performed in the past for Alzheimer's disease [16] but has generally been discontinued for ethical reasons [28], as the harm caused by the procedure cannot be offset by benefits arising from accurate diagnosis. The possible usage of clinical olfactory testing as a predictive risk factor for PD has also been critiqued [26]. Pharmacologic therapy of both Alzheimer's disease and Parkinson's disease is initiated empirically as the risks of therapy are low and therapy can be discontinued if it is ineffective or causes adverse effects. Surgical treatment of PD, however, which has included pallidotomy, thalamotomy, deep brain stimulation and neural transplantation, carries significant risk of complications, up to 40% overall [15, 25, 29, 33, 34, 36–39]. These therapies are thought to be ineffective for non-PD causes of Parkinsonism and therefore accurate diagnosis of PD is considered essential for patient selection. Estimates of the current clinical accuracy of the diagnosis of PD range between 65 and 90% [8, 13, 14, 20, 21, 27], with the higher accuracy figures being dependent on prolonged clinical observation and therapeutic trial with levodopa. Five years of observation with a favorable response to levodopa is recommended for surgical PD candidates [25]. It has been reported that patients with multiple system atrophy (MSA) misdiagnosed as PD have undergone placement of deep brain stimulators and have not had a lasting benefit [25]. As the characteristic glial cytoplasmic synuclein-immunoreactive inclusions of MSA are also present and diagnostic in the olfactory bulb, as reported by Kovacs et al. [23] (we have confirmed this finding in five MSA cases), olfactory bulb biopsy would differentiate between PD and MSA. Olfactory bulb biopsy might therefore be useful for the evaluation of candidates for surgical therapy of PD, where the risks of biopsy might be justified if it would spare non-PD subjects the greater risks associated with pallidotomy, thalamotomy, deep brain stimulation or neural transplantation [15, 25, 29, 33, 34, 36–39].

### Limitations of the current study

As this was an autopsy study, the entire olfactory bulb was available for examination. To achieve similar results in a biopsy setting, it is therefore recommended that the entire bulb be removed and examined. Examination of only part of the bulb may give false-negative results in some cases due to localized synucleinopathy.

## Conclusions

The presence of Lewy-type α-synucleinopathy in the olfactory bulb has greater than 90% sensitivity and specificity for neuropathologically confirmed PD and DLB and its severity correlates with the severity of synucleinopathy in other brain regions as well as with measures of cognition and motor function. Olfactory bulb biopsy might be considered in the setting of patient evaluation for surgical therapy for PD.

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## References

1. Adler CH (2005) Nonmotor complications in Parkinson's disease. Mov Disord 20 Suppl 11:S23–S29
2. Beach TG, Adler CH, Sue LI, Peirce JB, Bachalakuri J, sing-Hernandez JE, Lue LF, Caviness JN, Connor DJ, Sabbagh MN, Walker DG (2008) Reduced striatal tyrosine hydroxylase in incidental Lewy body disease. Acta Neuropathol 115:445–451
3. Beach TG, Sue LI, Walker DG, Roher AE, Lue L, Vedders L, Connor DJ, Sabbagh MN, Rogers J (2007) The Sun Health Research Institute Brain Donation Program: description and experience, 1987–2007. Cell Tissue Bank
4. Beach TG, Tago H, Nagai T, Kimura H, McGeer PL, McGeer EG (1987) Perfusion-fixation of the human brain for immunohistochemistry: comparison with immersion-fixation. J Neurosci Methods 19:183–192
5. Bloch A, Probst A, Bissig H, Adams H, Tolnay M (2006) Alpha-synuclein pathology of the spinal and peripheral autonomic nervous system in neurologically unimpaired elderly subjects. Neuropathol Appl Neurobiol 32:284–295
6. Braak H, Bohl JR, Muller CM, Rub U, de Vos RA, Del TK (2006) Stanley Fahn Lecture 2005: the staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. Mov Disord 21:2042–2051
7. Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, Sandmann-Keil D, Rub U (2002) Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). J Neurol 249 Suppl 3:1–5
8. Cornford ME, Chang L, Miller BL (1995) The neuropathology of Parkinsonism: an overview. Brain Cogn 28:321–341
9. Daniel SE, Hawkes CH (1992) Preliminary diagnosis of Parkinson's disease by olfactory bulb pathology. Lancet 340:186
10. Doty RL, Deems DA, Stellar S (1988) Olfactory dysfunction in Parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology 38:1237–1244
11. Fujishiro H, Tsuboi Y, Lin WL, Uchikado H, Dickson DW (2008) Co-localization of tau and alpha-synuclein in the olfactory bulb in Alzheimer's disease with amygdala Lewy bodies. Acta Neuropathol 116:17–24
12. Fujiwara H, Hasegawa M, Dohmae N, Kawashima A, Masliah E, Goldberg MS, Shen J, Takio K, Iwatsubo T (2002) Alpha-Synuclein is phosphorylated in synucleinopathy lesions. Nat Cell Biol 4:160–164
13. Gelb DJ, Oliver E, Gilman S (1999) Diagnostic criteria for Parkinson disease. Arch Neurol 56:33–39
14. Gibb WR (1992) Neuropathology of Parkinson's disease and related syndromes. Neurol Clin 10:361–376

