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CASE REPORT

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Rapidly progressive aphasia and motor neuron disease: a clinical, radiological, and pathological study of an autopsy case with circumscribed lobar atrophy

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Abstract This report concerns an autopsy case of rapidly progressive aphasia and motor neuron disease. The patient was a Japanese woman who was 75 years old at the time of death. The family history did not reveal hereditary burden. She developed language disturbances and difficulty in swallowing at age 74. Neurological examination 1 month after the disease onset revealed motor aphasia without dementia and bulbar sign, followed by muscle weakness of the four extremities. Neuroradiological examination revealed progressive atrophy of the anterior part of the left temporal lobe. She died of respiratory difficulty 10 months after the disease onset. Macroscopically, neuropathological examination showed circumscribed atrophy of the left perisylvian region and, histologically, neuronal loss in the cerebral cortex, including the primary motor area, substantia nigra, brain stem motor nuclei, and anterior horns of the spinal cord, in addition to obvious degeneration of the pyramidal tracts and presence of Bunina bodies. Ubiquitin-immunoreactive neuronal inclusions were present in the hippocampal dentate granular cells and frontotemporal cortical layer II neurons. Based on these clinicopathological findings and a review of the literature, we concluded that our case is the first reported case of amyotrophic lateral sclerosis with dementia that clinically showed rapidly progressive aphasia.

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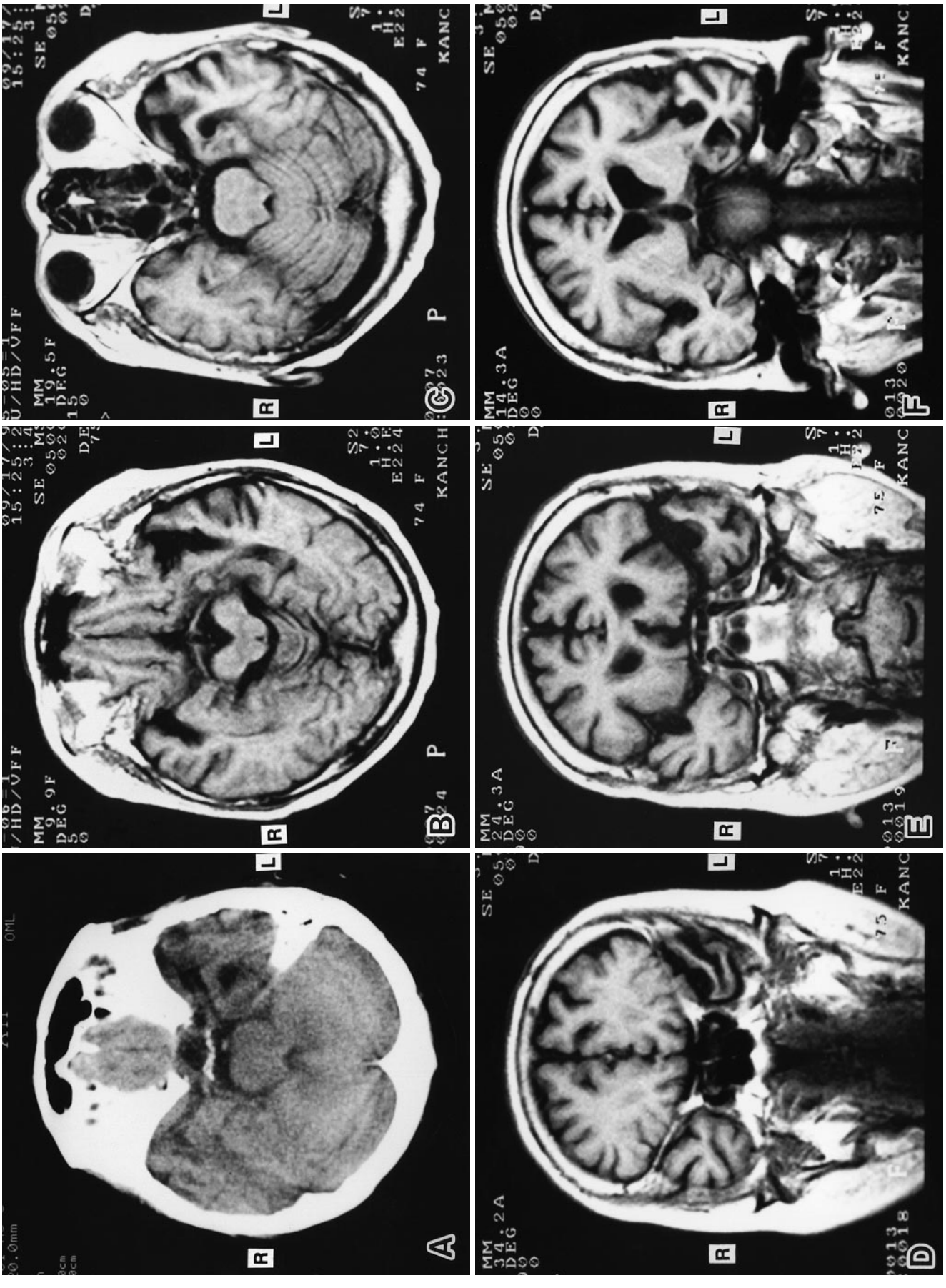
Introduction

