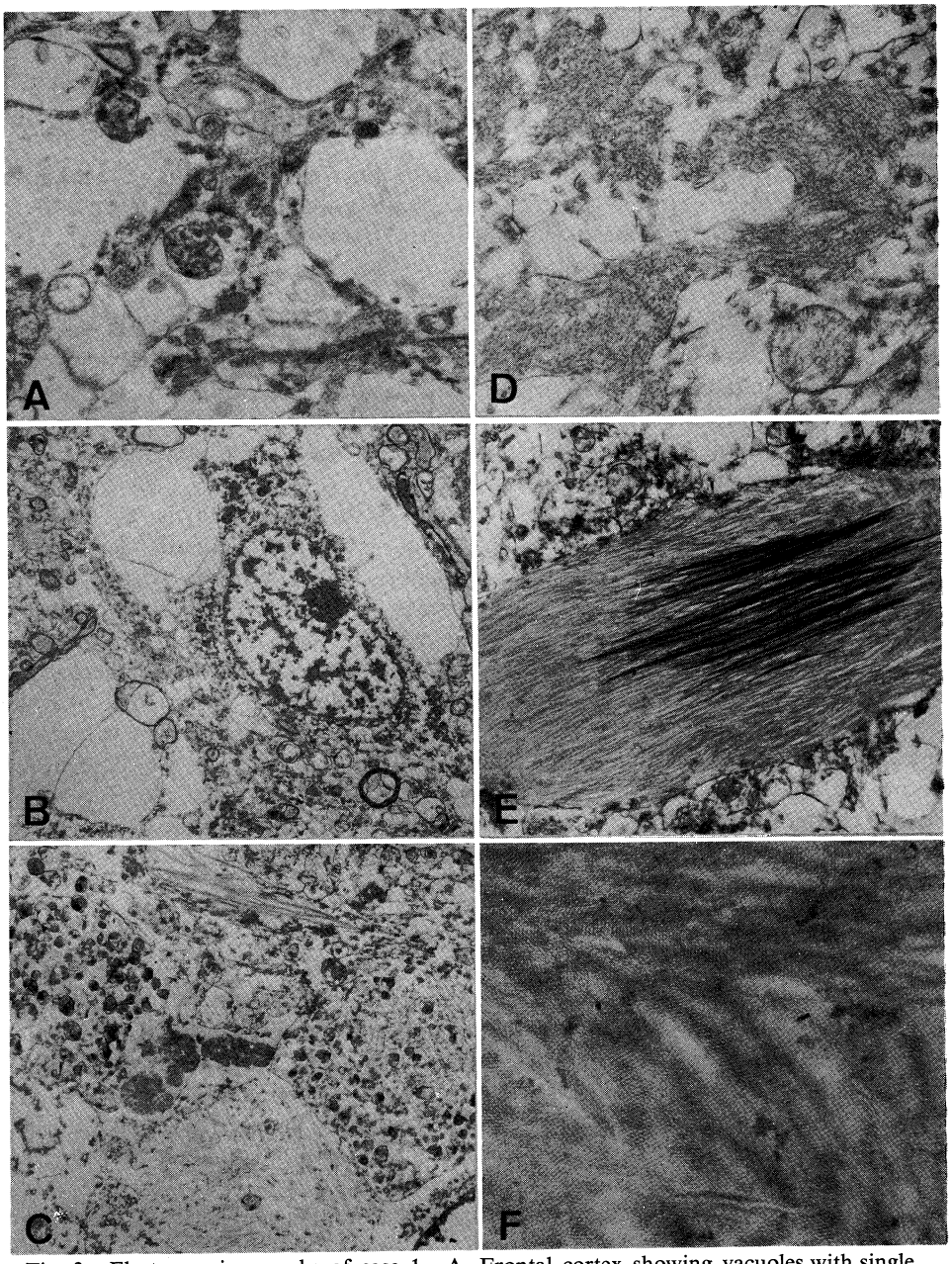

Fig. 3. Electron micrographs of case 1. A. Frontal cortex showing vacuoles with single or double limiting membranes. Some vacuoles contain synaptic vesicles inside of them. × 7,000. B. Frontal cortex showing vacuoles adjacent to the cytoplasmic membrane of a nerve cell. × 3,000. C. Senile plaque, which is composed of twisted tubules, lamellated or amorphous dense bodies and membranous or filamentous bodies, in the hippocampus. × 6,000. D. Senile plaque, showing amyloid filaments, in the

hippocampus. × 20,000. E. Hirano body, seen as accumulations of parallel filamentous bodies. × 10,000. F. Hirano body, showing lattice like structures, in the hippocampus. × 30,000.

pathologic reflexes were elicited.

