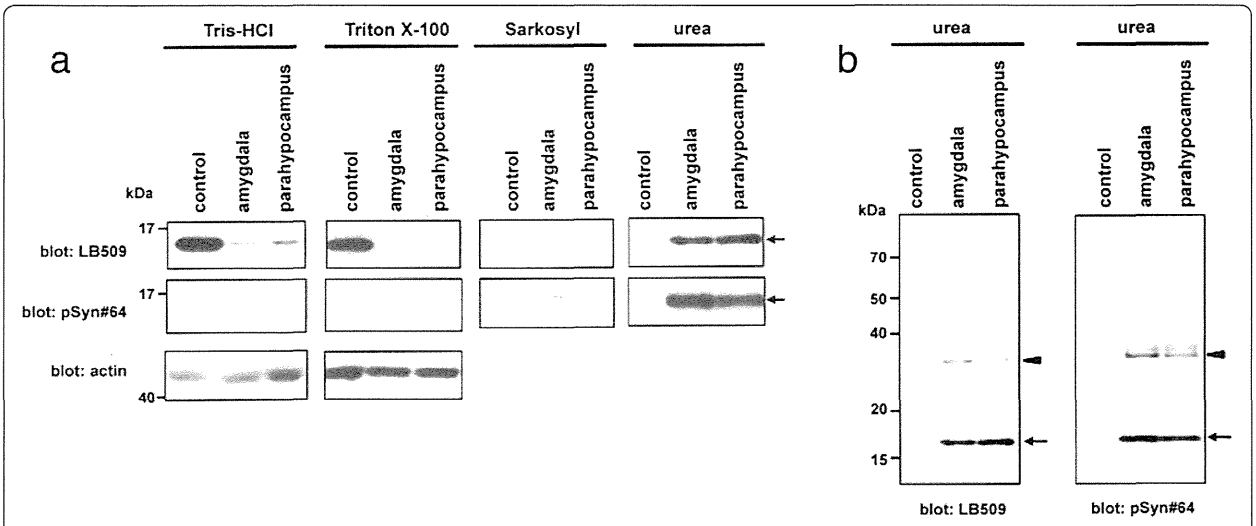

Figure 5 Biochemical analysis of α-synuclein in brain tissues. a The samples were sequentially fractionated by resolubilization with increasingly stringent buffers containing Tris-buffered saline, Triton X-100, sarkosyl, and urea. The samples were analyzed using the α-synuclein antibodies LB509 and pSyn#64. In the urea-extracted fraction, a phosphorylated α-synuclein band at approximately at ~15 kDa (arrow) was substantially accumulated in the brain (amygdala and parahippocampus) of the autopsied patient. Conversely, the level of α-synuclein in the Tris- and Triton X-100-soluble fractions was decreased. Anti-β-actin immunoblotting served as a loading control (bottom panel). **b** α-Synuclein-reactive fragments of dimers migrating at approximately ~30 kDa (arrowhead) and a smear at higher molecular weights were abundant in the urea-extracted fraction of the patient's brain.

was phosphorylated at serine 129. Moreover, the patient showed large amounts of α-synuclein-reactive high-molecular-weight smears, which might have represented α-synuclein oligomers (Figure 5b).

Genetic analysis

Sequence analysis revealed that the patient carried compound heterozygous mutations in the *PLA2G6* gene. A novel splice-site mutation in exon 9 (c.1187-2A > G) and a missense mutation (c.1612C > T, p.R538C) in exon 12 (Figure 6a) were identified in the patient. These mutations were absent in 120 normal control subjects. The p.R538C missense mutation was previously reported in patients with classical INAD [5]. Genetic analysis of the unaffected parents of the patient revealed that the father and mother were heterozygous carriers of the p.R538C missense and splice-site mutations, respectively (Figure 6b). No mutations were identified in *PANK2, SNCA, parkin, DJ-1, or PINK-1.* There was no pathological expansion of CAG repeats in the genes associated with SCA1, SCA2, DRPLA, or Huntington's disease.

We next investigated whether the splice-site mutation caused an alteration in the splicing of *PLA2G6* using RT-PCR analysis of total RNA extracted from the patient's frozen tissue. To examine the mRNA expression of *PLA2G6* in the patient's brain, two primer pairs were designed to amplify cDNA fragments encompassing exons 8 to 13 (primers A-C) and 9 to 13 (primers B-C), respectively (Figure 6c). In the control samples, two alternative splicing variants were amplified using the primer pairs A-C. Sequence analysis of the fragments in the control samples revealed that these variants corresponded to two previously reported isoforms of *PLA2G6* mRNA, with and without the 162-bp exon 9, respectively [17]. In the patient, the 700-bp fragment containing exon 9 was nearly undetectable by RT-PCR using the primer pair A-C. RT-PCR amplification using the primer pair B-C revealed that the 600-bp cDNA fragment containing exon 9 found in the control samples was less expressed in the patient (Figure 6d).

