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CASE REPORT

Frontotemporal lobar degeneration with ubiquitin pathology: an autopsy case presenting with semantic dementia and upper motor neuron signs with a clinical course of 19 years

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Abstract We report a case of a right-handed 74-year-old man who showed semantic dementia with a disease duration of 19 years. He initially presented with excessive use of pronouns and semantic paraphasia at the age of 55 years. Impairment of object recognition developed 5 years after the onset. Face recognition impairment and stereotypic behaviors developed 11 years after onset, and pyramidal signs 2 years before death. Pathological examination disclosed circumscribed severe atrophy in not only the bilateral temporal tips but also in the left precentral gyrus and pars opercularis in a motor speech field. Pyramidal tract involvement and loss of Betz cells were also evident. On the other hand, neurons in the anterior horns and hypoglossal nuclei were spared in number, although astrocytes were mildly proliferated. Ubiquitin-positive lesions were observed in the hippocampus, and frontal and temporal cortices. Neither Bunina bodies nor Pick bodies were present. These features clinically fit the international diagnostic criteria of semantic dementia and, histopathologically, frontotemporal lobar degeneration with motor neuron disease (FTLD-MND). This case suggests that (1) the distribution of cortical lesions associated with language disturbance is not uniform in FTLD-MND. It may be that only some cases of FTLD with ubiquitin pathology develop semantic dementia despite the high incidence of language disturbance, and (2) the precentral gyrus can be severely affected in FTLD-MND. After reviewing previous cases of FTLD-MND with a clinical course of more than 10 years, we also noticed that (3) FTLD-MND cases with a long disease duration often show upper motor neuron-predominant involvement.

Keywords Aphasia · Frontotemporal dementia · Ubiquitin · Pyramidal tract · Survival

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Introduction

Frontotemporal lobar degeneration (FTLD) is the second most common neurodegenerative dementia after

Alzheimer's disease in the presenium [10, 46], and it is clinically characterized by cerebral atrophy in the frontal and temporal lobes, and clinical features due to dysfunction in these regions [26]. Semantic dementia is one of the clinical subtypes of FTLD characterized by selective loss of semantic memory in contrast to preserved episodic memory. The impairment of semantic memory in the verbal domain results in *gogi* (word-meaning in Japanese) aphasia. In gogi aphasia, word comprehension and naming are severely impaired, whereas phonological and syntactic skills are preserved and spontaneous speech is fluent. Because of the semantic memory impairment, visual recognition of common objects is also disturbed despite preserved perceptual processing. In addition, some patients with semantic dementia exhibit impairment of face recognition resulting from loss of knowledge about persons' faces.

The pathological bases underlying FTLD can be divided into two groups according to the presence or absence of tau pathology. FTLD bearing tau pathology includes Pick's disease with Pick bodies (Pick's disease). Dementia lacking distinctive histologic features [19] and FTLD with ubiquitin pathology are major substrates of FTLD lacking tau pathology. The ubiquitin-positive lesions in FTLD with ubiquitin pathology are not immunoreactive for tau or α-synuclein, and they are found in the anterior horn cells in the spinal cord, dentate granular cells in the hippocampus, and/or frontal and temporal cortices. The ubiquitin-positive lesions in the cerebrum are also observed in some cases of amyotrophic lateral sclerosis without dementia, suggesting a potential disease continuum among amyotrophic lateral sclerosis, amyotrophic lateral sclerosis with dementia, and FTLD with ubiquitin pathology [12, 22, 25, 28, 29, 38, 42, 45]. FTLD with ubiquitin pathology comprises cases with histopathological features of motor neuron disease (MND) and cases without them [22]. FTLD with ubiquitin pathology but without clinical or pathological evidence of motor neuron involvement is called FTLD with ubiquitin-only immunoreactive changes (FTLD-U) [2], which was originally called motor neuron disease-inclusion dementia by Jackson et al. [13]. On the other hand, if MND was present clinically and/or pathologically, FTLD with ubiquitin pathology is called FTLD with MND (FTLD-MND) [2]. FTLD-MND includes cases showing severe corticospinal tract involvement and cases showing lower motor neuron-predominant involvement [12, 16]. The latter roughly corresponds to amyotrophic lateral sclerosis with dementia or dementia with motor neuron disease [23, 47]. In addition, some cases of FTLD-MND do not clinically exhibit any motor neuron signs despite the presence of pathological MND [2, 16].

The FTLD with ubiquitin pathology is a common pathological substrate in patients with FTLD, and its frequency is equal to or higher than that of Pick's disease [3, 14, 21, 24, 35]. However, data concerning the differences in neurological and neuropsychiatric features between FTLD-U, FTLD with a predominance of upper motor neuron involvement, and FTLD with a predominance of lower motor neuron involvement are very limited [16, 17]. Recent studies demonstrated that FTLD-U and FTLD-MND exhibit more diverse clinical phenotypes than expected, including semantic dementia [27, 32], corticobasal degeneration [7], progressive supranuclear palsy [30], and severe amnesia similar to Alzheimer's disease [6], in addition to frontotemporal dementia [13]. This diversity in clinical presentation suggests that the topographical distribution of neuronal loss in the cerebral cortex and subcortical nuclei is not uniform in cases of FTLD with ubiquitin pathology. Like the clinical symptoms, the length of survival and its predictive factors in FTLD with ubiquitin pathology also remain unclear. Therefore, the accumulation of detailed clinical and pathological findings in autopsied cases of FTLD with ubiquitin pathology is needed to make the clinical diagnosis of FTLD more precise.