The cerebrospinal fluid contained two lymphocytes per cubic millimeter ; CSF protein was 17 mg, and sugar 69 mg per deciliter. An electrocardiogram showed abnormal Q waves and suppressed T waves. CT scan of the brain demonstrated a small low density area in the white matter of the right cerebral hemisphere, together with moderate cortical atrophy and ventricular dilatation. An electroencephalogram revealed periodic synchronous discharges with a periodicity of 0.7 seconds (Fig. 4).

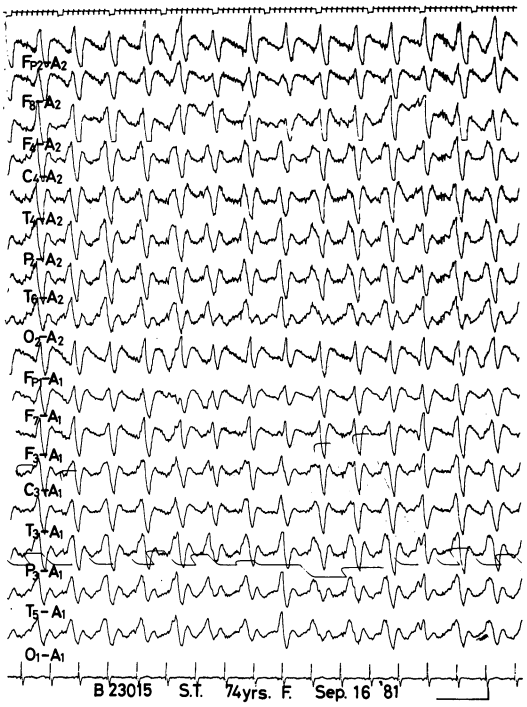

Fig. 4. Electroencephalogram of case 2 recorded two and a half months after onset of the illness and a half month before death showing typical periodic synchronous discharges with a periodicity of 0.7 seconds.

In September wheeze and tachypnea developed. She was intubated, and respirations were assisted. She died on October 2, after three months of the illness.

Autopsy Findings (A 81-156) :

The general autopsy disclosed confluent bronchopneumonia, systemic candidiasis, chronic pyelonephritis, old myocardial infarction, leiomyoma of the

stomach and fatty degeneration of the liver.

The brain weighed 940 g. The surface veins of the leptomeninges were congested. The cerebral gyri were moderately narrowed and the sulci were widened. The arteries at the cerebral base contained some atheromatous plaques. On coronal sections, the cerebral cortex were diffusely atrophic and brownly pigmented. These changes were most prominent in the occipital lobe. There was a small softened lesions in the deep white matter of the right parietal lobe. The lateral and third ventricles were moderately dilated. The cerebellar cortex was also suggestively atrophic. The dentate nuclei were deep brown in color.

Microscopically, there was a moderate infiltration of lymphocytes and macrophages in the leptomeninges. The nerve cells in the cerebral cortex were markedly diminished and protoplasmic astrocytes were proliferated. Small vacuoles less than 10 to 20 microns in diameter were scattered in the stroma. In Bodian's silver stainings, typical or compact senile plaques were found occasionally, with a small amount of Alzheimer's neurofibrillary changes. Nerve cell loss was most conspicuous in the occipital lobe. In addition, many microabscesses consisting of neutrophils, and small granulomatous lesions consisting of lymphocytes, histiocytes, epithelioid cells and some giant cells were found in the cerebral cortex. Periodic acid-Schiff stainings demonstrated hyphae and spores of candida albicans within these lesions. In the white matter of the cerebrum, there were no remarkable changes other than a softened lesion macroscopically observed.

In the hippocampus, nerve cells were well preserved. There was no stromal spongiosis. In Bodian's silver stainings, only small amounts of senile plaques and Alzheimer's neurofibrillary changes were found.

The basal ganglia and thalamus showed mild nerve cell loss, astrocytic gliosis and stromal spongiosis. These changes were more evident in the caudate nuclei and anterior nuclei of the thalamus. Pseudolimes were deposited in the blood vessel walls of the globus pallidus.

The molecular layer of the cerebellum was narrowed and loose with small vacuoles. Purkinje cells and granule cells were moderately decreased in number. The Bergmann glia were proliferated in the Purkinje cell layer. These changes seemed slightly greater in the vermis than in the hemispheres. Candidial microabscesses were found also in the cerebellum. The cerebellar white matter had no abnormalities. Numerous small brown pigments of 2 to 5 microns in diameter were found in the dentate nuclei, although the nerve cells in these areas were well preserved. These pigments were argentophilic and histochemically negative for calcium and iron. X-ray microanalysis of these pigments demonstrated peaks of sulfur and chlorine. There were no remarkable changes in the brainstem.

Electron microscopic examinations of the cerebral cortex revealed many vacuoles surrounded by single or double limiting membranes as in case 1.