15. Gill CE, Konrad PE, Davis TL, Charles D (2007) Deep brain stimulation for Parkinson's disease: the Vanderbilt University Medical Center experience, 1998–2004. Tenn Med 100:45–47
16. Harbaugh RE (1985) Brain biopsy in Alzheimer's disease: surgical technique and indications. Bull Clin Neurosci 50:39–43
17. Hawkes C (2006) Olfaction in neurodegenerative disorder. Adv Otorhinolaryngol 63:133–151
18. Hladik CL, White CL (2003) Comparison of digestive enzyme and formic acid pretreatment for optimal immunohistochemical demonstration of alpha-synuclein-immunoreactive cerebral cortical Lewy neurites. J Neuropathol Exp Neurol 62:554
19. Hubbard PS, Esiri MM, Reading M, McShane R, Nagy Z (2007) Alpha-synuclein pathology in the olfactory pathways of dementia patients. J Anat 211:117–124
20. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181–184
21. Hughes AJ, Daniel SE, Lees AJ (2001) Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology 57:1497–1499
22. Katzenschlager R, Lees AJ (2004) Olfaction and Parkinson's syndromes: its role in differential diagnosis. Curr Opin Neurol 17:417–423
23. Kovacs T, Papp MI, Cairns NJ, Khan MN, Lantos PL (2003) Olfactory bulb in multiple system atrophy. Mov Disord 18:938–942
24. Kranick SM, Duda JE (2008) Olfactory dysfunction in Parkinson's disease. Neurosignals 16:35–40
25. Lang AE, Houeto JL, Krack P, Kubu C, Lyons KE, Moro E, Ondo W, Pahwa R, Poewe W, Troster AI, Uitti R, Voon V (2006) Deep brain stimulation: preoperative issues. Mov Disord 21 Suppl 14:S171–S196
26. Linazasoro G (2008) Olfaction testing in PD: risky conclusions. Mov Disord 23:1060
27. Litvan I, MacIntyre A, Goetz CG, Wenning GK, Jellinger K, Verny M, Bartko JJ, Jankovic J, McKee A, Brandel JP, Chaudhuri KR, Lai EC, D'Olhaberriague L, Pearce RK, Agid Y (1998) Accuracy of the clinical diagnoses of Lewy body disease, Parkinson disease, and dementia with Lewy bodies: a clinicopathologic study. Arch Neurol 55:969–978
28. Mahendra B (1984) Some ethical issues in dementia research. J Med Ethics 10:29–31
29. Master Z, McLeod M, Mendez I (2007) Benefits, risks and ethical considerations in translation of stem cell research to clinical applications in Parkinson's disease. J Med Ethics 33:169–173
30. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del ST, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65:1863–1872
31. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 47:1113–1124
32. McKinnon JH, Demaerschalk BM, Caviness JN, Wellik KE, Adler CH, Wingerchuk DM (2007) Sniffing out Parkinson disease: can olfactory testing differentiate Parkinsonian disorders? Neurologist 13:382–385
33. Obeso JA, Rodriguez MC, Gorospe A, Guridi J, Alvarez L, Macias R (1997) Surgical treatment of Parkinson's disease. Baillieres Clin Neurol 6:125–145
34. Paluzzi A, Belli A, Bain P, Liu X, Aziz TM (2006) Operative and hardware complications of deep brain stimulation for movement disorders. Br J Neurosurg 20:290–295
35. Pearce RK, Hawkes CH, Daniel SE (1995) The anterior olfactory nucleus in Parkinson's disease. Mov Disord 10:283–287
36. Rodriguez RL, Fernandez HH, Haq I, Okun MS (2007) Pearls in patient selection for deep brain stimulation. Neurologist 13:253–260
37. Seijo FJ, varez-Vega MA, Gutierrez JC, Fdez-Glez F, Lozano B (2007) Complications in subthalamic nucleus stimulation surgery for treatment of Parkinson's disease. Review of 272 procedures. Acta Neurochir (Wien) 149:867–875
38. Subramanian T (2001) Cell transplantation for the treatment of Parkinson's disease. Semin Neurol 21:103–115
39. Tir M, Devos D, Blond S, Touzet G, Reyns N, Duhamel A, Waucquier N, Cottencin O, Dujardin K, Debailleul AM, Cassim F, Destee A, Defebvre L, Krystkowiak P (2007) Exhaustive, one-year follow-up of subthalamic nucleus deep brain stimulation in a large, single-center cohort of parkinsonian patients. Neurosurgery
40. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease (1997) Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. Neurobiol Aging 18:S1–S2