We, here, present an autopsy case of FTLD-MND that clinically exhibited semantic dementia. This case also showed pyramidal signs 17 years after the disease onset. Pathological examination revealed severe degeneration in the bilateral temporal tips, which might result in semantic dementia. The left precentral gyrus and bilateral corticospinal tract were severely affected, being consistent with the presence of pyramidal signs. Unexpectedly, however, this case also had severe involvement of the pars opercularis in Brodmann's area 44, a motor speech field.

Materials and methods

Conventional neuropathological examination

Brain tissue samples were fixed postmortem with 10% formaldehyde and embedded in paraffin. Ten-micrometer-thick sections from the frontal, temporal, parietal, insular, and cingulate cortices, hippocampus, amygdala, basal ganglia, midbrain, pons, medulla oblongata, cerebellum, and spinal cord were prepared. These sections were stained using the hematoxylin–eosin (H&E), Klüver–Barrera (KB), Holzer, methenamine silver, and Gallyas–Braak methods.

Immunohistochemistry

Sections from the various regions in the cerebrum and spinal cord were examined immunohistochemically using anti-ubiquitin (Z0458, rabbit, polyclonal, 1:5,000, Dako), anti-phosphorylated α-synuclein (pSyn#64, mouse, monoclonal, 1:1,000, Wako), anti-tau (AT8, mouse, monoclonal, 1:3,000, Innogenetics), anti-cystatin C (A0451, rabbit, polyclonal, 1:1,000, Dako), or anti-GFAP (GFAP, rabbit, polyclonal, 1:5,000, Dako) antibodies. Deparaffinized sections were incubated with 1% H_2O_2 in methanol for 20 min to eliminate endogenous peroxidase activity in the tissue. Sections were treated with 0.2% TritonX-100 for 5 min and washed in phosphate-buffered saline (PBS, pH 7.4). After blocking with 10% normal serum, sections were incubated overnight at 4°C with one of the primary antibodies in 0.05 M Tris–HCl buffer, pH 7.2, containing 0.1% Tween and 15 mM NaN_3. After three 10-min washes in PBS, sections were incubated in biotinylated anti-rabbit or anti-mouse secondary antibody for 1 h, and then in avidin-biotinylated horseradish peroxidase complex (ABC Elite kit, Vector) for 1 h. The peroxidase labeling was visualized with diaminobenzidine-nickel as the chromogen.

Results

Case report

Clinical course

The patient was a right-handed man who was 74 years old at the time of death. He worked as head of scientific research. He had no family or past history of neurological or psychiatric disorders. At the age of 55 years, one of his colleagues, a neurologist, became aware of his language disturbances, including word-finding difficulty, excessive use of pronouns, and semantic paraphasia in the daily conversation. He often said, 'This is that' and 'Do this for that man,' phrases that lacked precise substantive terms. Spontaneous speech was fluent, and its quantity was not reduced. His comprehension of language appeared to be well preserved, and there was no trouble in his academic work as a researcher and a chief editor and reviewer of a scientific journal. The neurologist colleague suspected that he was suffering from slowly progressive aphasia. By the age of 60, his wife was aware of his difficulty in naming common objects. He could not remember the names of vegetables that were served, although he recognized them to be vegetables. He could recall day-to-day events and appointments perfectly. Increasing difficulty in language skills led to dismissal from his position at age 63. Difficulty in understanding written materials, such as names of famous places, peoples' names, and words in newspapers, became obvious. At age 63, he had disturbance in reading and writing kanji. At age 63, the quantum of information in his speech was gradually reduced, although episodic memory and spatial function were normal. Face recognition was also still normal. Neither generalized dementia nor motor disturbance including parkinsonism and motor neuron signs was found. At age 65, he began to complain of difficulty in understanding daily conversations. His spontaneous speech output gradually reduced. At age 66, he was also aware of difficulty in recognizing faces. Thereafter, fixed routines, stereotypic behaviors, and compulsive behaviors gradually appeared. He repeatedly read the same book at his desk every morning. He walked complicated but regular routes alone for 30 min at a fixed time every afternoon. While walking, he obsessively trod on the white line painted on the road. At age 71, euphoria, severe aural and visual comprehension impairment of language, and mutism were evident. A Mini-Mental State Examination was off the scale. Spatial skills were well preserved. Neither parkinsonism, including tremor and rigidity, nor motor neuron signs were found. On the other hand, his wife did not feel his care to be a burden because he did not show severe self-centered or antisocial behaviors, and his daily living activities, except for incontinence, were surprisingly independent. Nine months after the last neurological examination, he began shuffling his right leg. Furthermore, a swallowing disturbance and a change of eating behaviors were noticed: he regularly put a common strong-flavored sauce on all foods and often overfilled his mouth. Face recognition was gravely impaired. Because of his difficulty in recognizing objects visually, he often tried to shave using a pencil.