Progressive aphasia is a clinical syndrome, proposed by Mesulam [13, 14], affecting the left perisylvian region and presenting with gradually worsening aphasia without generalized dementia at the initial stage. To date, a variety of diseases presenting with the syndrome have been reported, including Alzheimer-type dementia [6], Pick's disease with Pick bodies [5], corticobasal degeneration [1, 24, 25], dementia lacking distinctive histology (DLDH) [26] and other degenerative conditions [22].

Few reports concerning cases of progressive aphasia with amyotrophic lateral sclerosis (ALS) are available at present [4, 10], but judging from the present neuropathological criteria, the above-mentioned cases do not belong to the category of ALS with dementia [15, 19, 20, 27] or motor neuron disease-type dementia (MNDD) [18, 23].

We report here a Japanese autopsy case of rapidly progressive nonfluent aphasia with ALS, which also showed neuroradiologically progressive localized lobar atrophy in the brain. Neuropathological examination revealed not only macroscopically circumscribed atrophy of the left perisylvian region, but also histologically marked neuronal loss and astrocytosis in the circumscribed lobar atrophy with widespread ubiquitin-immunoreactive intraneuronal inclusions in the brain, in addition to neuropathology compatible with ALS. We believe that our case verifies the multiplicity of pathology underlying progressive aphasia and the diversity of clinicopathological features concerning ALS with dementia or MNDD.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◀ **Fig. 1** Brain CT and MRI showing progressive atrophy of the left temporal lobe. **A**–**C** CT (**A**) and MRI (**B**, **C**) 1 month after the disease onset. **D**–**F** MRI 6 months after the disease onset (*CT* computed tomography, *MRI* magnetic resonance imaging)

Case report

Clinical course

The patient was a Japanese woman who was 75 years old at the time of death. She had no family history of neurological disease. The patient developed language disturbance and difficulty in swallowing at age 74. About 1 month later, neurological examination revealed motor aphasia, forced laughter, dysarthria, and increased deep tendon reflexes in the extremities. Muscle weakness of the four extremities was not present. Hand grip test showed that the right side was 22 kg, with the left side being 21.5 kg. Using the Wechsler adult intelligence scale (WAIS), verbal intelligence quotient (IQ) could not calculated because of dysarthria; the performance IQ was 97. At this stage, electromyogram examination revealed neurogenic pattern in the upper extremities. About 5 months after the onset of the disease, the patient presented with muscle weakness of the upper and lower extremities. Neurological examination at this period showed severe motor aphasia, weakness of the facial muscle, atrophy and fasciculation of the tongue, moderate muscle weakness in the upper and lower extremities, and bilateral Babinski signs. About 6 months after the disease onset, she could not walk by herself, and tube feeding was started because of severe dysphagia. At 7 months after the onset of the disease, she could not understand sentences and phrases spoken by doctors and nurses. About 9 months after the disease onset, she could not move the four extremities. She died of respiratory disturbance about 10 months after the onset of the disease.

Neuroradiology

Brain computed tomography and magnetic resonance imaging at age 74, 1 month after the onset of the disease, showed slight atrophy of the anterior part of the left temporal lobe (Fig. 1A–C). At 6 months after the disease onset, when the patient could not walk by herself, atrophy of the anterior part of the left temporal lobe became prominent (Fig. 1D–F).

Pathological findings

The main pathological findings outside the central nervous system were neurogenic atrophy of the skeletal muscles and mild congestion with edema of the lungs (320 g; 280 g).