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ORIGINAL PAPER

# Clinicopathological characterization of Pick's disease versus frontotemporal lobar degeneration with ubiquitin/TDP-43-positive inclusions

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**Abstract** Although frontotemporal lobar degeneration with ubiquitin/TDP-43-positive inclusions (FTLD-TDP) and Pick's disease are common pathological substrates in sporadic FTLD, clinical differentiation of these diseases is difficult. We performed a retrospective review of medical records and semiquantitative examination of neuronal loss of 20 sporadic FTLD-TDP and 19 Pick's disease cases. Semantic dementia as the first syndrome developed only in FTLD-TDP patients. Impaired speech output in the early stage was five times more frequent in Pick's disease than in FTLD-TDP. The total frequency of asymmetric motor disturbances (e.g., parkinsonism, pyramidal signs, and contracture) during the course was significantly more frequent in FTLD-TDP (78%) than in Pick's disease cases (14%). Asymmetric pyramidal signs were found in 7 of 13 FTLD-TDP cases with corticospinal tract degeneration similar to primary lateral sclerosis. Frontotemporal dementia as the first syndrome was noted in both FTLD-TDP (28%) and Pick's disease cases (64%); however, only FTLD-TDP cases subsequently developed asymmetric motor disturbances, and some of the cases further exhibited hemineglect. Concordant with these clinical findings, degeneration in the temporal cortex, caudate nucleus, putamen, globus pallidus, substantia nigra, and corticospinal tract was significantly more severe in FTLD-TDP, and degeneration in the frontal cortex tended to be more severe in Pick's disease. Given these findings, the initial impairment of semantic memory or comprehension and subsequent asymmetric motor disturbances in sporadic FTLD patients predict sporadic FTLD-TDP rather than Pick's disease, while initial

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behavioral symptoms or non-fluent aphasia without subsequent asymmetric motor disturbances predict Pick's disease rather than sporadic FTLD-TDP.

**Keywords** Agnosia · Aphasia · Caudate nucleus · Corticobasal degeneration · Motor neuron disease · TDP-43

## Introduction

Frontotemporal lobar degeneration (FTLD), the second most common dementia in the presenium [59, 71] comprises three clinical subtypes characterized by behavioral and psychiatric symptoms resulting from dysfunction of the frontal and temporal lobes: frontotemporal dementia (FTD), progressive non-fluent aphasia (PA), and semantic dementia (SD) [48]. The most frequent underlying pathology of FTLD patients is FTLD with ubiquitin-positive, tau-negative inclusions, which occurs at a frequency of 40–60% of FTLD patients [47]. This pathological subtype has been called FTLD-U [9, 27], and the major pathological protein in FTLD-U was disclosed to be TAR-DNA binding protein 43 (TDP-43) [1, 49]. Thereafter, however, it was reported that a small proportion of FTLD-U cases lack TDP-43 pathology [31, 41, 61]. Therefore, it is currently recommended that FTLD with ubiquitin-positive and TDP-43-positive inclusions be called FTLD-TDP and FTLD with ubiquitin-positive but TDP-43-negative inclusions be called FTLD-UPS (ubiquitin proteosome system) [42]. Accordingly, in this paper, the term FTLD-U is used only when referring to previous studies in which TDP-43 pathology was not assessed.

