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Progressive Dementia with Motor Neuron Disease

An Additional Case Report and Neuropathological Review of 20 Cases in Japan

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Summary. A 68-year-old male had the characteristic clinical features of progressive dementia accompanied by motor neuron disease. The duration of his illness was 26 months. The chief findings from light microscopic studies were: diffue neuronal degeneration characterized by a simple atrophy and a mild disappearance of nerve cells throughout the CNS. Status spongiosus was observed in the basal ganglia. There were lesions similar to those of a motor neuron disease in the brain stem and spinal cord. Although there were no clinical symptoms of an extrapyramidal disease, severe involvement was seen in the substantia nigra. This patient belongs to the same group of cases of presenile dementia with motor neuron disease described by the author. A neuropathological review of 20 similar cases reported in Japan is discussed and the possibility of a new disease entity for these cases is suggested.

Key words: Progressive dementia – Motor neuron disease

Introduction

Presenile dementia with motor neuron disease is a progressive, fatal, chronic, degeneration of the CNS. The clinicopathological features have already been described by the author (Mitsuyama and Takamiya 1979; Mitsuyama and Tobo 1981; Mitsuyama 1984). About 30 clinical cases have been reported in Japan and an autopsy performed in 20 of them. We are interested in discovering whether the frequency and topology of lesions in the brain of patients with presenile dementia and motor neuron disease differed characteristically from the distribution found in cases of Alzheimer's disease (AD), Pick's disease (PD), Creutzfeldt-Jakob disease (CJD) or progressive subcortical gliosis (PSG).

The aim of this report is to describe the clinicopathological findings of one additional case and to review the neuropathology of those cases previously reported in Japan.

Case Report

A 68-year-old male experienced gradual intellectual deterioration. There was no history to suggest a precipitating cause, and his birth and development had been normal. He had five siblings and three children, all of whom are alive and well. There was no history of mental illness in any of the families.

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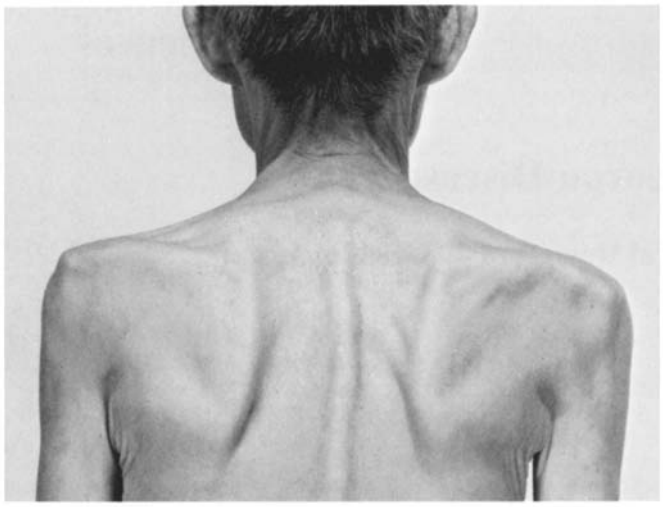
According to his wife, his decline began in approximately 1981, when he was noted to have difficulty in calculations and recent memory. He was hospitalized in June 1982 at the Miyazaki Medical College Hospital, and on admission his personal appearance indicated apathy. No evidence of neurological deficiency was demonstrated except for moderate dementia. At the time of admission, he was oriented as to time, place and person, although his recent and past memory faculties were slightly defective and he seemed to lack insight. He was able to handle simple spelling or maths, could follow one stage commands, answered questions with one or two words, and offered a minimum of spontaneous speech. Routine tasks took him longer and the results were imperfect. A CT-scan revealed a slight cerebral atrophy with no focal lesions. Senile dementia was diagnosed at the initial examination.

During the following months, his dementia progressed, and muscule wasting with fasciculation in the upper extremities, dysarthria, and dysphagia also developed (Figs. 1, 2). His speech became unclear as dysphasia progressively developed, and his vocabulary became more limited until he was completely mute. The characterstics signs of bulbar palsy were observed, but other signs of cranial nerve dysfunction were absent. There was no unequivocal evidence of upper corticospinal motor neuron dysfunction, and static tremor was generally unobserved. By July 1983 his level of functioning had deteriorated to the point where he could only maintain personal, hygenic requirements. His mood was often euphoric without any reason. His condition progressively deteriorated until August 1983, when he became bedridden, uncommunicative and incontinent. Generalized rigidity with cogwheeling in all extremities, myoclonus or tremor were not observed. Deep tendon reflexes were always hypoactive and equal, and there was no evidence of pyramidal tract degeneration. Pathological sucking and grasp reflexes were not noticed and there was no glabellar reflex at any time. Sensory function seemed to be intact, and his personality traits were maintained until the disease was advanced. The remaining findings from a general physical and neurological examination were normal.