The weight of the brain was 1070 g after fixation. Macroscopic examination showed circumscribed atrophy of the left perisylvian region including pars opercularis of the inferior frontal gyrus and first temporal gyrus (Fig. 2A–D). The anterior part of the first temporal gyrus was severely atrophic (Fig. 2A–D). Slight atrophy was obvious in the oral part of the left parahippocampal gyrus, left lateral occipitotemporal gyrus, left inferior temporal gyrus, and left amygdala. Depigmentation of the substantia nigra was evident. Atrophy of the anterior roots and anterior horns of the spinal cord, prominently in the cervical cords, was evident. Bilateral pyramidal tracts were white and degenerated in the thoracic spinal cords. Histological examination revealed neuronal loss of Betz cells, with a small grouping of lipofuscin-laden macrophages in the holes from which Betz cells had presumably disappeared in the primary motor cortex. Degeneration of the pyramidal tracts was evident in the spinal cord (Fig. 3A). Neuronal loss with astrocytosis was also evident in the left first temporal gyrus (Fig. 2E, F), left second temporal gyrus, left lateral occipitotemporal gyrus, bilateral parahippocampal gyri, bilateral pes hippocampi, and bilateral basolateral groups of the amygdala. Neuronal loss was not evident in the caudate nucleus, putamen, pallidum, subthalamic nucleus, and thalamus. Neuronal loss was obvious in the substantia nigra. Neurons of the locus ceruleus, dentate nucleus, pontine nucleus, trochlear nucleus, and abducens nucleus were preserved. Purkinje cells of the cerebellum were also preserved. Neuronal loss with presence of Bunina bodies was evident in the facial nucleus, hypoglossal nu-

Fig. 2 **A** Left cerebrum after stripping of the leptomeninges reveals circumscribed atrophy of the left perisylvian region, including pars opercularis of the inferior frontal gyrus and the first temporal gyrus. **B** Coronal section through the anterior part of the cerebrum showing prominent atrophy of the left temporal pole. **C**, **D** Coronal section through the anterior part of the left temporal lobe showing prominent atrophy with loss of myelin and fibrillary gliosis of the first and second temporal gyrus. **E**, **F** Left first temporal cortex showing prominent neuronal loss (**E**) and fibrillary gliosis (**F**) with artificial cleft, prominently in the superficial layers. **C** Klüver-Barrera stain; **D**, **F** Holzer stain. **E** H&E stain. *Bars* **C**, **D** 10 mm, **E**, **F** 200 μm