The histopathological hallmarks of FTLD-U and FTLD-TDP are ubiquitin- and/or TDP-43-positive dystrophic neurites, neuronal cytoplasmic inclusions (NCIs), and neuronal intranuclear inclusions (NIIs) in the affected cortex, hippocampal dentate gyrus, and striatum [1, 40, 49]. Mutations of the progranulin gene (*PGRN*) were identified in 15–25% of FTLD-U cases, 5–10% of all FTLD patients, and 10–20% of familial FTLD cases [3, 10, 16, 39, 57, 58]. Some FTLD-U cases have corticospinal tract degeneration similar to primary lateral sclerosis (PLS), but minimal or no involvement of the lower motor neurons [13, 23]. The pathogenic relationship between FTLD-TDP with or without PLS-like lesions and amyotrophic lateral sclerosis (ALS) remains unclear. The second most common pathological substrate in FTLD patients is considered to be Pick's disease, and it was found at a frequency of about 10–30% in two autopsy series of FTLD [29, 47]. Originally, the term Pick's disease referred to pathologically heterogeneous cases that have circumscribed frontotemporal atrophy [52, 56], but it is now used only for cases having tau-positive Pick bodies [70].

It is currently known that FTLD comprises various pathological entities besides FTLD-TDP and Pick's disease, such as corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), neuronal intermediate filament inclusion disease (NIFID) [8, 28], basophilic inclusion body disease (BIBD) [46, 74], dementia lacking distinctive histological features (DLDH) [35], and Alzheimer's disease with atypical cerebral atrophy. Identifying these underlying pathologies during life of the patient is crucial for future specific pathology-based treatments [14, 20, 60]. Therefore, a few studies that tried to clarify the clinical differences between variable pathological entities in FTLD patients have been conducted [14, 34]. However, because the number of such comprehensive studies is yet very limited, the clinical data available to predict pathologies related to FTLD are not adequate for physicians in various clinical settings.

Approximately 60% of FTLD patients in Western countries lack a family history of FTLD [57, 58], and family histories are even more rare in Japanese FTLD patients [22, 25, 71]. However, the differences between common pathologies in sporadic FTLD patients, especially sporadic FTLD-TDP and Pick's disease, have not been fully investigated. In this paper, we first compared the clinical features in a postmortem series of sporadic FTLD-TDP and Pick's disease with special attention to (1) the spectrum of symptoms within 1 year after the onset, (2) the characteristics and frequencies of behavioral, language, and motor disturbances during the course, and (3) the evolution of the clinical presentation from early to end stages. To understand the pathological bases of the clinical features, we assessed the distribution and severity of neuronal loss, which often correlate more closely with clinical features than those of inclusions [13], in representative anatomical regions in the central nervous system in cases of FTLD-TDP and Pick's disease. In addition, in FTLD-TDP cases, the relationship between the histopathological subtypes of TDP-43 pathology and clinical features was examined.

## Materials and methods

### Subjects

A case series of FTLD-TDP ($n = 20$) and Pick's disease ($n = 19$), as well as nine cases of FTLD-TDP with motor neuron disease (FTLD-MND) as a disease control for TDP-43 immunohistochemistry, were examined in this study (Table 1). These cases were selected from two neuropathological series evaluated at the Tokyo Institute of Psychiatry from 1974 to 2007 and at the Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences from 1924 to 2007, respectively. The inclusion criterion was the availability of fixed tissues for the histological diagnosis. No subject in this study had a family history of dementia or motor neuron disease. All of the cases were pathologically classified