Because the motor impairment in his right leg deteriorated further, he was again admitted to a psychiatric hospital at age 71. On admission, evident euphoria, total aphasia, pica, forced crying, rigidity in the right lower, and to a lesser degree, in the right upper extremities were observed. Deep tendon reflexes were normal, and Babinski, Chadock, and Hoffman signs were not found. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed severe lobar atrophy in the bilateral temporal tips, especially on the left side, and a remarkably dilated Sylvian fissure (Fig. 1a–h). The insular cortex was also atrophic in the left side. In the other regions, only diffuse cortical atrophy was found. Single-photon emission computed

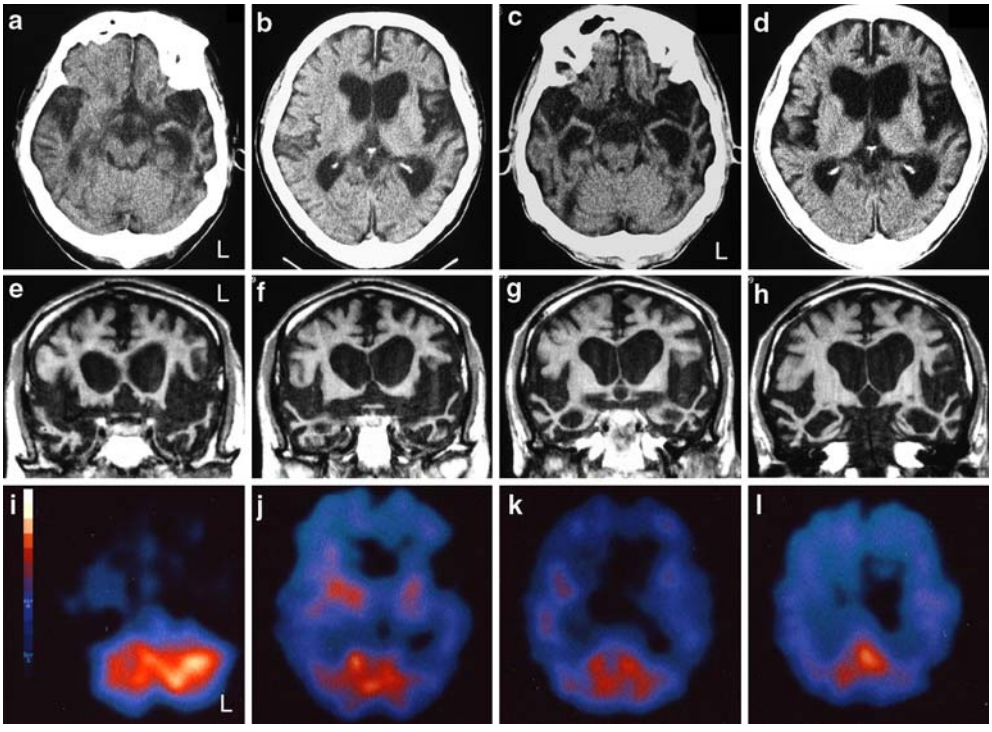

Fig. 1 **a**, **b** Brain CT at the age of 71 years. Severe atrophy in the bilateral temporal lobes, especially in the left side, and remarkable dilation in the Sylvian fissure are already observed. **c**, **d** Brain CT at the age of 74 years. Temporal atrophy is more severe than that in **a** and **b**. The bilateral frontal cortices and left insular cortex are also evidently atrophic. **e**–**h** Brain MRI at the age of 73 years. The bilateral temporal lobes, predominant in the left side, are severely atrophic. **i**–**l** Single-photon emission computed tomography at the age of 73 years. Remarkable hypoperfusion is found in the bilateral frontal and temporal cortices and basal ganglia, which is predominant in the left side

tomography (SPECT) disclosed severe left-side predominant hypoperfusion in the temporal and frontal regions and basal ganglia (Fig. 1i–l). On the other hand, although he appeared to have severe generalized dementia, the care staff felt that he was unexpectedly cooperative in his physical care. At age 72, pyramidal signs, including increased deep tendon reflexes and bilateral ankle clonus, first occurred. Spasticity or Babinski reflex was not found. Rigidity was evident in all four extremities, especially in the right side. He finally became bedridden, and he died of pneumonia at age 74, 19 years after the disease onset. No respiratory support was given throughout the clinical course. The clinical course, and neurological and cognitive profile of this case fit the international diagnostic criteria for semantic dementia [26, 36].