Hemoglobin was 12.5 g/100 ml, and the white blood cell count was 6,000/mm^3 with 55% granular leukocytes, 4.0% eosinophils and 35.5% lymphocytes. Routine biochemical tests revealed normal serum electrolytes (including calcium), urea, creatinine, liver enzymes, thyroxine, and glucose. Cerebrospinal fluid analysis and skull and chest radiographs were within the normal limits. A second CT-scan (Fig. 3), 1 year after the first study, showed progressive brain atrophy with no focal lesions, edema, or hemorrhage. An EEG revealed a dif-



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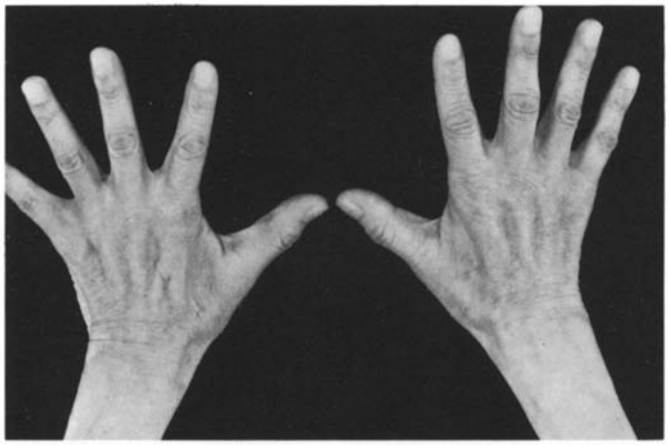

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Figs. 1, 2. Muscle atrophy in the shoulder and hands

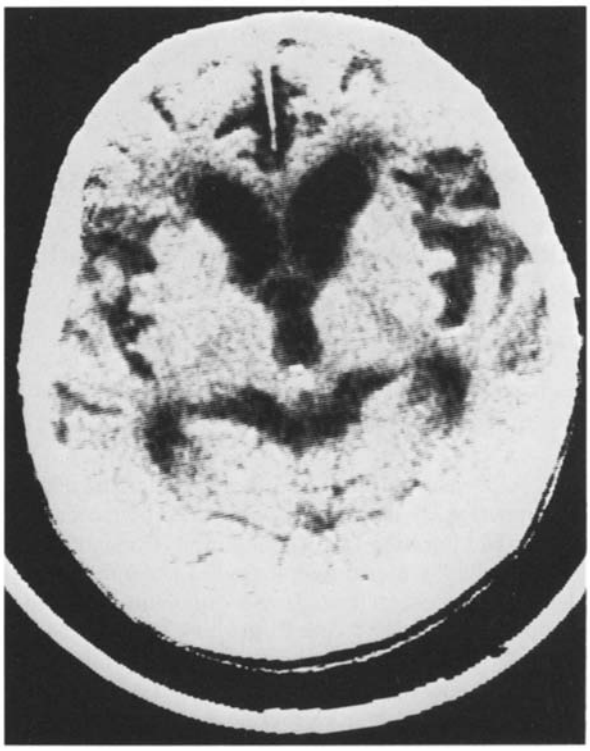

Fig. 3. CT-scan, 1.5 years after the onset of illness, shows fronto-temporal lobe atrophy

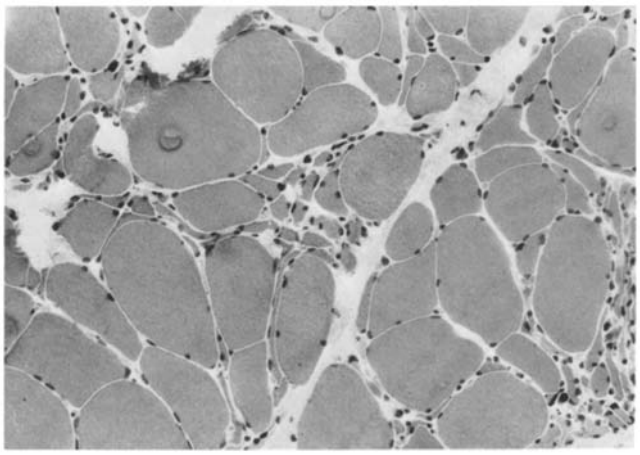

Fig. 4. Muscle from the right biceps shows neurogenic atrophy (H-E, × 450)