Discussion

INAD is a rare, autosomal-recessive neurodegenerative disorder with infant onset, and patients usually die in childhood [1,4,6]. In an INAD cohort with *PLA2G6* mutations previously described by Gregory et al., symptoms began between 5 months and 2.5 years of age [1]. Wu et al. reported that half of INAD patients with a disease course of 2–5 years became vegetative [6]. In this study, the patient's initial neurological manifestation was cerebellar ataxia at the age of 3 years, which was later accompanied by mental retardation, dystonia, and seizures. The patient survived until the age of 20 years. His clinical phenotype was atypical for INAD; the disease onset and progression were delayed and slower, and there was no indication of truncal hypotonia, neuro-ophthalmologic abnormalities, or fast rhythms on an electroencephalogram throughout the clinical course.

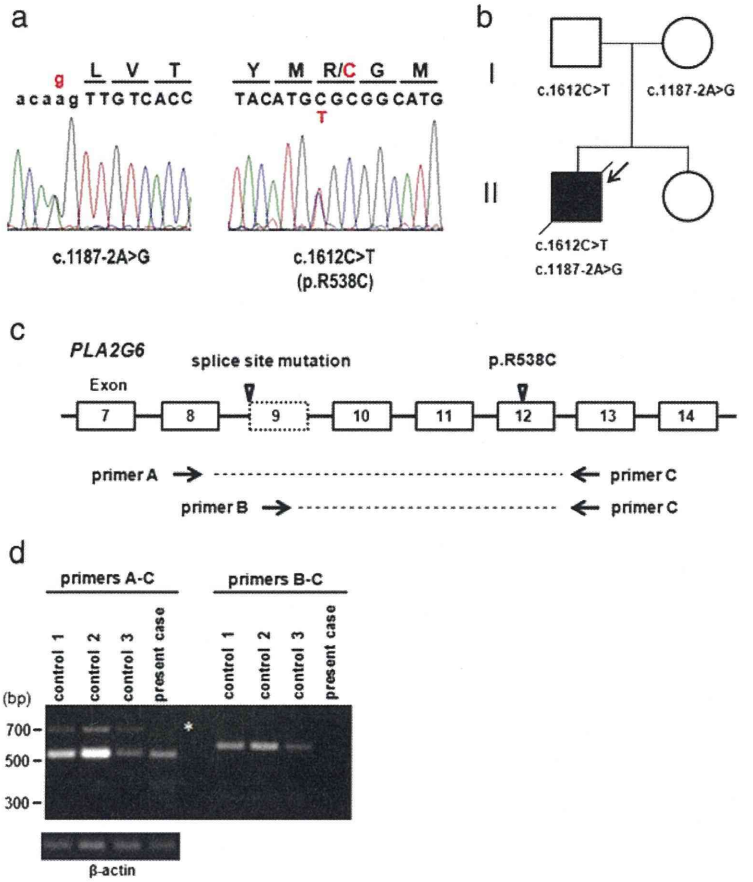

Figure 6 Identification of compound heterozygous mutations in *PLA2G6* in the patient. a Mutation analysis of *PLA2G6* in the patient. Sequence analysis of the patient's genomic DNA revealed two mutations: a 5′ splice-site mutation in exon 9 (c.1187-2A > G) and a missense mutation (c.1612C > T, p.R538C) in exon 12. The capital and small letters represent nucleotides in exons and introns, respectively. **b** Pedigree of the patient with *PLA2G6* mutations. Circle, female; square, male; slash through symbol, deceased individual; closed symbol, affected individual. An arrow denotes the proband. The father and mother each carried one of the compound heterozygous mutations found in the patient. **c** Schematic illustration of exon-intron structure of *PLA2G6*. Boxes represent exons. The positions of the mutations in the patient are shown. Two primer pairs were designed to amplify cDNA fragments encompassing exons 8 to 13 (primers A-C) and 9 to 13 (primers B-C). **d** Reverse transcription (RT)-PCR analysis of the patient's brain. In the patient, a 700-bp fragment containing exon 9 was nearly undetectable by RT-PCR using the primer pair A-C. RT-PCR amplification using the primer pair B-C revealed a 600-bp cDNA fragment containing exon 9, which was recognized in control samples but was less noticeable in the autopsied patient. Amplification of β-actin mRNA was used as an internal control.