Neuropathological findings

The brain weight was 905 g after fixation (cerebrum 755 g, cerebellum and brainstem 150 g). Macroscopically, severe cortical atrophy was observed in the tips of the bilateral temporal lobes, especially in the left side (Fig. 2a–e). The gyri in these regions showed knife-blade atrophy. Atrophy was also evident in the left pars opercularis and precentral gyrus (Fig. 2a). The bilateral frontal cortex, especially in the left side, was moderately atrophic. On coronal sections, cortical atrophy was evident in the bilateral gyrus rectus, superior, middle, and inferior temporal gyri, parahippocampal gyrus, and anterior portion of the insular cortex. In these regions, the boundary between the white and gray matters was unclear. The bilateral lateral ventricles, especially in the left side, were dilated. The caudate nucleus and putamen were mildly atrophic, but the globus pallidus, thalamus, and subthalamic nucleus appeared to be unremarkable. The volume of the hippocampus appeared to be spared. The bilateral amygdala showed severe atrophy. The substantia nigra and locus coeruleus were well pigmented. The cerebellum, pons, medulla, and spinal cord were unremarkable.

Histopathologically, neuronal loss was most remarkable in the temporal cortex, which was more evident in the anterior rather than in the posterior portion. Severe fibrous gliosis was found in the subcortical white matter in the bilateral temporal lobes, inferior frontal gyrus, and pars opercularis (Fig. 3a, b). The primary motor cortex demonstrated loss of Betz cells, with a small grouping of lipofuscin-laden macrophages in the holes from which

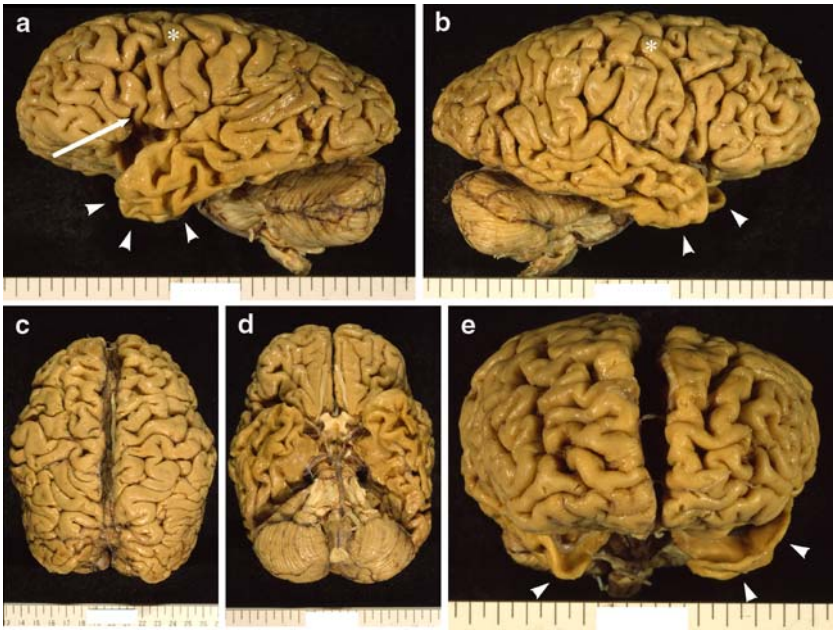

Fig. 2 The cerebrum after stripping the leptomeninges. **a** The left hemisphere demonstrates severe cortical atrophy involving the anterior portion of the temporal lobe (*arrowheads*). The pars opercularis (*arrow*) and precentral gyrus (*asterisk*) were also severely atrophic, resulting in a remarkably dilated Sylvian fissure. **b** The sulci in the anterior portion of the right temporal lobe are severely dilated, although the degree is milder than that in the left side (**a**). The precentral gyrus and pars opercularis also appear to be better preserved than those on the left side (**a**). **c** The cerebral atrophy in the frontal convexity is relatively mild compared with the temporal lobe (**d**). **d** The sulci in the bilateral temporal base are greatly enlarged. The sulci in the frontal base are relatively spared. **e** The severe cortical atrophy showing a knife-blade appearance in the bilateral temporal tips (*arrowheads*). The atrophy is more evident on the left side

Betz cells had presumably disappeared (Figs. 4a, b). The bilateral pyramidal tract was evidently degenerated at the levels of the thoracic, lumbar, and sacral cords (Fig. 4d, e). The degeneration of the pyramidal tract was also found at the level of the medulla oblongata (Fig. 4c), although it was rather mild compared with that in the spinal cord. Myelin pallor, gliosis, and macrophages were found in the pyramidal tract in these regions. Clarke's column and the posterior spinocerebellar tract were preserved. At the levels of the sacral and lumbar cords, the anterior horn cells were spared in number, while astrocytes in the anterior horns were mildly proliferated. Likewise, neurons in the hypoglossal nuclei were well preserved, although astrocytes in this site were mildly proliferated. No Bunina bodies were seen in the anterior horn cells or neurons in the hypoglossal nuclei.