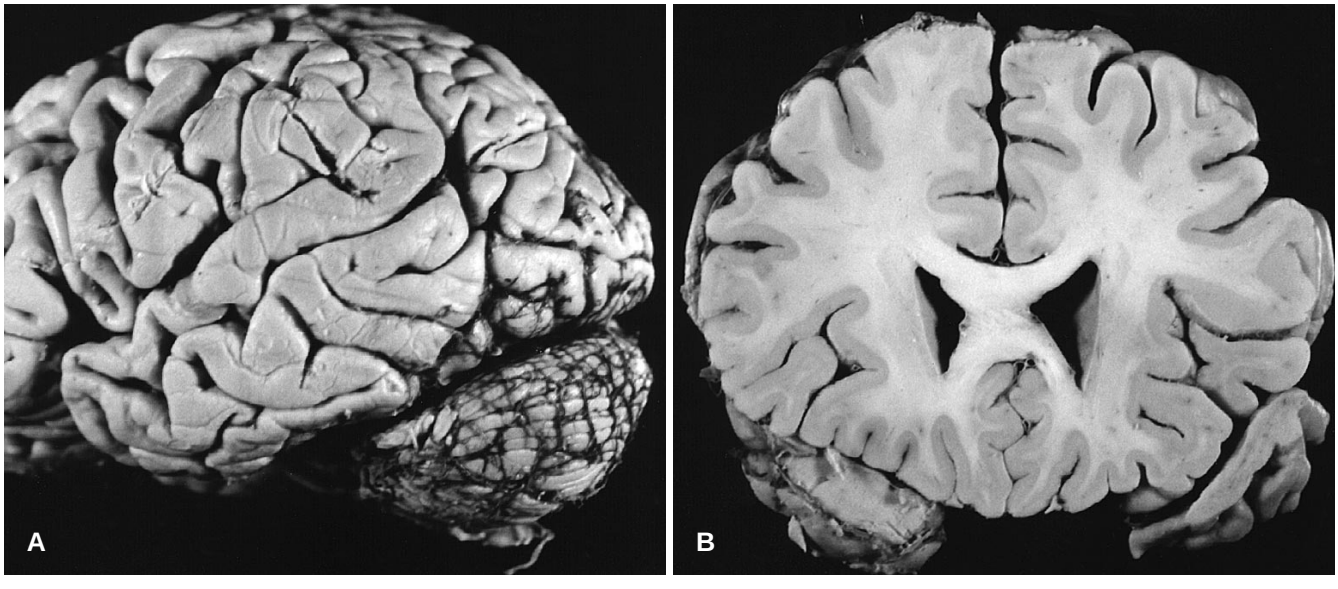
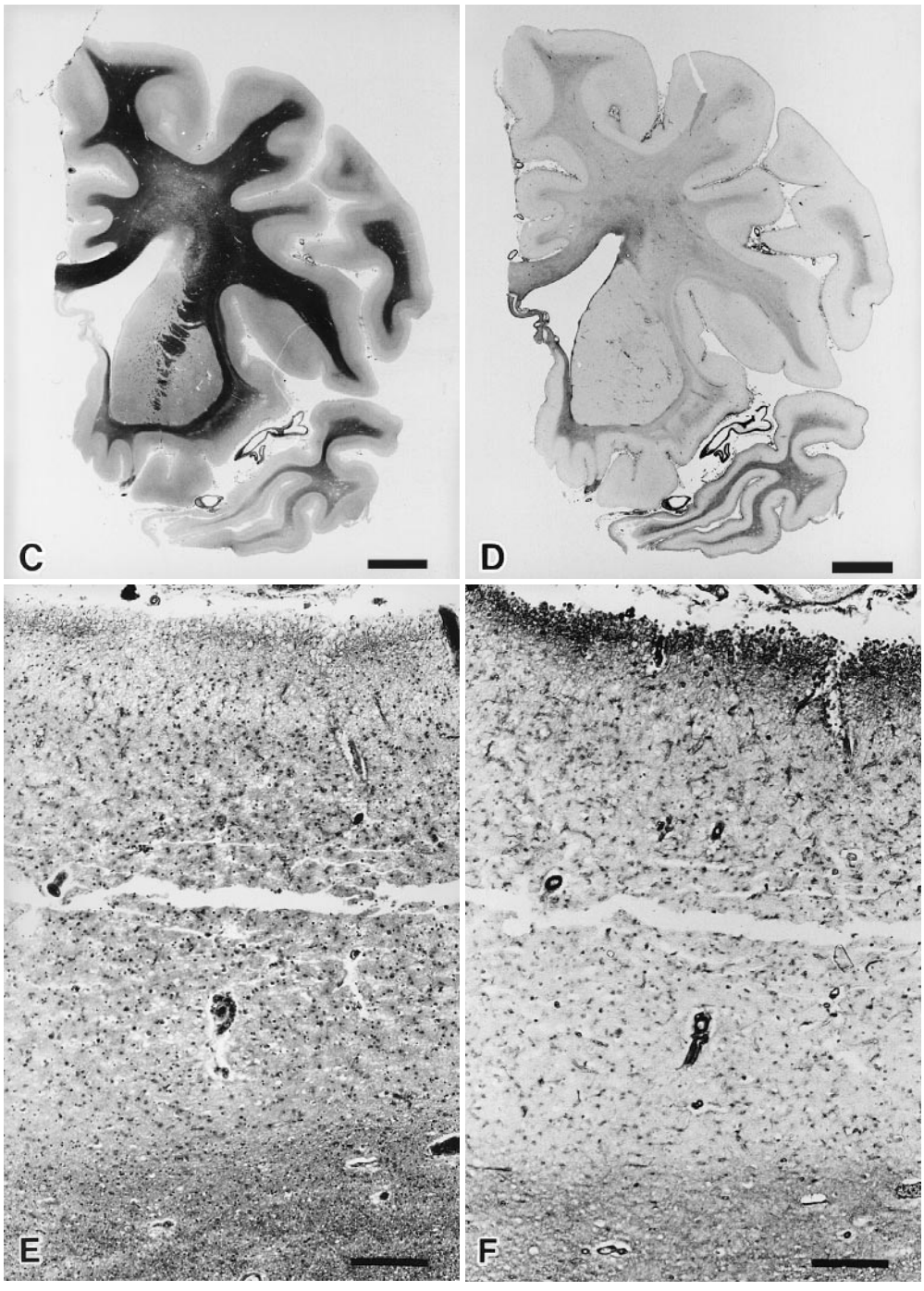


Fig. 2 C–F



clei, and anterior horns of the spinal cord (Fig. 3B, C). Onuf's nucleus of the second sacral cord was preserved. No senile plaques were seen using methenamine silver stain. A small number of neurofibrillary tangles (NFT) were present in the hippocampus, with a small to moderate number of NFT in the parahippocampal gyrus.