Gregory et al. previously described six patients in their patient registry with *PLA2G6* mutation who exhibited variable clinical phenotypes with late onset (average 4.4 years, range 1.5-6.5 years) [1,2]. This phenotype was referred to as atypical neuroaxonal dystrophy (ANAD). The clinical phenotype of our patient might be classified as ANAD. Moreover, patients with a slower disease progression and heterogeneous clinical pictures have been occasionally described in other series of INAD patients [7,8]. Currently, it is speculated that patients with mutant forms of the *PLA2G6* gene display a complete absence of protein, which is associated with a severe INAD profile, whereas patients with compound heterozygous mutations potentially exhibit residual protein function and have a less severe phenotype [18]. Our genetic findings further support this genotype-phenotype correlation.

To the best of our knowledge, there have only been two reports that describe the CNS neuropathology of genetically confirmed patients with a *PLA2G6* gene mutation, as summarized in Table 1 [1,8]. The neuropathological features, including neuroaxonal spheroids, cerebellar degeneration, and brain iron accumulation, were described in INAD before the discovery of its causal gene [3]. Moreover, the presence of LB and NFT pathology has been described in neuroaxonal dystrophy with *PLA2G6* gene mutation [1,8]. On the basis of disease onset, patients 1–4 in Table 1 might be classified as ANAD or early onset dystonia-parkinsonism; however, no components of the pathological findings differed

Table 1 Summary of the neuropathological findings in autopsied patients with *PLA2G6* gene mutations in the literature

Patient	Age at onset	Age at death	Spheroids in the CNS	Spheroids in the PNS	Neuronal loss in the cerebellum	Accumulation of alpha synuclein	Accumulation of tau	Brain iron
1[8]	18 y	36 y	+	NA	gc and Pc	+	+	+
2[1]	3 y	23 y	+	-	gc and Pc	+	+	+
3[8]	childhood	18 y	+	NA	gc and Pc	+	+	+
4[8]	14 m	8 y	+	NA	gc and Pc	+	+	+
5[8]	infant	8 y	+	NA	NA	+	-	NA
Our patient	3 y	20 y	+	-	gc and Pc	+	+	+

Abbreviation: CNS = central nervous system; gc = granule cell; NA = not assessed; Pc = Purkinje cell; PNS = peripheral nervous system.

between these clinical phenotypes. In the current patient, neuronal loss, LB pathology, NFT pathology, and the presence of axonal spheroids were marked in the limbic system, fronto-temporal lobes, and SN. These pathological findings might be responsible for progressive cortical atrophy, psychomotor regression, and parkinsonism. Iron deposition broadly extended throughout the basal ganglia and midbrain compared to what was predicted from the T2 low-intensity area on MRI. Furthermore, loss of cerebellar neurons, particularly granule cells, was both striking and consistent with the cerebellar ataxia that was diagnosed in the early phase of the disease.

LB pathology has been identified in all six patients reviewed [1,8]. A recent study reported that LB pathology was not observed in patients with the *PANK2* gene mutation [19]. Moreover, earlier case reports describing neuroaxonal dystrophy or brain iron accumulation with abundant LBs may have been describing patients with *PLA2G6* gene mutations [20-22]. We demonstrated that the morphological, ultrastructural, and biochemical properties of LBs in this patient were identical to those in PD and diffuse Lewy body disease (DLB) patients [12,16,23]. Furthermore, the spatial distribution of LB pathology showed cortical involvement that exceeded that of the end stage of sporadic PD or the diffuse neocortical type of DLB [13,14]. Previous autopsy reports of INAD and ANAD have also described marked cortical involvement of LBs [1,8]. In contrast, the dorsal nucleus of the vagus nerve and olfactory bulbs were mildly affected in our patient, and the cardiac nerve fibers and enteral nerve plexus contained no p-α-synuclein aggregation, although these regions have been described as constant and early affected regions in sporadic PD and DLB [24,25]. The distribution of LB pathology in INAD and ANAD may tend to be more severe in the cerebral cortices compared to the medulla oblongata or peripheral autonomic neurons, which differs from the typical topography observed in sporadic PD and DLB. NFT pathology was another neuropathologial characteristic of interest in patients with INAD and ANAD. In our patient, NFTs and p-tau-positive threads predominantly appeared in the limbic system, which was similar to AD in Braak's stage IV [15]. However, neither this nor previously reported patients with *PLA2G6* gene mutations exhibited senile plaques, which contrasts with the typical neuropathology observed in AD [15]. Importantly, NFT pathology has been frequently observed in patients with sporadic PD or DLB [26,27], and LBs and NFTs often coexist in the same neurons, particularly those located in the limbic areas [26]. Our double-immunofluorescence results are consistent with findings in sporadic PD and DLB. Thus, further investigation in multiple patients on the association between NFTs and LB pathology and the implications of NFT pathology in INAD and ANAD are required.