**Table 1** Demographic data of subjects

| | FTLD-TDP | | | | Pick's disease |
|---|---|---|---|---|---|
| | All FTLD-TDP | FTLD-TDP-PLS(+) | FTLD-TDP-PLS(−) | FTLD-TDP-PLS(ne) | |
| N (male/female) | 20 (14/6) | 14 (10/4) | 4 (3/1) | 2 (1/1) | 19 (9/10) |
| Age at onset (years) | 54.5 ± 8.2 | 52.9 ± 7.4 | 62.7 ± 7.2 | 52.0 ± 11.3 | 55.9 ± 7.5 |
| Age at death (years) | 62.6 ± 9.6 | 62.5 ± 8.8 | 64.2 ± 11.3 | 60.5 ± 17.7 | 66.2 ± 8.3 |
| Duration (years) | 9.2 ± 5.7 | 9.8 ± 6.2 | 6.3 ± 2.5 | 8.9 ± 5.9 | 8.6 ± 5.0 |
| Family history (*n*) | 0 | 0 | 0 | 0 | 0 |
| Brain weight (g) | 1049 ± 207 | 1016 ± 189 | 1170 ± 314 | 1,150[a] | 1012 ± 216 |
| TDP-43 pathology | | | | | |
| Type 1 [*n* (%)] | 11 (55.0) | 8 (57.1) | 2 (50.0) | 1 (50.0) | – |
| Type 2 [*n* (%)] | 5 (25.0) | 3 (21.4) | 1 (25.0) | 1 (50.0) | – |
| Type 3 [*n* (%)] | 4 (20.0) | 3 (21.4) | 1 (25.0) | 0 (0.0) | – |
| Type 4 [*n* (%)] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | – |

The age at onset, age at death, duration, and brain weight were mean ± standard deviation

*FTLD-TDP-PLS(+)* FTLD-TDP with PLS-like corticospinal tract degeneration, *FTLD-TDP-PLS(−)* FTLD-TDP without PLS-like corticospinal tract degeneration, *FTLD-TDP-PLS(ne)* FTLD-TDP cases of which medulla oblongata or spinal cord tissue could not be histopathologically examined

[a] The brain weight in one case of FTLD-TDP-PLS(ne) was not available

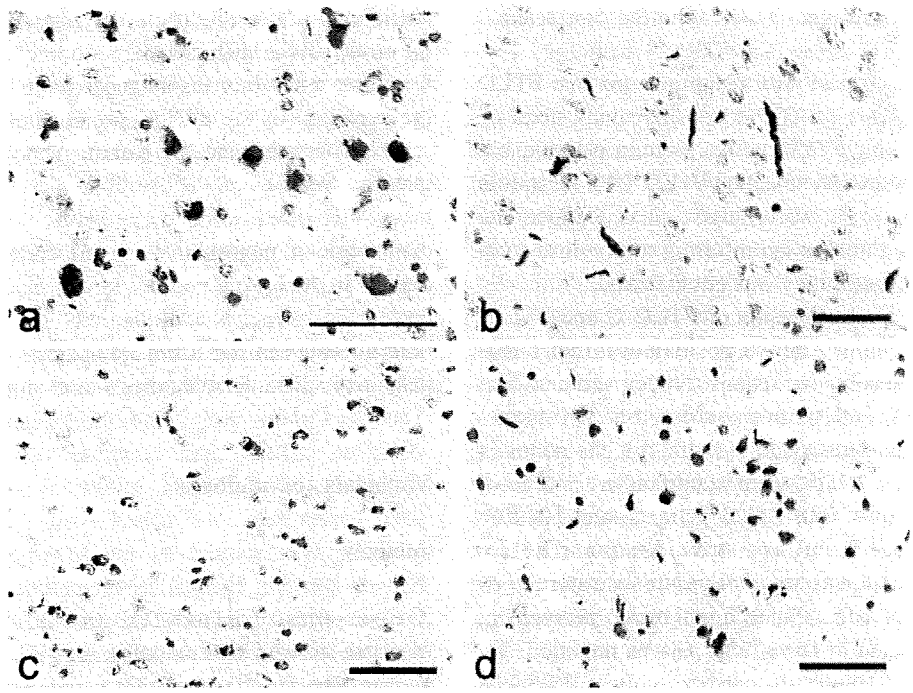


**Fig. 1** Diagnostic pathological changes in FTLD-TDP and Pick's disease. **a** Numerous tau-positive Pick bodies in the deep layer of the temporal cortex. **b** Type 1 histology of FTLD-TDP. Long and relatively thick TDP-43-positive dystrophic neurites but no neuronal inclusions are seen. The temporal cortex. **c** Type 2 histology of FTLD-TDP. Many TDP-43-positive neuronal cytoplasmic inclusions in the frontal cortex are seen. No neuronal intranuclear inclusions are found. **d** Type 3 histology of FTLD-TDP. Many TDP-43-positive short dystrophic neurites and neuronal cytoplasmic inclusions are seen in the cortical layer II in the temporal cortex. None of our FTLD-TDP cases had neuronal intranuclear inclusions. **a** AT-8 immunohistochemistry, **b–d** Phosphorylated TDP-43 immunohistochemistry. All *scale bars* 50 μm