Immunocytochemistry using antibodies against ubiquitin (polyclonal; Dako, Denmark) and monoclonal (from Dr. H. Mori; Tokyo Institute of Psychiatry) revealed neuronal inclusions, including skeins of thread-like structures, in the neurons of the anterior horns of the spinal cord and hypoglossal nuclei (Fig. 3D). Ubiquitin-immunoreactive neuronal inclusions were also present in the hippocampal dentate granular cells (Fig. 3E), frontotemporal layer II neurons, and amygdala.

Discussion

Progressive aphasia has been increasingly recognized as a clinical presentation of primary cerebral degeneration. The debate regarding the nosological status of progressive aphasia still remains unresolved, especially whether patients represent focal presentations of Alzheimer's disease or of Pick's disease, or whether it constitutes a distinct entity. Our case, belonging to the category of ALS with dementia or MNDD, supports the opinion

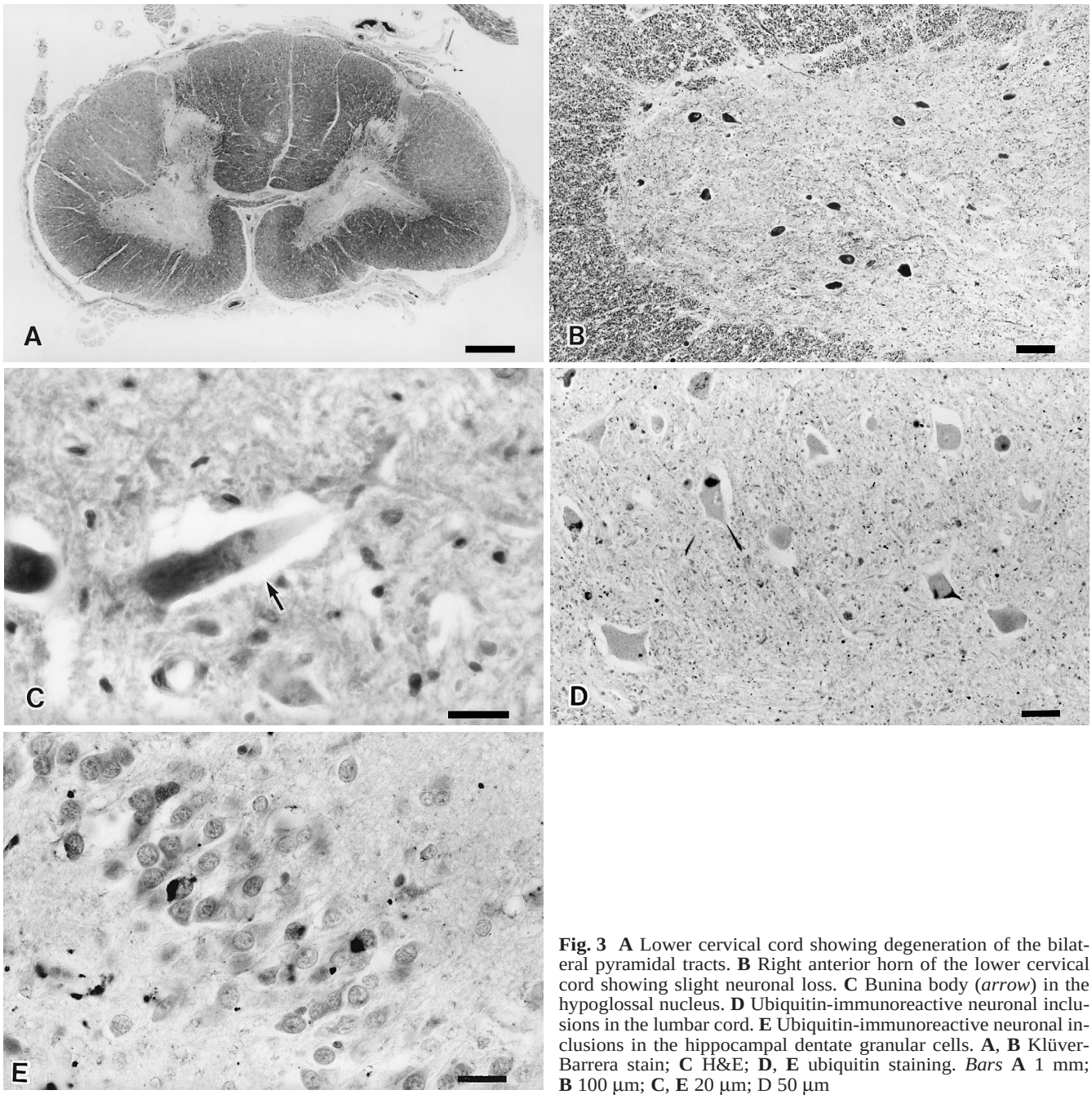


Fig. 3 **A** Lower cervical cord showing degeneration of the bilateral pyramidal tracts. **B** Right anterior horn of the lower cervical cord showing slight neuronal loss. **C** Bunina body (*arrow*) in the hypoglossal nucleus. **D** Ubiquitin-immunoreactive neuronal inclusions in the lumbar cord. **E** Ubiquitin-immunoreactive neuronal inclusions in the hippocampal dentate granular cells. **A**, **B** Klüver-Barrera stain; **C** H&E; **D**, **E** ubiquitin staining. *Bars* **A** 1 mm; **B** 100 μm; **C**, **E** 20 μm; D 50 μm

proposed by Snowden et al. [22] that progressive aphasia forms part of a spectrum of clinical presentations of non-Alzheimer lobar atrophy. According to Turner et al. [26], who reported three autopsy cases of DLDH presenting with clinical features of progressive nonfluent aphasia, a literature review of progressive aphasia cases with adequate clinical and neuropathological descriptions revealed that the most common neuropathology underlying progressive nonfluent aphasia was DLDH. Our patient, who had clinical features of progressive nonfluent aphasia, shows that ALS with dementia or MNDD is one of the pathologies underlying progressive nonfluent aphasia.

ALS is a progressive neurodegenerative disorder clinically characterized by lower and upper motor neuron signs, with marked degeneration of the upper and lower motor neurons of the brain and spinal cord. ALS with dementia [15, 19, 20, 27] or MNDD [18, 23] is a variant of ALS and/or a subgroup of frontotemporal dementia. According to Mitsuyama [15], who reviewed the clinicopathological findings of 26 cases of ALS with dementia in Japan, the pathological features include nonspecific mild degenerative changes throughout the central nervous system with pathological findings of motor neuron disease. As autopsy cases of ALS with dementia have accumulated in Japan, the variety of pathological findings