The *PLA2G6* gene encodes iPLA2-Via, which is a critical protein in lipid membrane homeostasis [28]. Recent reports using Pla2g6-knockout mice demonstrated the presence of axonal spheroids in which tubulovesicular membranes accumulated [29-32]. In contrast, the pathological mechanism that contributes to LB formation in INAD and ANAD remains to be elucidated. LBs are secondarily present in several situations other than sporadic PD/DLB (e.g., sporadic or familial AD or Niemann-Pick disease type C) or may be incidentally found in healthy elderly individuals [33-36]. However, our neuropathological results and previous studies have demonstrated that LB pathology in patients with *PLA2G6* gene mutations shows a high prevalence and displays an extremely severe phenotype, particularly in the cerebral cortices. These findings suggest that defects in PLA2G6 primarily contribute to the formation of LBs.

Conclusions

Our results demonstrate the clinical heterogeneity of neuroaxonal dystrophy with *PLA2G6* gene mutations and support a genetic clinical view that compound heterozygous mutations that potentially result in residual protein function are associated with a less severe

phenotype. Neuropathologically, CNS involvement with LBs was striking and exhibited a unique topography compared with PD. Thus, further investigations on the process of LB formation caused by loss of *PLA2G6* gene function may provide new insights into the pathological mechanism of neuroaxonal dystrophy and LB formation.

Consent

Written informed consent was obtained from the patient's parents for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in chief of this journal.

Competing interests

There are no competing interests in the report.

Authors' contributions

YR, MM, and MY performed clinical and pathological analysis. TI, HY, and HH carried out the biochemical and genetic studies and drafted the manuscript. GS, KM, and YG helped to draft the manuscript. All authors read and approved the final manuscript.

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CASE REPORT

Senile onset frontotemporal lobar degeneration with TAR-DNA binding protein 43 proteinopathy primarily presenting with wasteful habits

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Key words: *abnormal behaviour, frontotemporal dementia, frontotemporal lobar degeneration, TDP-43, wasteful habits.*

Abstract

We present an autopsied case of a senile Japanese woman with sporadic frontotemporal lobar degeneration (FTLD) presenting as frontotemporal dementia. Disease onset was at the age of 70 and presented as a behaviour disorder, particularly involving wasteful habits. The patient had repeated incidents of making expensive purchases and then had difficulty making payments. Following these symptoms, she showed other changes of character such as lethargy and apathy. She gradually showed signs of parkinsonism including rigidity and bradykinesia, and in the terminal stage, an akinetic mutism state with quadriplegia in flexion was observed. Head magnetic resonance imaging revealed severe frontotemporal lobe atrophy with severe lateral ventricular dilatation and frontal white matter degeneration. At autopsy, the brain weighed 930 g and the frontotemporal cerebral cortex showed neuron loss with gliosis, tissue rarefaction and spongiform change, particularly in the superficial layers. Pathologic degeneration was more severe in the anterior portion of the frontal lobe with extensive white matter degeneration. Immunostaining for phosphorylated TAR-DNA binding protein 43 (TDP-43) revealed numerous neuronal cytoplasmic inclusions and extensive short dystrophic neuritis, particularly in the frontotemporal cortex. Many TDP-43-positive cytoplasmic inclusions were also observed in the dentate gyrus of the hippocampus. The patient was pathologically diagnosed with FTLD with TDP-43-positive inclusions (FTLD-TDP) without motor neuron disease. The immunohistochemical findings corresponded to type A of the FTLD-TDP pathology classification system.