fuse slowing of background activities with no lateralized discharges. There were no high voltage periodic synchronous spikes, spike and wave rhythm, or triphasic complexes. An EMG revealed frequent fibrillation and fasciculation. A MNU showed polyphasic waves and nerve conduction velocity was normal. A muscle specimen from the right deltoid was interpreted as showing neurogenic atrophy (Fig. 4). A psychological examination at the age of 67 years revealed an IQ of 66 and indications of moderate dementia. He had several generalized tonic-clonic convulsions in the terminal stage which were probably caused by an hypoxic condition. His condition continued to deteriorate and he died on December 20, 1983 from recurrent bronchopneumina. In conclusion, the clinical features exhibited by this patient suggested a predominant cerebral degenerative disease with involvement of the motor neuron system. Other motor neuron diseases, e.g., cervical spondylic myelopathy, multiple sclerosis, polyneuropathy, and mercury intoxication could all be excluded. A provisional diagnosis of progressive dementia with motor neuron disease was made.

Postmortem Examination

General pathology revealed bronchopneumonia, myocardial atrophy and chronic cystitis. The brain weighed 1,330 g and exhibited mild to moderate convolutional atrophy of the cerebrum, most marked in the frontal and temporal areas. The ventricular system was slightly dilated symmetrically. Slight depigmentation of the substantia nigra was demonstrated.

On microscopic examination, mild spongiform change, mild neuronal loss, and mild gliosis were found in the cerebral cortices, corpus striatum, thalami and cerebellar cortex. The spongiform change was predominantly laminar, affecting mainly the superficial layers with no involvment in the deep layers (Fig. 5). These changes were most severe in the frontal cortex and less severe in the occipital cortex and hippocampus. A number of changes involving discrete, subacute, nonspecific, hypoxic vascular nerve cell lesions were pronounced in the occipital cortex (Fig. 6). These were mainly laminar and limited largely to the third layer. In addition, we found these

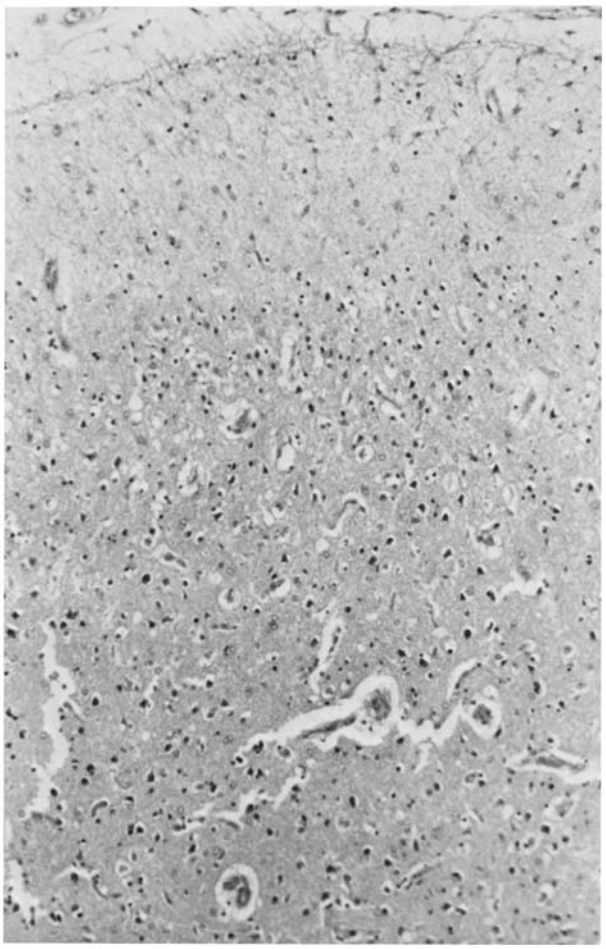

Fig. 5. Mild sponginess in the superficial layer of the frontal cortex (H-E, × 350)

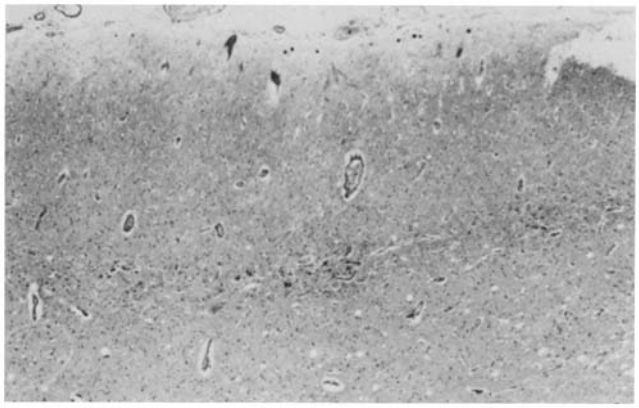

Fig. 6. Laminar necrosis in the third layer of the occipital cortex (PAS, × 135)