of ALS with dementia has increased. According to Nakano et al. [17] and Nakano [16], the temporal lobe including the medial cortex of the temporal tip and a part of the pes hippocampi is usually involved in ALS with dementia. Moreover, Nakano [16] noticed that in approximately 10% of patients with ALS without dementia, the temporal lobe including the medial cortex of the temporal tip and a part of the pes hippocampi was also affected. The neuropathological findings in our case, including neuronal loss in the medial cortex of the temporal lobe and in parts of the pes hippocampi, were fundamentally consistent with the neuropathological findings proposed by Nakano [16]. Furthermore, according to the recent advancements in the immunohistochemistry of neuropathology, the definition of pathology of ALS with dementia has been augmented. In the brain of patients with ALS with dementia, anti-ubiquitin immunohistochemistry revealed the presence of characteristic intraneuronal inclusions in the cortical layer and hippocampal dentate granular cells [19, 20, 27]. In 1991, Okamoto et al. [19], who neuropathologically examined 27 patients with sporadic ALS, including a patient diagnosed as having ALS with dementia, reported that there were ubiquitin-positive intraneuronal inclusions in the extramotor cortex of 7 out of 27 patients with sporadic ALS. Furthermore, they noted that in a patient with ALS with dementia, ubiquitin-immunoreactive intraneuronal inclusions were observed in many small neurons in the second layer of the frontal cortex. Later, Okamoto et al. [20] reported that ubiquitin-positive intraneuronal inclusions were found in the extramotor cortices of 10 presenile patients diagnosed as having ALS with dementia and without hereditary burden. In 1992, Wightmann et al. [27], who examined 33 patients with ALS, including 14 patients diagnosed as having ALS with dementia, showed that ubiquitin-positive inclusions in small neurons of the hippocampus, entorhinal area, and neocortex were a characteristic feature of degeneration of the non-motor cortex in ALS, and that they were particularly associated with cognitive impairment and frontal lobe type dementia.