INTRODUCTION

Frontotemporal lobar degeneration (FTLD) encompasses heterogeneous clinical syndromes with varying histopathology. It is characterized by variations in motor skills, speech, and behavioural and psychiatric symptoms based on dysfunction of the frontotemporal lobes.[1–3] Clinically, FTLD comprises mainly three subtypes: frontotemporal dementia (FTD), progressive non-fluent aphasia (PNFA) and semantic dementia (SD).[2] (Other subtypes of progressive apraxia have also been observed.)[1] FTD patients have been observed with or without motor neuron disease (MND).[1–3] The terms FTD, PNFA, SD and progressive apraxia refer to distinctive clinical syndromes, which are thought to be determined chiefly by the distribution of pathological change within the brain.[1] More than half of FTLD cases are clinically classified as FTD type.[1]

The most frequent underlying pathology of FTLD patients is FTLD with ubiquitin-positive/tau-negative inclusions. This pathological subtype had been called FTLD-U.[3] In 2006, the major pathogenic protein in FTLD-U cases was identified as TAR-DNA binding protein 43 (TDP-43),[4] and cases with TDP-43 are now

referred to as FTLD-TDP. Further clinicopathological investigation of FTLD-TDP is required to aid diagnosis by autopsy, and there are few case reports with detailed clinicopathologic descriptions. Moreover, because the Japanese FTLD-TDP cases mainly consist of sporadic cases with MND, there are fewer case reports of FTLD-TDP without MND from Japan than there are from Europe and the USA, where there are many familial cases with various genetic mutations.[5,6] Herein we report the case of a senile Japanese woman with sporadic FTLD-TDP without MND who showed unique clinical manifestations of behavioural disorders.

CASE REPORT

Clinical summary

A 70-year-old right-handed Japanese woman developed behavioural disorders, particularly characterized by wasteful habits. The patient was born, raised and lived in Mie prefecture in Japan and had an unremarkable medical history without any psychiatric disorder. There was no family history of psychiatric or neurodegenerative disorders, and no parental consanguinity. Although she lived on only her pension, she frequently went to beauty salons and made expensive purchases, including furniture, nutrition supplements, and health foods. After 1 year, she began to have difficulty making payments on the goods purchased and gradually showed character changes such as poor spontaneity, apathy and lethargy. She entered an old-age home at the age of 72 because she had become bankrupt and was no longer able to dress, feed or clean herself. She was not conscious of her disease and was diagnosed with Alzheimer's disease in a psychiatric hospital. Because she was non-cooperative in testing, it was hard to screen for memory loss and disorientation.

While living in the elderly residential institution, the patient no longer took care of herself; however, there was no sign of violent behaviour. She was reluctant to go to the restroom, and urinated and defecated on the floor of the residence. Donepezil hydrochloride was administrated for several months, but no effectiveness was apparent. Gradually, she showed increasing bradykinesia and, by the age of 73, rarely moved from her room. Daily living activities and conversational ability were decreased, and she began using a wheelchair. Neurological examination at the age of 74 revealed masked face with forced laughing, vertical gaze palsy with preserved oculocephalic reflex, bilateral grasp reflex and imitation behaviour of the right upper extremity. She could hardly talk at this stage, but aphasia symptoms such as semantic dementia were not apparent. Apraxia and rigospasticity of the left upper extremity appeared and gradually showed flexion posture with contractures. Lower motor neuron signs such as decrease of deep tendon reflex, muscular atrophy, and fasciculation were not recognized. Head magnetic resonance imaging showed severe frontotemporal atrophy with lateral ventricular dilatation, predominantly on the right side. Single-photon emission computed tomography scans detected severely decreased cerebral blood flow diffusely in the bilateral frontotemporal lobe.

The clinical diagnosis was modified to FTD; administration of amantadine hydrochloride was ineffective. The patient became bedridden, and gastrostomy was performed 6 years after the initial onset of symptoms. Magnetic resonance imaging performed when she was 77 years old, 6 months before her death, showed further progression of severe frontotemporal lobe atrophy with severe ventricular dilatation with extensive white matter degeneration of the frontal lobe (Fig. 1). Diffusion-weighted imaging showed no high signal intensity lesions. She displayed an akinetic mutism state and quadriplegia in flexion with contracture of the extremities joints in the terminal stage. The patient died of aspiration pneumonia 7 years after onset. Mechanical ventilation and tracheotomy were not performed because the patient's respiration was preserved without any assistance until shortly before death.

Pathologic findings

Macroscopic appearance

Autopsy was limited to the brain and upper cervical cord. The brain weighed 930 g before fixation. Macroscopically, severe frontotemporal lobe atrophy was observed predominantly on the right side (Figs 2,3a). The frontal portion of the frontal lobe and frontal base showed more apparent atrophy. The cerebellum and brainstem were preserved from atrophy. Depigmentation was apparent in the substantia nigra, whereas the locus ceruleus was preserved. Arteriosclerotic change was not apparent in the major vessels of the cerebral surface, including the vertebro-basilar artery.