Neurons were mildly reduced in the rostral portion of the hippocampus. In the subiculum and

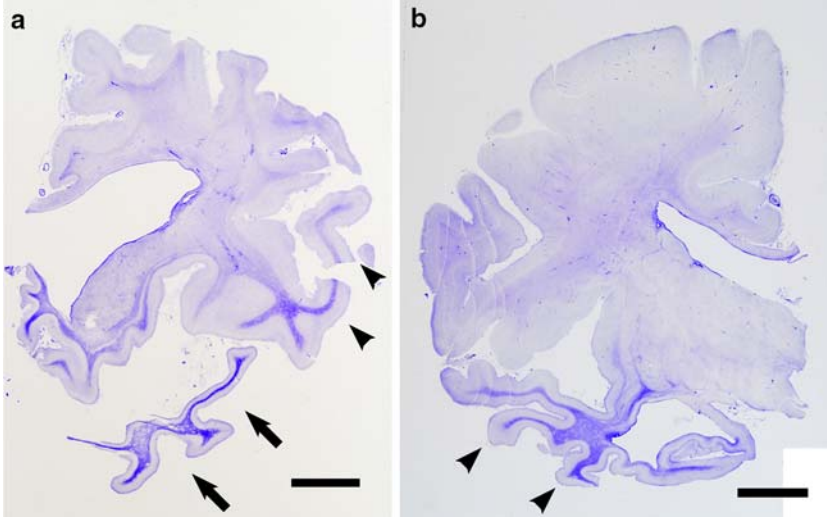

Fig. 3 **a** A coronal section of the left hemisphere at the level of the head of the caudate nucleus shows severe gliosis in the subcortical white matter in the temporal tip (*arrows*). Severe gliosis is also demonstrated in the white matter in the pars opercularis (*arrowheads*). **b** Severe gliosis is also evident in the white matter of the right temporal lobe at the level of the rostral portion of the hippocampus (*arrowheads*). Scale bar: **a** 1 cm: **b** 1 cm. Holzer stain

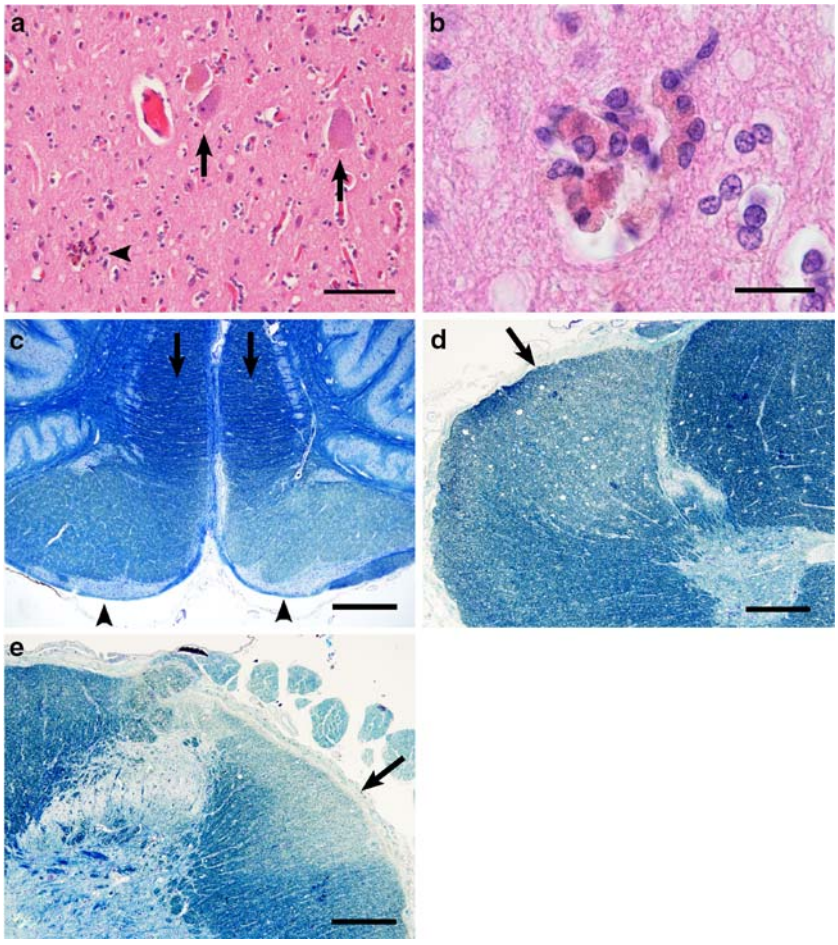

Fig. 4 **a** The primary motor cortex showing loss of Betz cells, with a small grouping of lipofuscin-laden macrophages in the holes from which Betz cells had presumably disappeared (*arrowhead*). Surviving Betz cells are also found (*arrows*). **b** Higher power micrograph of the small grouping of lipofuscin-laden macrophages in the holes marked by an *arrowhead* in **a**. **c** Loss of myelin in the bilateral pyramidal tract at the level of the medulla (*arrowheads*). Loss of myelin in the bilateral pyramidal tract is evident in comparison with the medial lemniscus (*arrows*). **d** The thoracic cord, showing loss of myelin in the pyramidal tract (*arrow*). **e** The lumbar cord, showing evident pallor of the pyramidal tract (*arrow*). Scale bar: **a** 10 μm; **b** 2 μm; **c** 1 mm; **d**, **e** 0.5 mm; **a**, **b** Hematoxylin–eosin stain; **c**–**e** Klüver–Barrera stain