Fig. 7. Focal sponginess in the left putamen (H-E, × 90)

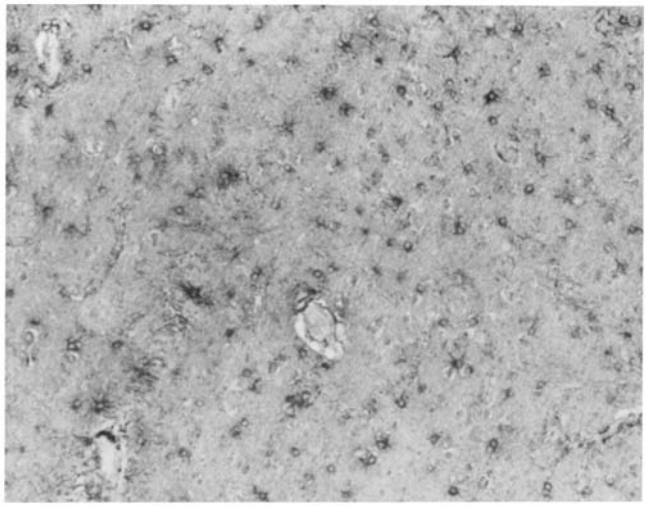

Fig. 8. Astrocytic gliosis in the left frontal cortex (GFAP, × 337)

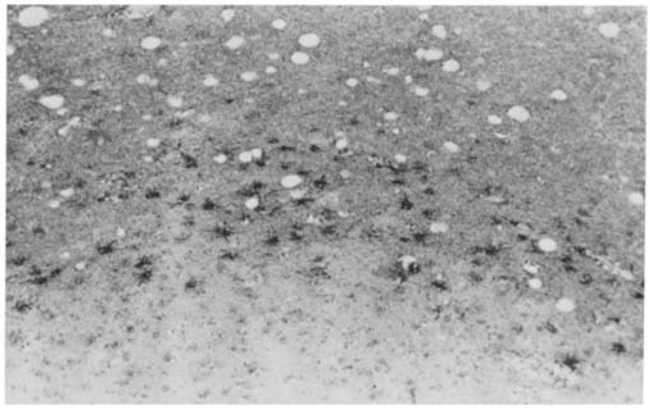

Fig. 9. Astrogliosis in the subcortical white matter of the left frontal lobe (GFAP, × 225)

changes limited to endofolium and subiculum of the hippocampus in the allocortex. Localized status spongiosus was observed in the striatum (Fig. 7). There was a mild rarefaction of the myelin sheath in the deep white matter of the cerebral hemispheres. We noted widespread hyperplasia and hypertrophy of astrocytes in both the grey and subcortical white mater prominent in the frontal lobe (Figs. 8, 9). No gitter cells, inflammatory cells, or cytoplasmic or intranuclear inclusion bodies were found. There was no evidence of pathological changes in the nucleus basalis of Meynert. In the substantia nigra, there was a severe lesion as indicated by reduction in the number of pigmented cells, the presence of phagocytes containing melanin granules, and fibrous gliosis (Fig. 10). No Lewy bodies or Alzheimer's neurofibrillary tangles were

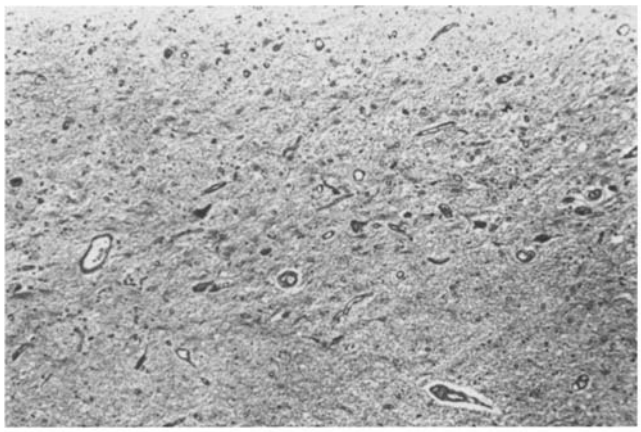

Fig. 10. Neuronal loss and gliosis in substantia nigra (H-E, × 450)