according to the following criteria: (1) Pick's disease (FTLD with Pick bodies [9]) was defined as the presence of tau- and Bodian-positive intraneuronal spherical or oval inclusions (Fig. 1a). (2) FTLD-TDP was diagnosed by the presence of ubiquitin-positive and TDP-43-positive but tau- and α-synuclein-negative NCIs, NIIs, and/or dystrophic neurites in the affected cerebral cortex and hippocampal dentate gyrus (Figs. 1b–d). Further, in this study, cases

having pyramidal tract degeneration, but lacking histopathological evidence of lower motor neuron degeneration or the formation of Bunina bodies in the lower motor neurons, were classified as 'FTLD-TDP with PLS-like corticospinal tract degeneration' [FTLD-TDP-PLS(+)]. FTLD-TDP cases without degeneration of the pyramidal tract or lower motor neuron pathology were classified as 'FTLD-TDP without PLS-like corticospinal tract degeneration' [FTLD-TDP-PLS(−)]. If neither medulla oblongata nor spinal cord tissue could be histopathologically examined, the case was classified as 'FTLD-TDP-PLS(ne)'. Cases with ubiquitin-positive but TDP-43-negative inclusions (called atypical FTLD-U [41] or FTLD-UPS [42]) were excluded. One case that was previously reported as DLDH but in which ubiquitin/TDP-43 pathology was revealed by reexamination was included in FTLD-TDP [53]. (3) The definition of FTLD-MND was based on dementia and histopathological evidence of ALS (i.e., degeneration in the pyramidal tract, loss of the lower motor neurons, and the presence of Bunina bodies and ubiquitin/TDP-43-positive inclusions in the lower motor neurons).

## Clinical features in sporadic FTLD-U and Pick's disease

All of the available clinical information on sporadic FTLD-TDP and Pick's disease cases was retrospectively reviewed blind to any pathological information with special attention to the following descriptions: psychiatric and behavioral symptoms (irritability, euphoria, disinhibition, self-centered personality change, verbal or behavioral stereotypy, and oral tendency and pica), language disturbance (naming difficulty, impaired auditory comprehension, reduced utterance, and impaired speech output), semantic memory impairment (impaired comprehension and impaired recognition of common objects, faces, and written words), and asymmetric motor symptoms (parkinsonism; pyramidal signs including Babinski sign, clonus, and hypertonia; contracture; and lower motor neuron signs), and other cognitive symptoms (memory impairment, apraxia, and unilateral spatial agnosia). The term impaired speech output was used only when the nature of the impairment (e.g., apraxia of speech, phonemic paraphasias, stuttering, or hesitation in the utterance) was recorded. The term reduced speech output was used when the reduction of speech output was recorded without detailed explanation of its nature. Five Pick's disease cases and two FTLD-TDP cases [one FTLD-TDP-PLS(+) and one FTLD-TDP-PLS(−) cases] were excluded from the clinical examination because clinical information was inadequate. One Pick's disease case who suffered from young onset schizophrenia but lacked dementia during the course was also excluded when calculating the frequency of each symptom.

We first examined (1) the frequencies of early symptoms and (2) the frequencies of symptoms that developed during the course in all FTLD-TDP, FTLD-TDP-PLS(+), FTLD-TDP-PLS(−), FTLD-TDP-PLS(ne), and Pick's disease groups. Early symptoms were defined as all symptoms that developed within 1 year after the onset. Most of the FTLD patients sequentially developed several key clinical symptoms or syndromes with the disease progression. Therefore, we subsequently compared (3) the evolving patterns of clinical syndromes between FTLD-TDP and Pick's disease cases.