Moreover, the concept of ALS with dementia or MNDD has been challenged. It is increasingly recognized that frontotemporal dementia with ubiquitin-positive inclusions in the non-motor cortex is a common form of non-Alzheimer's degenerative dementia with circumscribed atrophy [8]. Bergmann et al. [2], who examined histological and immunohistochemical findings in 20 cases of frontotemporal degeneration, including 8 cases of dementia of the frontal lobe [3, 12], 7 cases of Pick's disease with Pick bodies, and 5 cases of ALS with dementia, reported that ubiquitin-positive and tau-negative inclusions in cortical, hippocampal, and motor neurons were found not only in patients with ALS with dementia, but also in patients with dementia of the frontal lobe. They suggested that there was a common pathogenesis between ALS with dementia and dementia of the frontal lobe. Furthermore, Jackson et al. [7], who reported 9 cases of frontotemporal dementia with ubiquitin-immunoreactive inclusions in the hippocampal dentate granular cells and without neuronal loss or ubiquitin-immunoreactive inclusions in the hypoglossal nuclei, proposed the term "motor neurone disease-inclusion dementia" (MNDID) for these cases. The neuropathology of our case, showing circumscribed atrophy in the left frontotemporal lobe with ubiquitin-immunoreactive inclusions in the hippocampal dentate granular cells and frontotemporal cortical layer II neurons in addition to a pathology compatible with ALS, deserve mentioning as an example of the diversity of clinicopathological features of ALS with dementia or MNDD.

As mentioned in the introduction, few patients with neuropathologically confirmed progressive aphasia with ALS have been reported. In 1987, Kirshner et al. [10], who reported two autopsy cases of progressive aphasia without dementia, described a case (patient 2), in which language difficulty developed at age 58 and progressive muscular wasting of the upper and lower extremities with widespread fasciculation appeared 12 months before the patient's death. However, neuropathological examination showed only a focal, linear vacuolation with gliosis limited to the left inferior frontal gyrus without pathology compatible with ALS. Therefore, we cannot judge that the patient had ALS. According to Caselli et al. [4], who reported 7 cases of rapidly progressive aphasic dementia and motor neuron disease including 3 autopsy cases, only 1 autopsy case (patient 1) showed prominent atrophy in the left frontal operculum and left anterior temporal gyrus with degeneration of the pyramidal tracts and loss of neurons in the cervical spinal cords on neuropathological examination. However, they did not describe whether Bunina bodies were present in the neurons of anterior horns of the spinal cord, or whether ubiquitin-immunoreactive intraneuronal inclusions were present in the hippocampal dentate granular cells. Therefore, we cannot regard the autopsy cases reported by Caselli et al. as belonging to the category of ALS with dementia or MNDD. Moreover, according to Mann [11], who recently reviewed frontotemporal dementia including ALS with dementia, no instances of progressive aphasia combined with ALS have apparently been reported in which the cortical histology was that of Pick-type. Based on a review of the literature, we believe that our case is the first reported case of ALS with dementia or MNDD that clinically showed rapidly progressive aphasia.

With regard to the clinicopathological correlation of progressive aphasia and MNDID [7], the autopsy case of progressive aphasia reported by Kinoshita et al. [9] is of some interest. Neuropathological examination of the case showed many ubiquitinated neurites and a few ubiquitin-immunoreactive neuronal inclusions in the cerebral cortex, in addition to severe neuronal loss and astrocytosis with a spongy state in the frontal cortex and neostriatium. However, the hypoglossal nucleus in that case was preserved. We think that there is an undeniable possibility that the case reported by Kinoshita et al. had the pathological features of MNDID. According to Schwarz et al. [21], who reported an autopsy case of progressive aphasia with a duration of 14 years and without the clinical features of ALS, neuropathological examination of the case

revealed not only severe neuronal loss with spongy state of the anterior parts of the temporal lobes, but also ubiquitin- immunoreactive inclusions in the hippocampal dentate granular cells without loss of neurons in the hypoglossal nuclei. We speculate that the case reported by Schwarz et al. (1998) belonged to a variant of MNDID showing clinical features of progressive aphasia and pathological features compatible with MNDID, including ubiquitin- immunoreactive inclusions in the hippocampal dentate granular cells.