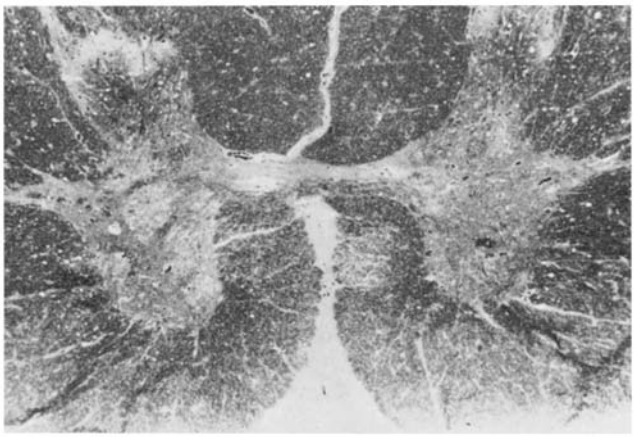

Fig. 11. Marked loss of anterior horn cells in the thoracic cord (PAS, × 150)

evident. The locus ceruleus was not affected. In the medulla oblongata, there was a marked loss of neurons in the hypoglossal nuclei and loss of anterior horn cells in the cervical and thoracic cords was demonstrated (Fig. 11). There was no definite presence of lesions in the corticospinal tract. The anterior roots showed moderate atrophy. None of the changes of Alzheimer's disease (neurofibrillary tangles, senile plaques, granulovacuolar degeneration) could be demonstrated.

Neuropathological Review

The neuropathological findings of similar cases with a title of presenile dementia and motor neuron disease reported in Japan can be summed-up as follows (Table 1).

(1) At postmortem examination the brain usually appears normal. The brain weights are from 1,000 to 1,440 g and the average is 1,210 g. Gross inspection of the brain in the majority of these cases shows atrophy that varies from slight to moderate and is mainly in the frontal and/or temporal lobes. The ventricles may be dilated and the blood vessels may appear healthy.

(2) The most outstanding features of light microscopic findings are widespread degenerative changes, characterized by simple atrophy and pigment atrophy with excessive lipofuscin of nerve cells. A mild disappearance of nerve cells is seen in all cases. These lesions are usually in the superficial layers of the cerebral cortex. The frontal and temporal lobes seem to be most affected. Lesions in the cerebral cortex are less extensive than those seen in AD or CJD.

(3) A spongy change in the cerebral cortex is frequently present (18 of 20 cases). It is usually very mild, and it is difficult to exclude the possibility of the vacuolization resulting from cortical atrophy. The vacuolization is limited to the second and third layers of the cerebral cortex, with no involvement of the deeper layers. Definite status spongiosus can be observed in the basal ganglia and brain stem (Shirabe et al. 1970; present case).

(4) The white matter usually appears normal with no loss of myelin but fibrillary gliosis is frequently present in the subcortical white matter of the frontotemporal lobes. Diffuse fibrillary gliosis in the deep white matter of the cerebrum has been reported in some cases (Kaiya 1972; Muramoto et al. 1980; Nakahara et al. 1981; Ando and Miyakawa 1982; Hamamoto et al. 1982). Gliosis in the basal ganglia and inferior olivary nuclei is occasionally observed without severe involvement of the neuronal structure (Kaiya 1972; Kawagoe and Nakayma 1979; Muramoto et al. 1980; Akai et al. 1982; Ando and Miyakawa 1982; Iwamura et al. 1984; Shiyokawa et al. 1984; present case).

(5) Lesions in the spinal cord and brain stem of a patient with a motor neuron disease are the most characteristic finding. Neuronal loss of hypoglossal nuclei is characteristic and occasional involvement of the ambiguus or facial nuclei may be detected (Shirabe et al. 1970; Iwamura et al. 1984; Shiyokawa et al. 1984). In addition to the neuronal loss of the anterior horn cells, degeneration of the tracts, but with no particular pattern, can be seen in a majority of the cases. Lesions in the spinal cord are mainly limited to the cervical and thoracic cords. The lumbar cord is usually spared. Although half of these cases reveal corticospinal tract degeneration, it is usually mild, and not as systemic as those seen in classical sporadic amyotrophic lateral sclerosis (ALS). Anterior roots are atrophic in all these cases.

(6) Neuronal loss and gliosis in the substantia nigra or pallidum are frequently reported (10 of 20 cases). Alzheimer's neurofibrillary tangles or Lewy bodies are not present in the substantia nigra in these cases. Glial nodule has been reported only in the case of Kaiya (Kaiya 1972).

(7) Senile plaques, Alzheimer's neurofibrillary tangles or granulovacuolar degeneration are infrequently found.