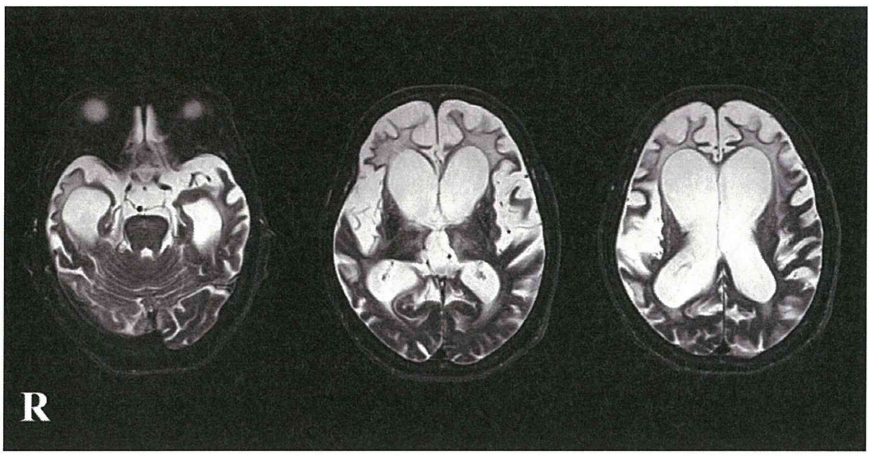

Figure 1 Head magnetic resonance imaging obtained when the present patient was 77 years old, 6.5 years after the onset of dementia. Severe frontotemporal atrophy and lateral ventricular dilatation are apparent. Anterior and inferior horns of the lateral ventricles are markedly dilated. Extensive white matter degeneration of the frontal lobe is also apparent. There is no apparent cerebrovascular lesion. R: right side.

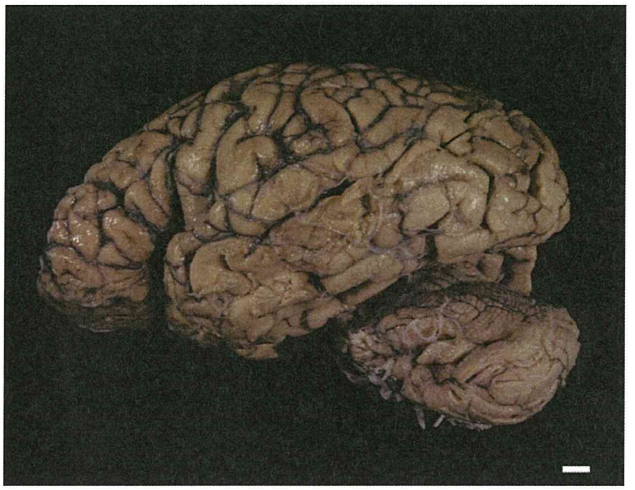

Figure 2 Macrophotograph of the formalin fixed brain. Frontotemporal lobe atrophy is apparent, particularly in the anterior portion of the frontal lobe. The cerebellum is relatively preserved. Scale bar: 10 mm.

Microscopic appearance

The frontotemporal cerebral cortex showed extensive tissue rarefaction and spongiform change, particularly in the superficial layer of the cerebral cortex (Fig. 3b); degeneration was more severe in the anterior portion of the frontal lobe (Fig. 3c). In the severely affected frontal lobe, diffuse neuron loss with gliosis was observed in the cortex, and severe tissue rarefaction with gliosis was observed in the white matter. In the precentral gyrus, Betz cells were relatively preserved in number, but spongiform change and gliosis were observed in the superficial layer. The neuron loss and gliosis was relatively mild in the amygdala and parahippocampal gyrus. The caudate nucleus and putamen showed moderate neuron loss with gliosis and tissue rarefaction. The globus pallidus and subthalamic nucleus showed mild neuron loss. The medial thalamus showed mild neuron loss with gliosis, whereas the lateral thalamus was preserved. In the cerebral white matter, myelin pallor was extensively observed in the frontotemporal lobe, particularly in the frontal portion, although U-fibre, the corpus callosum and internal capsule were relatively preserved. The substantia nigra showed severe neuron loss, whereas the locus ceruleus showed mild neuron loss. The dorsal nucleus of the vagal nerve and hypoglossal nucleus showed no apparent neuron loss. The cerebral peduncle, pontine longitudinal fibre and pyramid of the medulla oblongata were preserved, and pyramidal tract degeneration was not recognized in the upper cervical cord. Bunina bodies were not evident.