parahippocampal gyrus, neuronal loss was evident. The dentate granular cells were preserved. In the amygdala, neurons were severely reduced in number, and tissue rarefaction was also evident in the basolateral rather than in the corticomedial group. In the caudate nucleus, the ventral portion showed severe neuronal loss and tissue rarefaction, and the dorsal portion had moderate neuronal loss and gliosis. The putamen showed moderate neuronal loss and gliosis. In the substantia nigra, pigmented neurons were mildly reduced in the central portion, and free melanin was encountered. The number of neurons in the locus coeruleus was not reduced. A few neurofibrillary tangles were found in the parahippocampal gyrus and CA1 region of the hippocampus on Gallyas-Braak-stained sections. A few senile plaques were scattered in the frontal cortex only on the methenamine silver-stained sections. Neurons in the nucleus basalis of Meynert, globus pallidus, subthalamic nucleus, thalamus, oculomotor nucleus, trochlear nucleus, pontine nucleus, dorsal vagal nucleus, inferior olivary nucleus, and dentate nucleus and cerebellebar cortex in the cerebellum were spared. Although a few ballooned neurons were encountered in the cingulate cortex, neither Pick bodies nor Lewy bodies were encountered in any region.

Ubiquitin immunohistochemistry demonstrated ubiquitin-positive inclusions and neurites in the rostral portion of the hippocampal dentate gyrus (Fig. 5a), parahippocampal gyrus, amygdala, caudate nucleus, putamen, and frontal (Fig. 5b), temporal, parietal, and occipital cortices. In the cerebral cortex, the ubiquitin-positive neurites were preferentially distributed in the superficial cortical layers. In the pars opercularis and precentral gyrus, many ubiquitin-positive inclusions and neurites were observed in both the superficial and deep cortical layers. The density of the ubiquitin-positive lesions in these regions was higher than it was in the adjacent insular cortex and the more severely affected temporal cortex. Neither anti-tau nor anti-α-synuclein antibody labeled these ubiquitin-positive lesions. No ubiquitin-positive lesions were found in the hypoglossal nuclei and anterior horn in the spinal cord.

Discussion

The present case clinically showed semantic dementia until the middle of the course, and frontotemporal dementia and upper motor neuron signs also in the

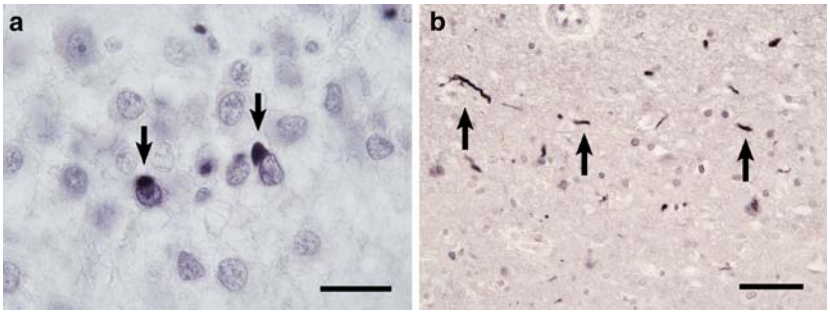

Fig. 5 **a** Motor neuron disease-type inclusions in the granular cells in the hippocampus. **b** Ubiquitin-positive neurites in the superficial layers in the gyrus rectus. Scale bar: **a** 2 μm; **b** 5 μm. Ubiquitin immunohistochemistry

later stage. On the other hand, clinical signs of lower motor neuron involvement including weakness, muscle atrophy, and fasciculations were not clear, although swallowing difficulty was observed. Histopathologically, the lower motor neurons in the spinal anterior horns and hypoglossal nuclei were relatively spared in number, although mild astrocytosis was found in these sites. In addition, neither ubiquitin-positive inclusions nor Bunina bodies were found in lower motor neurons. In contrast, the present case had histopathologic evidence of upper motor neuron degeneration. Because FTLD-U is defined as FTLD with ubiquitin pathology but without abnormalities of the motor neurons [2], it may be appropriate to diagnose this case as FTLD-MND rather than FTLD-U based on the evidence of upper motor neuron involvement.

This case had several findings that are significant in considering the clinical presentation of FTLD-MND: (1) the sites severely affected in the cerebral cortex included not only the bilateral temporal tips but also the left precentral gyrus and pars opercularis (the pars opercularis is in a motor speech field), (2) the disease duration was very long for FTLD-MND, because the survival time in FTLD-MND is usually less than 5 years [15], and (3) motor neuron signs initially occurred 17 years after the disease onset, and only 2 years before the patient died.