(8) In the majority of cases neurogenic muscle atrophy is also present.

Discussion

The clinicopathological findings in this case confirmed a presenile dementia with motor neuron disease. The term "presenile" may not be appropriate to describe this patient who developed dementia at the age of 66. Similar cases with the onset at an older age have been reported in other countries (Wikstrom et al. 1982). A title of progressive dementia with motor neuron disease would be better for these cases. According to the previous description of the clinical features (Mitsuyama and Takamiya 1979; Mitsuyama and Tobo 1981), all patients developed a motor neuron disease concurrently with progressive dementia. No patient had a history of stroke or focal neurological signs due to an ischemic attack. The

Table 1. Neuropathological review of cases reported in Japan

Cases	Sex, age at onset (yr) duration of illness (mo) clinical diagnosis	Macroscopic findings of CNS	Microscopic findings of CNS
Harada et al. (1966)	Male, 58–59, 48–60 Unclasssified presenile dementia with progressive spinal muscle atrophy	1,280 g Slight diffuse atrophy	Neuronal loss and degeneration in cerebral cortex and anterior horn cells of spinal cord. Astrogliosis in subcortical white matter. Gliosis in the anterior horn of spinal cord. Marked demyelination of the corticospinal tract. Neuronal loss in the hypoglossal nuclei. Gliosis in the pallidum and inferior olivary nuclei. Neuronal loss and gliosis in the Ammon's horn. Old tiny infarct in the left putamen
Tsujiyama et al. (1967)	Male, 40, 40 Progressive dementia like PD with amyotrophic lateral sclerosis	1,140 g Temporal lobe atrophy	Neuronal loss and degeneration in cerebral cortex and anterior horn cells of spinal cord. Astrogliosis in subcortical white matter. Mild sponginess in cerebral cortex. Demyelination in the frontotemporal lobe white matter with gliosis. Gliosis in the caudate, amygdala and hypothalamic nuclei
Yuasa (1970)	Female, 53, 27 Dementia with amyotrophic lateral sclerosis	1,100 g Frontoparietal lobe atrophy. Marked atrophy in the superior temporal lobe	Neuronal loss and degeneration in the frontal lobes. Mild sponginess in cerebral cortex. Astrogliosis in cerebral white matter. Mild fibrillary gliosis in the frontotemporal lobe white matter. Neuronal degeneration with gliosis in the caudatum, putamen and pallidum. Neuronal loss with gliosis in substantia nigra. Corticospinal tract degeneration. Neuronal loss of hypoglossal nuclei and anterior horn cells of spinal cord
Shirabe et al. (1970)	Female, 38, 15 Amyotrophic lateral sclerosis with dementia	1,290 g Frontotemporal lobe atrophy	Neuronal loss and degeneration in cerebral cortex. Mild sponginess with gliosis in cerebral cortex. Mild gliosis in cerebral white matter. Mild gliosis in putamen and pallidum. Corticospinal tract degeneration. Mild sponginess in substantia nigra. Neuronal loss of hypoglossal nuclei, n. ambiguus and anterior horn cells of spinal cord
Mitsuyama and Takamatsu (1971)	Female, 58, 24 Dementia with amyotrophy	1,070 g Frontal lobe atrophy	Neuronal loss and degeneration in cerebral cortex. Mild sponginess in cerebral cortex. Mild gliosis in cerebral white matter. Neuronal loss in hypoglossal nuclei and anterior horn cells of spinal cord
Kaiya (1972)	Male, 45, 21 Presenile dementia with amyotrophic lateral sclerosis	1,280 g Frontal lobe atrophy	Neuronal loss and degeneration in cerebral cortex. Diffuse fibrillary gliosis in cerebral white matter. Slight gliosis in striatum, thalamus and hypothalamus. Marked neuronal loss with gliosis in substantia nigra. Neuronal loss in hypoglossal nuclei. Gliosis in frontopontine and corticospinal tract
Amamiya et al. (1974)	Female, 69, 18 Dementia with amyotrophic lateral sclerosis	1,230 g Frontal lobe atrophy	Neuronal loss and degeneration in cerebral cortex. Neuronal loss in anterior horn cells of spinal cord. Demyelination of corticospinal tract
Mizutani et al. (1977)	Male, 58, 9 Presenile dementia	1,380 g	Neuronal loss and degeneration in cerebral cortex. Fibrillary gliosis in frontotemporal lobe white matter. Neuronal loss in substantia nigra. Demyelination of corticospinal tract
Oiwake et al. (1979)	Male, 47, 13 Amyotrophic lateral sclerosis with temporal lobe atrophy	1,440 g Temporal lobe atrophy	Neuronal loss and degeneration in temporal lobe cortex. Marked fibrillary gliosis in temporal lobe white matter. Neuronal loss of hypoglossal nuclei and anterior horn cells of spinal cord. Incomplete demyelination of corticospinal tract
Kawagoe and Nakayma (1979)	Female, 56, 20 Dementia with amyotrophy	1,250 g Frontal lobe atrophy	Neuronal loss and degeneration in cerebral cortex. Mild fibrillary gliosis in cerebral white matter. Slight gliosis in pallidum and inferior olivary nuclei. Neuronal loss in anterior horn cells of spinal cord. Neuronal loss in substantia nigra
Muramoto et al. (1980)	Female, 54, 36 Presenile dementia resembling PD associated with amyotrophic lateral sclerosis	1,040 g Fronto temporal atrophy	Neuronal loss and degeneration in cerebral cortex. Mild sponginess in cerebral cortex. Fibrillary gliosis in cerebral white matter. Gliosis in basal ganglia and substantia nigra. Neuronal loss in hypoglossal nuclei and anterior horn cells of spinal cord. Mild demyelination of corticospinal tract