Numerous neuronal cytoplasmic inclusions and short dystrophic neuritis were extensively recognized in the frontotemporal cortex, particularly in the superficial layer, by immunohistochemistry of phosphorylated TDP-43 (Fig. 3d). TDP-43-positive neuronal cytoplasmic inclusions and dystrophic neurites were also observed in the dentate gyrus of the hippocampus (Fig. 3e), putamen and caudate nucleus. TDP-43-positive neuronal intranuclear inclusions were also observed in these regions. A small number of these TDP-43-positive structures were also observed in the globus pallidus, thalamus, quadrigeminal bodies, substantia nigra, pontine nucleus and inferior olivary nucleus. Some TDP-43-positive glial

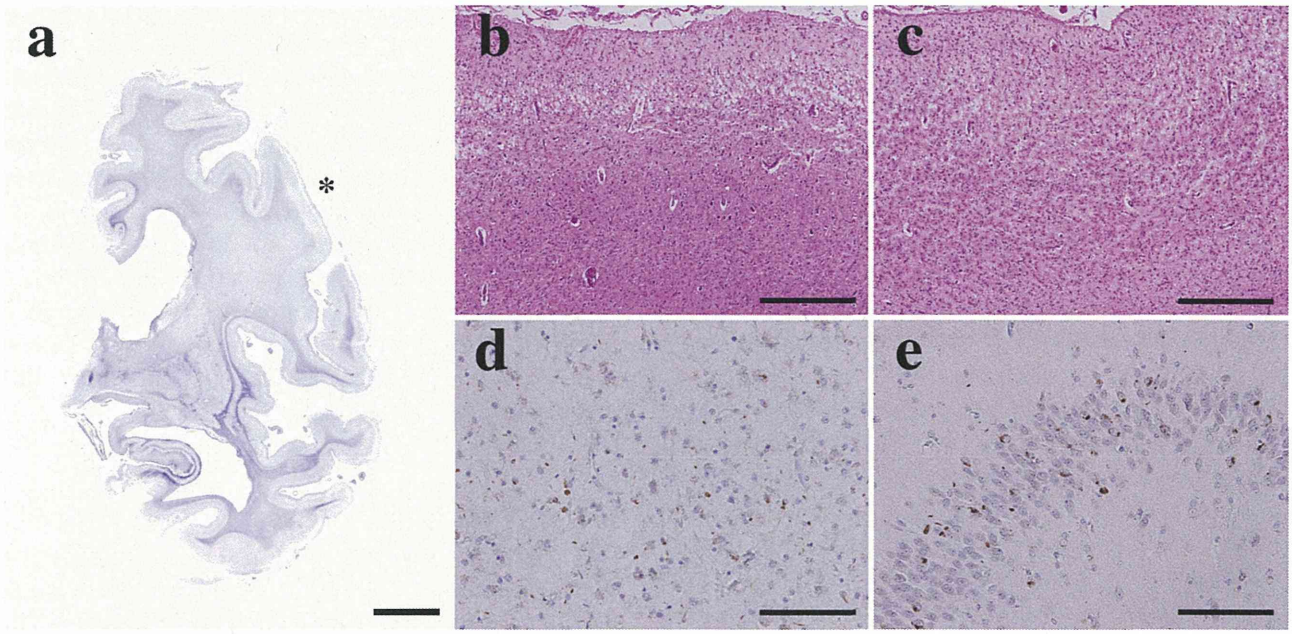

Figure 3 Representative macroscopic and microscopic images of the brain. (a) Macroscopic image of the coronal section of the right cerebral hemisphere at the level of the hippocampus. Dilatation of the anterior and inferior horns of the lateral ventricle is apparent. Fibrous gliosis is apparent in the white matter, particularly in the parahippocampal gyrus, temporal cortex and corpus callosum. Precentral gyrus (*) is relatively preserved from fibrous gliosis. (b) Tissue rarefaction and spongiform change are apparent in the superficial layer of the cortex (the posterior portion of the superior frontal gyrus). (c) Diffuse severe neuron loss with gliosis is extensive in the cerebral cortex. Tissue rarefaction and spongiform change are conspicuous in the superficial layer (the anterior portion of the middle frontal gyrus). (d) Numerous TDP-43-positive neuronal cytoplasmic inclusions and short dystrophic neurites are apparent, especially in the superficial layer of the cerebral cortex (the posterior portion of the superior frontal gyrus). (e) Many neuronal cytoplasmic inclusions immunopositive for TDP-43 are visible in the dentate gyrus of the hippocampus. Staining: (a) Holzer staining; (b,c) haematoxylin and eosin staining; (d,e) phosphorylated TDP-43 immunostaining (The antibody provided by Dr Masato Hasegawa, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan). Scale bars: (a) 10 mm; (b,c) 500 μm; (d,e) 100 μm. TDP-43, TAR-DNA binding protein 43.

inclusions were also recognized in these regions, but few were found in the cerebral white matter of the frontal lobe.