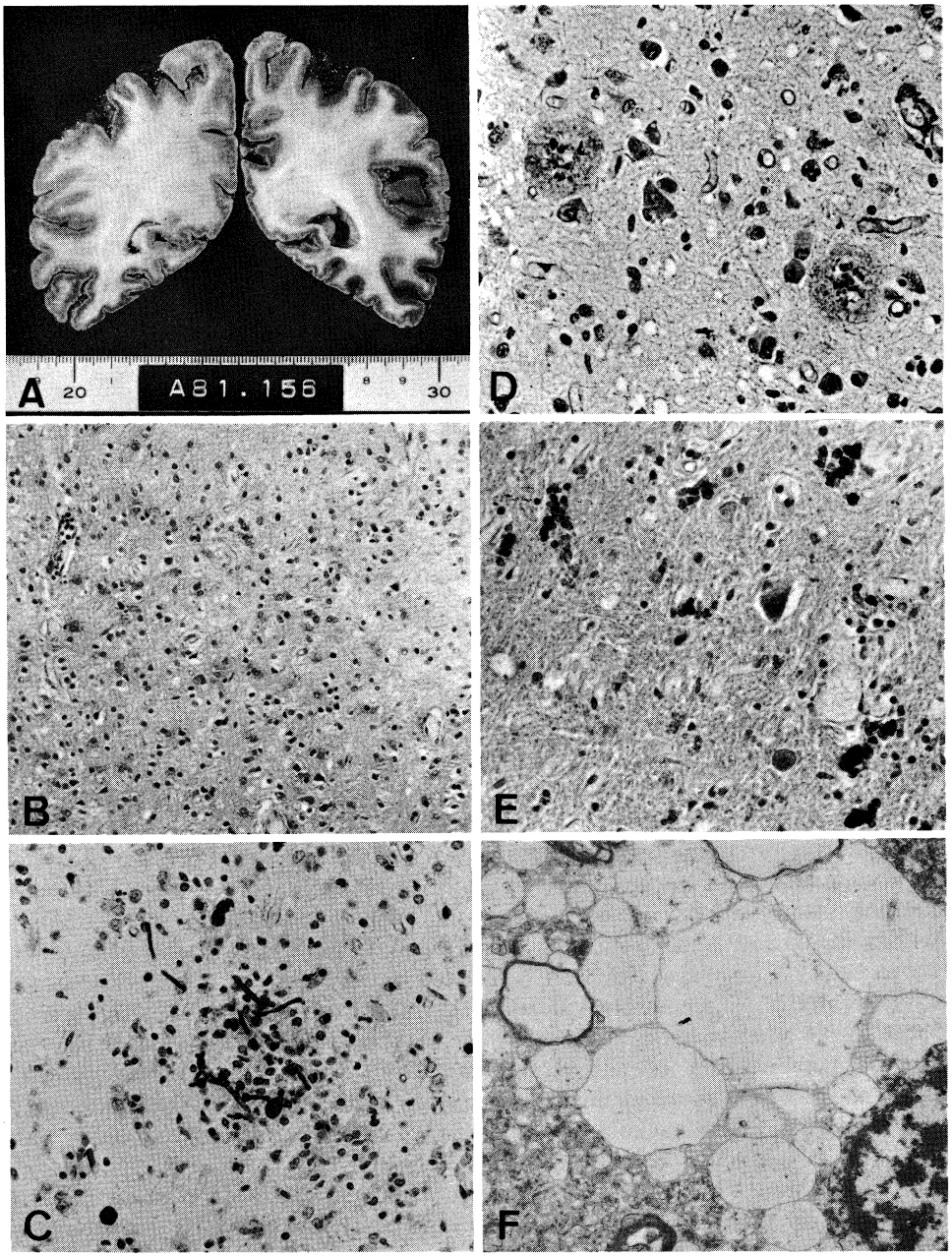

Fig. 5. Photograph, photomicrographs and electron micrograph of case 2. A. Coronal view of the occipital lobes. The cortex is atrophic, especially in the medial and inferior surfaces. The white matter is well preserved. B. Occipital cortex showing marked nerve cell loss, astrocytic gliosis and stromal spongiosis. HE, × 100.
C. Candidial microabscess in the occipital cortex. PAS, × 200. D. Senile plaques in the temporal cortex. Bodian, × 200. E. Dentate nucleus of the cerebellum scattered

with many brown pigments of 2 to 5 microns in diameter. HE, × 200. F. Occipital cortex showing many vacuoles surrounded by single or double limiting membranes. Some vacuoles are surrounded by thin myelin lamellae. × 6,000.