The clinical symptoms in the present case are roughly explained by the distribution of neuronal loss in the cerebral cortex: the impairment of semantic memory and recognition of objects and faces corresponded to the severe involvement of the bilateral temporal tips. The clinicopathological entity FTLD-U was originally proposed by Jackson et al. [13] as motor neuron disease-inclusion dementia. They noted that language disturbance was very frequent in FTLD-U, and that it was characterized by a progressive decline in spontaneous speech output, reduction of fluency, and word finding and naming difficulty with preservation of comprehension. Some of these symptoms are inconsistent with the features of language disturbance in semantic dementia. Thereafter, several cases of FTLD-U and FTLD-MND that presented clinically with semantic dementia were reported [27, 32, 34]. Further, it was reported that FTLD with ubiquitin pathology is one of the major pathological bases in patients with semantic dementia. For example, Hodges et al. [8] reported that four of nine patients (44%) with semantic dementia were pathologically diagnosed as having FTLD with ubiquitin pathology. Davies et al. [1] also reported that 13 of 18 patients (72%) with semantic dementia had FTLD with ubiquitin pathology. Their 13 cases comprised 8 FTLD-U cases (62% of FTLD with ubiquitin pathology) and 5 FTLD-MND cases (38% of FTLD with ubiquitin pathology). Interestingly, however, several studies disclosed that most of the patients with FTLD with ubiquitin pathology did not exhibit semantic dementia clinically. Kertesz et al. [18] reported that among 18 cases of FTLD with ubiquitin pathology, no case presented with semantic dementia as an onset symptom, and only one case showed it during the clinical course. Josephs et al. [17] also noted that among 39 cases of FTLD with ubiquitin pathology, including 21 FTLD-U and 18 FTLD-MND cases, no case exhibited semantic dementia. Godbolt et al. [5] and Shi et al. [35] reported that only about 20% of cases of FTLD with ubiquitin pathology exhibited semantic dementia. Taking these findings into consideration, it is likely that FTLD with ubiquitin pathology, including FTLD-U and FTLD-MND, is a major pathological basis in patients with semantic dementia, but such cases are no more than a minority of cases of FTLD with ubiquitin pathology. This view is consistent with the report of Jackson et al. [13], who described few characteristics of semantic dementia in the first nine cases of FTLD-U.

Interestingly, the present case also showed severe atrophy in the pars opercularis in a motor speech field. Why the present case clinically exhibited gogi aphasia (word-meaning aphasia) but not features of motor aphasia may be explained by the chronological order of the involvement of the temporal tips and a motor speech field, and the difference in the severity between these regions. Although Pick's disease rarely produces severe atrophy in the pars opercularis [4,

Table 1 Previous cases of FTLD-MND with disease duration of over 10 years

	Ikeda et al. [11]				Tsuchiya et al. [40]	Davies et al. [1]	Toyoshima et al. [38]	Present case
	(Case 8)	(Case 10)	(Case 11)	(Case 12)		(Case 10)[a]		
Clinical features								
Sex	M	F	F	M	F	M	M	M
Age at onset (years)	51	48	58	58	30	51	51	55
Onset age of motor neuron signs (years)	60	54	72	66	44	60	61	72
Age at death (years)	61	60	72	74	45	61	62	74
Total disease duration (years)	10	12	14	16	15	10	11	19
Survival time after the development of motor neuron signs (years)	2	6	1	8	0.75	1	1	2
Initial symptoms	FTD, aphasia	Delusional state, amnesia, aphasia	FTD, amnesia, aphasia	Amnesia, aphasia	FTD amnesia	FTD	FTD	SD
Upper motor neuron signs								
Increased deep tendon reflex	+	+	+	+	+	ND	ND	+
Pathological reflex	+	+	+	+	+	ND	ND	–
Spasticity	ND	ND	ND	ND	+	ND	ND	–
Clonus	ND.	ND	ND	ND	ND	ND	ND	+
Lower motor neuron signs								
Weakness	–	–	–	-	+	ND	+	–
Muscle atrophy	–	–	–	-	+	ND	ND	–
Swallowing disturbance	–	+	–	-	+	ND	ND	+[b]
Fasciculation	–	–	–	-	ND	ND	ND	–
Pathological features								
Brain weight (g)	1,060	890	915	920	1,040	ND	1,370	905
Loss of Betz cells	+	+	+	+	ND	ND	+	+
Corticospinal tract degeneration	Mild	Severe	Moderate	Severe	Severe	Severe	Mild	Severe
Loss of the lower motor neurons	–	Mild	Mild	Mild	Severe	–	Severe	–
Ubiquitin-positive inclusions								
In the hippocampus or temporal cortex	+	+	+	+	+	–[c]	+	+
In the lower motor neurons	+	+	+	+	+	–	+	–
Bunina body	–	–	–	–	–[d]	–	+	–