References

1. Arima K, Uesugi H, Fujita I, Sakurai Y, Oyanagi S, Andoh S, Izumiyama Y, Inose T (1994) Corticonigral degeneration with neuronal achromasia presenting with primary progressiv aphasia: ultrastructural and immunocytochemical studies. J Neurol Sci 127: 186–197
2. Bergmann M, Kuchelmeister K, Schmid KW, Kretzschmar HA, Schröder R (1996) Different variants of frontotemporal dementia: a neuropathological and immunohistochemical study. Acta Neuropathol 92: 170–179
3. Brun A (1987) Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. Arch Gerontol Geriatr 6: 193–208
4. Caselli RJ, Windebank AJ, Petersen RC, Komori T, Parisi JE, Okazaki H, Kokmen E, Irerson R, Dinapoli RP, Graff-Radford NR, Stein SD (1993) Rapidly progressive aphasic dementia and motor neuron disease. Ann Neurol 33: 200–207
5. Graff-Radford NR, Damasio AR, Hyman BT, Hart MN, Tranel D, Damasio H, Van Hoesen GW, Rezai K (1990) Progressive aphasia in a patient with Pick's disease: a neuropsychological, radiologic, and anatomic study. Neurology 40: 620–626
6. Green J, Morris JC, Sandson J, McKeel DW Jr, Miller JW (1990) Progressive aphasia: A precursor of global dementia? Neurology 40: 423–429
7. Jackson M, Lennox G, Lowe J (1996) Motor neuron disease-inclusion dementia. Neurodegeneration 5: 339–350
8. Jellinger KA (1997) Pick's disease with amyotrophic lateral sclerosis. J Neurol Sci 152: 227–228
9. Kinoshita A, Tomimoto H, Tachibana N, Suenaga T, Kawamata T, Kimura T, Akiguchi I, Kimura J (1996) A case of primary progressive aphasia with abnormally ubiquitinated neurites in the cerebral cortex. Acta Neuropathol 92: 520–524
10. Kirshner HS, Tanridag O, Thurman L, Whetsell WO Jr (1987) Progressive aphasia without dementia: two cases with focal spongiform degeneration. Ann Neurol 22: 527–532
11. Mann DMA (1998) Dementia of frontal type and dementias with subcortical gliosis. Brain Pathol 8: 325–338
12. Mann DMA, South PW (1993) The topographic distribution of brain atrophy in frontal lobe dementia. Acta Neuropathol 85: 334–340
13. Mesulam M-M (1982) Slowly progressive aphasia without generalized dementia. Ann Neurol 11: 592–598
14. Mesulam M-M (1987) Primary progressive aphasia – differentiation from Alzheimer's disease. Ann Neurol 22: 533–534
15. Mitsuyama Y (1984) Presenile dementia with motor neuron disease in Japan: clinico-pathological review of 26 cases. J Neurol Neurosurg Psychiatry 47: 953–959
16. Nakano I (1993) Temporal lobe lesions in amyotrophic lateral sclerosis with or without dementia: a neuropathological study. Neuropathology 13: 215–227
17. Nakano I, Iwatsubo T, Hashizume Y, Mizutani T, Mannen T (1992) Amyotrophic lateral sclerosis with dementia – Lesions in the apical cortex and some deeper structures of the temporal lobes. Neuropathology 12: 69–77
18. Neary D, Snowden JS, Mann DMA, Northen B, Goulding PJ, Macdermott N (1990) Frontal lobe dementia and motor neuron disease. J Neurol Neurosurg Psychiatry 53: 23–32
19. Okamoto K, Hirai S, Yamazaki T, Sun X, Nakazato Y (1991) New ubiquitin-positive intraneuronal inclusions in the extramotor cortices in patients with amyotrophic lateral sclerosis. Neurosci Lett 129: 233–236
20. Okamoto K, Murakami N, Kusaka H, Yoshida M, Hashizume Y, Nakazato Y, Matsubara E, Hirai S (1992) Ubiquitin-positive intraneuronal inclusions in the extramotor cortices of presenile dementia patients with motor neuron disease. J Neurol 239: 426–430
21. Schwarz M, Bleser R De, Poeck K, Weis J (1998) A case of primary progressive aphasia. A 14-year follow-up study with neuropathological findings. Brain 121: 115–126
22. Snowden JS, Neary D, Mann DMA, Coulding PJ, Testa HJ (1992) Progressive language disorder due to lobar atrophy. Ann Neurol 31: 174–183
23. The Lund and Manchester Groups (1994) Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry 57: 416–418
24. Tsuchiya K, Uchihara T, Oda T, Arima K, Ikeda K, Shimada H (1997) Basal ganglia lesions in corticobasal degeneration differ from those in Pick's disease and progressive supranuclear palsy: a topographic neuropathological study of six autopsy cases. Neuropathology 17: 208–216
25. Tsuchiya K, Ikeda K, Uchihara T, Oda T, Shimada H (1997) Distribution of cerebral cortical lesions in corticobasal degeneration: a clinicopathological study of five autopsy cases in Japan. Acta Neuropathol 94: 416–424
26. Turner RS, Kenyou LC, Trojanowski JQ, Gonatas N, Grossman M (1996) Clinical, neuroimaging, and pathologic features of progressive nonfluent aphasia. Ann Neurol 39: 166–173
27. Wightman G, Anderson VER, Martin J, Swash M, Anderton BH, Neary D, Mann D, Luthert P, Leigh PN (1992) Hippocampal and neocortical ubiquitin-immunoreactive inclusions in amyotrophic lateral sclerosis with dementia. Neurosci Lett 139: 269–274