DISCUSSION

The clinical symptoms and signs of these two cases presented here were quite similar. Both patients developed visual disturbance, mental confusion, rigidity of the extremities and myoclonic jerks. Electroencephalograms revealed characteristic periodic synchronous discharges. One patient died after five months and the other after three months. These clinical pictures were so typical of Creutzfeldt-Jakob disease that the diagnoses were made before the patients' death.

Neuropathological findings were also similar in two cases and coincided with those of Creutzfeldt-Jakob disease. Marked nerve cell loss, protoplasmic astrocytosis and stromal spongiosis were observed in the cerebral cortex, especially in the occipital and temporal lobes. There were mild to moderate similar changes also in the basal ganglia, thalamus and cerebellum. In the first case, the vacuoles in the temporal lobes were extraordinarily large and occasionally fused with each other,

From the clinicopathological standpoint, Creutzfeldt-Jakob disease has been divided into several subtypes[2,3] such as subacute spongiform encephalopathy type, simple poliodystrophy type, thalamic type, cerebellar type or ataxic form[10], and amyotrophic type. In addition to these subtypes, panencephalopathic type[11], which is said to be prevalent especially in Japan, has been recently recognized. According to this classification, our two cases might belong to the subacute spongiform encephalopathy type of Creutzfeldt-Jakob disease.

Electron microscopically, spongiosis in the stroma of both cases was observed as accumulations of vacuoles of various sizes, usually with single or double limiting membranes in the neuropil. Some vacuoles contained synaptic vesicles within them, and some were situated adjacent to the cytoplasmic membrane of nerve cells. These vacuoles were suspected as resulting from the dilatation of axon terminals as previously indicated by other investigators[1,12-14]. The precise locations of other vacuoles scattered in the neuropil were not determined because of poor preservation of fine structures. Other reported examinations with biopsied specimens in which fine structures were well preserved have demonstrated the membrane bound vacuoles in the axons, dendrites and cell bodies of neurons, and also in astrocytic cell bodies and processes[15].

In the first case, as unusual findings for Creutzfeldt-Jakob disease, many typical senile plaques, neurofibrillary changes and Hirano bodies were found in the hippocampus, and primitive senile plaques in the cerebral cortex. These senile changes seemed to far exceed the patient's age.

Recently, several cases of Creutzfeldt-Jakob disease have been described with kuru plaques predominantly in the cerebellum and occasionally in other parts of the brain[16-18]. The similarities between Creutzfeldt-Jakob disease and

kuru, together with stromal spongiosis and transmissibility to animals, have been further emphasized by this common histopathological finding[19]. The plaques in our first case were distributed mainly in the hippocampus and cerebral cortex, different from kuru plaques, and the morphology was also apparently different from that of kuru plaques which are made of an amyloid containing dense mass. Electron microscopic examinations of the plaques in our case revealed that they were composed of twisted tubules, lamellated or amorphous dense bodies, membranous or filamentous bodies, a small amount of amyloid filaments and some other bodies. These features were nearly equal to senile plaques previously documented[20]. In our case, there were also many neurofibrillary changes and Hirano bodies. Electron microscopic examinations of these two structures were also identical to those of previously described findings[21]. Senile changes of the second case were thought just to be equivalent to the patient's age.

Formerly, the absence of senile plaques and Alzheimer's neurofibrillary changes was thought to be an important diagnostic feature of Creutzfeldt-Jakob disease. Recently, however, there have been several case reports of Creutzfeldt-Jakob disease with these senile changes reminiscent of Alzheimer's disease[2,22–26]. Reviewing these papers, although relatively aged people appear to show more intense senile changes, the senile changes of these cases seemed to exceed their ages as in our case. It is improper to think that the existence of these senile changes is merely an incidental occurrence. It may be more reasonable to consider that these cases of Creutzfeldt-Jakob disease with senile changes have some relationship to Alzheimer's disease.

In recent years, the possibility of transmissibility of Alzheimer's disease has been discussed, especially in familial cases[9]. From this point of view, it is interesting that both Creutzfeldt-Jakob disease and Alzheimer's disease have the same pathological senile changes. It may be that an agent causing Creutzfeldt-Jakob disease is promoting early senility, or Creutzfeldt-Jakob disease and Alzheimer's disease have something in common with pathological senility. Or it may be that both diseases are caused by a similar transmissible agent.

An unusual finding in the second case was the presence of brown pigments of 2 to 5 microns in diameter in the dentate nuclei. These pigments were different from calcification, ferrugination, neuromelanin and lipofuscin in their shape, size, color and chemical constitution. They are thought to be a kind of senile change, other than lipofuscin, and composed mainly of organic compounds containing sulfur and chlorine. Probably they are unrelated to Creutzfeldt-Jakob disease. Similar pigments have been reported by Akashi et al.[27] Their precise nature is obscure at the present time.

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