FTD frontotemporal dementia, *SD* semantic dementia, + present, – absent, *ND* not described

[a] A table in a paper by Davies et al. [1] showed that case 8 (duration of 19.5 years) had dysphasia late in clinical course. However, because in the text, case 7 (duration of 9.3 years) showed it, we omitted this case

[b] The possibility that the swallowing difficulty was due to upper motor neuron involvement or hyperorality could not be excluded

[c] Ubiquitin-positive inclusions were found in the inferior olivary nucleus

[d] The absence of Bunina bodies was verified by ourselves, although it was not described in an original report

33], the vulnerability of this site in FTLD with ubiquitin pathology is unclear. As far as we know, in two reported cases of FTLD with ubiquitin pathology including one case of FTLD-MND [39] and one of FTLD-U [34], severe atrophy in the pars opercularis was observed. Considering that cases of FTLD with ubiquitin pathology frequently lack features of semantic dementia despite the high incidence of language disturbance, the distribution of cortical lesions associated with language disturbance might not be uniform in FTLD with ubiquitin pathology. Further pathological studies focusing on the lesions responsible for language disturbance in FTLD-U and FTLD-MND are needed.

The severe involvement of the primary motor cortex observed in the present case is noteworthy because this site was historically considered to be usually spared in so-called 'Pick's disease', which includes histopathologically heterogeneous cases bearing lobar atrophy. However, recent studies have disclosed that this is not necessarily true in Pick's disease (with Pick bodies). For example, the primary motor cortex was severely affected in some cases of Pick's disease, and such cases frequently exhibited upper motor neuron signs [4, 20,

37, 41, 43]. In contrast to Pick's disease, pathological data concerning the distribution of cortical lesions in FTLD-U and FTLD-MND are limited at present. A recent voxel-based morphometric study using magnetic resonance imaging demonstrated that FTLD-U cases had significant cortical atrophy in the bilateral frontal, temporal, and parietal regions, and FTLD-MND cases had cortical atrophy in the bilateral frontal regions [44]. Further accumulation of detailed pathological findings concerning the distribution of cortical lesions, including the involvement of the primary motor cortex in FTLD-MND, are awaited. In particular, the relationship between the distribution of lesions and characteristics of motor neuron disease, such as a predominance of upper or lower motor neuron involvement, should be clarified in the future.

Along with the accumulation of data about the natural history of patients with FTLD, the survival time was reported to be influenced by the existence of clinical or pathological MND [15, 16]. In addition, several studies suggested that even when the influence of clinical MND is excluded, tau-negative pathology is associated with short disease duration in FTLD [9, 31]. On the other hand, the relationship between survival time and the characteristics of motor neuron degeneration, such as upper motor neuron-predominant involvement or lower motor neuron-predominant involvement, has hardly been explored in FTLD-MND. In a previous study on the pathological features of motor neuron involvement in FTLD [12], the disease duration in FTLD-MND cases showing lower motor neuron-predominant involvement (0.8–6 years, mean: 2.3 ± 1.8 years) was obviously shorter than that in FTLD-MND cases showing upper motor-predominant MND (3–16 years, mean: 9.9 ± 5.1 years). As far as we know, only eight cases of FTLD-MND, including ours, with a clinical course of more than 10 years have been reported [1, 11, 38, 40]. The clinical and pathological characteristics are summarized in Table 1. All cases were early onset, with the age at onset ranging from 30 to 58 years. The longest total disease duration was 19 years (our case). The interval from disease onset to the development of motor neuron signs was 6–17 years. All the cases, except two lacking detailed clinical descriptions, presented with upper motor neuron signs, whereas lower motor neuron signs were relatively rare. Pathologically, all cases but one had obvious degeneration in the pyramidal tract. In contrast, lower motor neurons were spared in three cases, affected mildly in three cases, and affected severely in two cases. Upper motor neuron-predominant involvement was evident in six cases, and lower motor neuron-predominant involvement was observed in one case. All cases had ubiquitin-positive lesions, but Bunina bodies were found in only one case. The survival time after the appearance of motor neuron signs was 1 year or less in two cases with severe involvement of the lower motor neurons. On the other hand, the survival was more than 6 years in 2 out of 6 cases with a predominance of upper motor neuron involvement. These findings suggest that: (1) FTLD-MND cases with very long disease duration often show upper motor neuron-predominant involvement both clinically and pathologically, (2) motor neuron signs can develop 6 years or more after the disease onset, (3) FTLD-MND patients often die within 2 years after the appearance of motor neuron signs, especially when lower motor neurons are severely affected, but (4) some patients with upper motor neuron-predominant involvement survive longer, even if motor neuron signs have developed. In addition, these findings led us to speculate that some patients with FTLD-U develop motor neuron degeneration, which is often upper predominant, if the survival duration is extended. Considering these findings, clinicians managing a patient with FTLD should monitor the occurrence of motor neuron signs and their clinical characteristics throughout the disease course to counsel on the prognosis and deliver appropriate medical care.

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