Table 1 (continued)

Cases	Sex, age at onset (yr) duration of illness (mo) clinical diagnosis	Macroscopic findings of CNS	Microscopic findings of CNS
Nakahara et al. (1981)	Male, 60, 72 Motor neuron disease with dementia	1,090 g Temporal lobe atrophy	Neuronal loss and degeneration in cerebral cortex. Mild fibrillary gliosis in cerebral white matter. Plenty of senile plaques and Alzheimer's neurofibrillary tangles in cerebral cortex. Neuronal loss with gliosis in anterior horn cells of spinal cord
Akai et al. (1982)	Female, 54, 39 Presenile dementia with motor neuron disease	1,150 g Temporal lobe atrophy	Neuronal loss and degeneration in cerebral cortex. Mild sponginess in cerebral cortex. Marked gliosis in temporofrontal lobe white matter, amygdala, striatum and thalamus. Neuronal loss in hypoglossal nuclei and anterior horn cells of spinal cord. Alzheimer's neurofibrillary tangles in temporal cortex and granulovacuolar degeneration in hippocampus
Ando and Miyakawa (1982)	Female, 51, 72 Dementia with degeneration of motor neurons	1,250 g Temporal lobe atrophy	Neuronal loss and degeneration in cerebral cortex. Fibrillary gliosis in cerebral white matter. Gliosis in caudate, putamen and substantia nigra. Neuronal loss of hypoglossal nuclei and anterior horn cells of spinal cord
Sato et al. (1982)	Male, 56, 12 Presenile dementia with motor	? Frontal lobe atrophy	Neuronal loss and degeneration in cerebral cortex. Fibrillary gliosis in cerebral white matter. Mild spongines in cerebral cortex. Neuronal loss in anterior horn cells of spinal cord
Hamamoto et al. (1982)	Male, 60, 36 Presenile dementia with amyotrophy	1,340 g	Neuronal loss and degeneration in cerebral cortex. Fibrillary gliosis in cerebral white matter. Neuronal loss and gliosis in anterior horn of spinal cord. Senile plaques in cerebral cortex
Iwamura et al. (1984)	Male, 44, 32 Presenile dementia with motor neuron disease	1,000 g Frontotemporal atrophy	Neuronal loss and degeneration in cerebral cortex. Fibrillary gliosis in frontotemporal lobe white matter. Neuronal loss with gliosis in pallidum and thalamus. Neuronal loss in hypoglossal and facial nuclei. Neuronal loss in anterior horn cells of spinal cord. Neuronal loss and gliosis in substantia nigra
Shiyokawa et al. (1984)	Female, 62, 42 Dementia with amyotrophy	1,200 g Frontotemporal atrophy	Neuronal loss and degeneration in cerebral cortex. Fibrillary gliosis in frontotemporal lobe white matter. Neuronal loss of anterior horn cells, substantia in nigra and dentate nucleus. Gliosis in pallidum and subthalamicus. Neuronal loss in hypoglossal and facial nuclei
Motoyoshi et al. (1984)	Male, 50, 12 Amyotrophic lateral sclerosis with dementia	?	Neuronal loss and degeneration in cerebral cortex. Gliosis in subcortical white matter. Neuronal loss of anterior horn cells. Demyelination of corticospinal tract
Present case	Male, 66, 26 Progressive dementia with motor neuron disease	1,330 g Frontal lobe atrophy	Neuronal loss and degeneration in cerebral cortex. Mild gliosis in cerebral cortex and subcortical white matter. Mild sponginess in cerebral cortex. Neuronal loss in hypoglossal nuclei and anterior horn cells of spinal cord. Neuronal loss and gliosis in substantia nigra