A few neurofibrillary tangles were observed that corresponded to Braak stage I. Senile plaques, Pick bodies, argyrophilic grains, Lewy bodies, astrocytic plaques or tuft-shaped astrocytes were not recognized.

DISCUSSION

Because the patient's clinical symptoms primarily reflected a behaviour disorder and character change, we thought the present case corresponded to the FTD subtype of FTLD. Although no apparent aphasia symptoms suggestive of PNFA or SD were apparent, the patient's spontaneous speech gradually decreased and progressed to mutism. Frontal lobe signs, apraxia and left side dominant parkinsonism were also observed in the advanced stage, whereas there were no apparent lower motor neuron signs throughout the total disease stage. Although these clinical findings do not contradict the clinical criteria of FTD in FTLD,[2] the supportive criteria of onset before 65 years and positive family history were not applicable to the present patient.

The patient's initial symptoms of wasteful habits are a novel observation for the pathogenesis of FTLD. Although it is difficult to identify the region associated with these symptoms, the anterior portion of the frontal lobe severely affected in the present cases was suspected, at least in part, of corresponding with this region. To our knowledge there have been no recorded cases of FTD that developed wasteful habits, but this symptom could be adapted to the core diagnostic features of early impairment in regulation of personal conduct for FTD in FTLD.[2] This patient showed other core diagnostic features of FTD such as insidious onset and gradual progression, early decline

in social interpersonal conduct, early emotional blunting and early loss of insight. Furthermore, the patient showed some supportive diagnostic features such as decline in personal hygiene and grooming, aspontaneity of speech, mutism, primitive reflexes, akinesia and rigidity.

Pathologically, the patient was diagnosed as FTLD-TDP without MND, and the most severe pathologic involvement was observed in the anterior portion of the frontal lobe with extensive white matter degeneration. The clinical syndrome of FTLD is strongly influenced by the macroscopic distribution of the cerebral atrophy.[1] A predictable relationship between clinical syndrome and topographical distribution has been suspected, and differences in the topographical underlying pathology are present even at the end stage of disease.[1] Usually, FTD is associated with frontal and anterior temporal atrophy, whereas FTD/MND is associated with more circumscribed frontal lobe atrophy, PNFA with strikingly asymmetric atrophy extending throughout the left hemisphere, and SD with bilateral, albeit often asymmetrical, atrophy of the temporal lobes.[1] However, the clinical phenotype cannot predict the specific underlying histology such as tauopathy, TDP-proteinopathy or other proteinopathies.[1] The presence of tau pathology such as progressive supranuclear palsy and corticobasal degeneration has accounted for approximately half of all FTLD cases and is strongly influenced by clinical phenotype.[1]

The immunohistochemical findings, such as multiple neuronal cytoplasmic inclusions, numerous short dystrophic neurites and predominantly superficial cortical layer pathology, seen in the present case corresponds to type A of the new harmonized FTLD-TDP pathology classification system proposed by Mackenzie *et al.*[7] Although, FTD has shown a variable relationship with the underlying histopathology, about half of the FTD cases with TDP-43 proteinopathy showed type A pathology.[1] Furthermore, the majority of FTLD-TDP type A corresponds with the clinical phenotype of FTD or PNFA.[7]

Vertical gaze palsy with preserved oculocephalic reflex was clinically observed in the present case, and the brainstem region associated with eye movement was pathologically preserved. Thus, vertical gaze palsy was suspected because of supranuclear oculomotor abnormalities and may be related to the frontal lobe lesion, particularly in the frontal eye fields.

In conclusion, the present case showed a novel and interesting initial symptom of wasteful habits. The symptoms corresponded with the core diagnostic features of early impairment in regulation of personal conduct within the diagnostic criteria for FTD. Detailed examination of the clinicopathological findings in each FTLD-TDP case with definite diagnosis is necessary to further understand FTLD.

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