mean duration of the clinical illness was 30 months (in the present case the duration was approximately 26 months). From the onset of the disease evidence of organic dementia was apparent and the early symptoms were usually limited to failing memory or mood change. There were a number of emotional abnormalities, particularly in the early stages of the illness. Most of the patients with progressive dementia and motor neuron disease had speech disturbances, in the early, middle, or final stages of their clinical course. Visual/spatial problems were not observed. Dementia became more profound as the illness progressed, with increasing memory loss, intellectual deterioration, lack of insight and poor judgement. Self-neglect increased and with the latter development of incontinence. There was only 1 case with generalized tonic-clonic seizures, and in only 3 out of 20 cases was Parkinson's syndrome, such as tremor or rigidity observed (Harada et al. 1966; Tsujiyama et al. 1967; Shiyokawa et al. 1984). The patients usually died of recurrent bronchopneumonia.

The neuropathological changes seen in the case presented here were typical of presenile dementia with motor neuron disease as have been previously described. Widespread and nonspecific cortical neuronal damage was evident, together with the involvement of the brain stem and spinal cord. There was some evidence to suggest partial basal ganglia damage. Only mild nonspecific neuropathological changes were seen in this case and classic status spongiosus was present only in the basal ganglia. In the first neuropathologically examined case of presenile dementia with motor neuron disease in Japan, Yuasa (Yuasa, 1964; Yuasa 1970) reported similar findings in the cerebrum and spinal cord. Clinically and histopathologically, there is some resemblance to CJD, ALS and PSG. The neuropathological features of CJD consist of a triad of findings in the grey matter structures: status spongiosus, neuronal loss, and proliferation of astrocytes. The microscopic findings regarding the nucleus basalis of Meynert and related structures were not prominent in this case. In all these cases studied in detail there was no evidence of pathological change (Mitsuyama and Takamatsu 1971; Iwamura et al. 1984; present case). The findings were much different from those of AD. The absence of any neuropathological evidence of other diseases suggests that cases of progressive dementia with motor neuron disease are etiologically different from Parkinson's disease, ALS, or AD.

In contrast to the cases of CJD or PSG reported in Japan, lesions in the white matter were usually mild in the cases of progressive dementia with motor neuron disease. We consider some other persistent influence upon neuronal damage possible, e.g., as a result of respiratory disturbances in these patients due to severe muscular wasting during their clinical course. In the case presented here, we found subacute, hypoxic/ischemic nerve cell loss. We are of the opinion that the lesions occurred as a result of reduction in ventilation and/or circulation during the illness.

Although authors (Mitsuyama and Takamiya 1979; Mitsuyama and Tobo 1981) have stressed that the lack of extrapyramidal symptoms is one of the characteristic clinical features in cases of progressive dementia with motor neuron disease, we observed moderate to severe lesions in the substantia nigra and basal ganglia in one-half of these cases. No patient suffered from Parkinson's disease. The clinical course and mental status are very similar in patients with and without lesions in the substantia nigra and pallidum. We cannot exactly conclude from this small study that progressive dementia with motor neuron disease is a single disease. It may include different conditions, although we do not know how many. We think that from the clinicopathological point of view, it could be very important to recognize the discrepancy between the pathological and clinical symptoms in certain cases. The diagnosis of progressive dementia with motor neuron disease is highly dependent upon the clinical symptomatology, and it is surprizing that identical lesions in the substantia nigra and the basal ganglia were demonstrated without the evidence of neurological deficiencies.

Similar cases have been reported in other countries (Von Baunmühl 1937; Myrianthopoulos and Smith 1962; Poppe and Tennstedt 1963; Von Matt 1964; Miauf and Jellinger 1969; Hudson 1981; Wikstrom et al. 1982), and there are many opinions concerning a resemblance between this condition and CJD or ALS. The etiology of the disease is unclear, and at the time of writing there is no solid evidence in these cases. The findings reported in this study reinforce the need for further investigation to establish how the particular clinical pattern in typical cases of progressive dementia with motor neuron disease might arise. There has been speculation that syndromes of ALS and dementia, and AD may be caused by a slow virus (Salazar et al. 1983; Wisniewski 1978). There is also the possibility that a slow virus infection exists among these cases with progressive dementia and motor neuron disease.

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