Clinical syndromes of FTLD determined in each clinical stage were defined according to the consensus criteria [48]: (1) FTD was defined by progressive behavioral disturbances including personality change, disinhibited and self-centered behaviors, and stereotypic behaviors. (2) SD was characterized by fluent speech output and loss of concept knowledge, resulting in loss of understanding of nominal terms, impaired recognition of both faces and common objects, and impaired comprehension. (3) PA was defined by progressive, non-fluent spontaneous speech. When the clinical picture at some stage did not fit these representative syndromes, the most dominant symptoms at the stage, such as impaired comprehension, memory impairment, delusional state, gait disturbance, asymmetric parkinsonism, or unilateral spatial agnosia, were directly used to explain the clinical picture in that stage.

Clinical information was interpreted by a senior psychogeriatrician (O.Y.) with a special interest in dementia and checked by a specialist of neuropsychology including aphasiology (M.K.).

## Conventional neuropathology and immunohistochemical examination

Brain tissue samples from all subjects were fixed postmortem with 10% formaldehyde and embedded in paraffin. Sections (10 μm thick) from the frontal, temporal, parietal, occipital, insular, and cingulate cortices, hippocampus, amygdala, basal ganglia, midbrain, pons, medulla oblongata, cerebellum, and spinal cord were prepared. These sections were stained by the hematoxylin–eosin (H&E), Klüver–Barrera, Holzer, methenamine silver, Bodian, and Gallyas–Braak methods. A genetic study was not done because frozen tissue samples were not available.

Sections from representative regions of the cerebrum, brainstem, and spinal cord were examined immunohistochemically using antibodies to ubiquitin (Z0458, rabbit, polyclonal, 1:5,000, Dako, Glostrup, Denmark), phosphorylated tau (AT8, mouse, monoclonal, 1:3,000, Innogenetics, Ghent, Belgium), phosphorylated α-synuclein (1175, rabbit, polyclonal, 1:1000, [50]), phosphorylated TDP-43 (pS409/410, rabbit, polyclonal, 1:1,000 [19]), and glial fibrillary acidic protein (GFAP, rabbit, polyclonal, 1:5,000, Dako). 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% Triton×-100 for 5 min and washed in phosphate-buffered saline (PBS, pH 7.4). When using anti-ubiquitin, sections were pretreated by autoclaving for 10 min in 10 mM sodium citrate buffer at 120°C. After blocking with 10% normal serum, sections were incubated for 72 h 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 secondary antibody for 1 h, and then in avidin-biotinylated horseradish peroxidase complex (ABC Elite kit, Vector, Burlingame, CA, USA) for 1 h. The peroxidase labeling was visualized with 0.2% 3,3′-diaminobenzidine (DAB) as the chromogen. Sections were counterstained with hematoxylin.

### Assessment of neuronal loss associated with glial proliferation

The distribution and severity of neuronal loss associated with gliosis in the representative sites of the cerebral cortex (Figs. 2a–h), basal ganglia (Figs. 3a–f), and brainstem nuclei were assessed on H&E-, KB-, and GFAP-stained sections according to the grading system employed in our previous studies [67–69, 72, 74]. Briefly, stage 0 indicated no neuronal loss, stage 1 mild neuronal loss, stage 2 moderate neuronal loss, and stage 3 severe neuronal loss. The frontal and temporal cortices, caudate nucleus, and putamen were assessed at two levels, and the most severe grade was recorded as the stage in each region.

Degeneration of the corticospinal tract and frontopontine tract at the level of the cerebral peduncle was assessed by the evidence of loss of myelin, glial proliferation, and the presence of macrophages [69, 72, 74], and indicated as stage 0 (absent) or stage 1 (present). The severity of the degeneration of the corticospinal tract at the level of the medulla oblongata was indicated as stage 0 (no degeneration), neither loss of myelin nor glial proliferation was found; stage 1 (mild degeneration), slight myelin loss and gliosis without atrophy of the tract; stage 2 (moderate degeneration), evident myelin loss and gliosis with slight atrophy of the tract; and stage 3 (severe degeneration), evident myelin loss and gliosis with severe atrophy of the tract.

Macroscopic atrophy of the basal ganglia at the level of the temporal pole on the coronal slice was assessed using the modified staging system originally reported by Broe

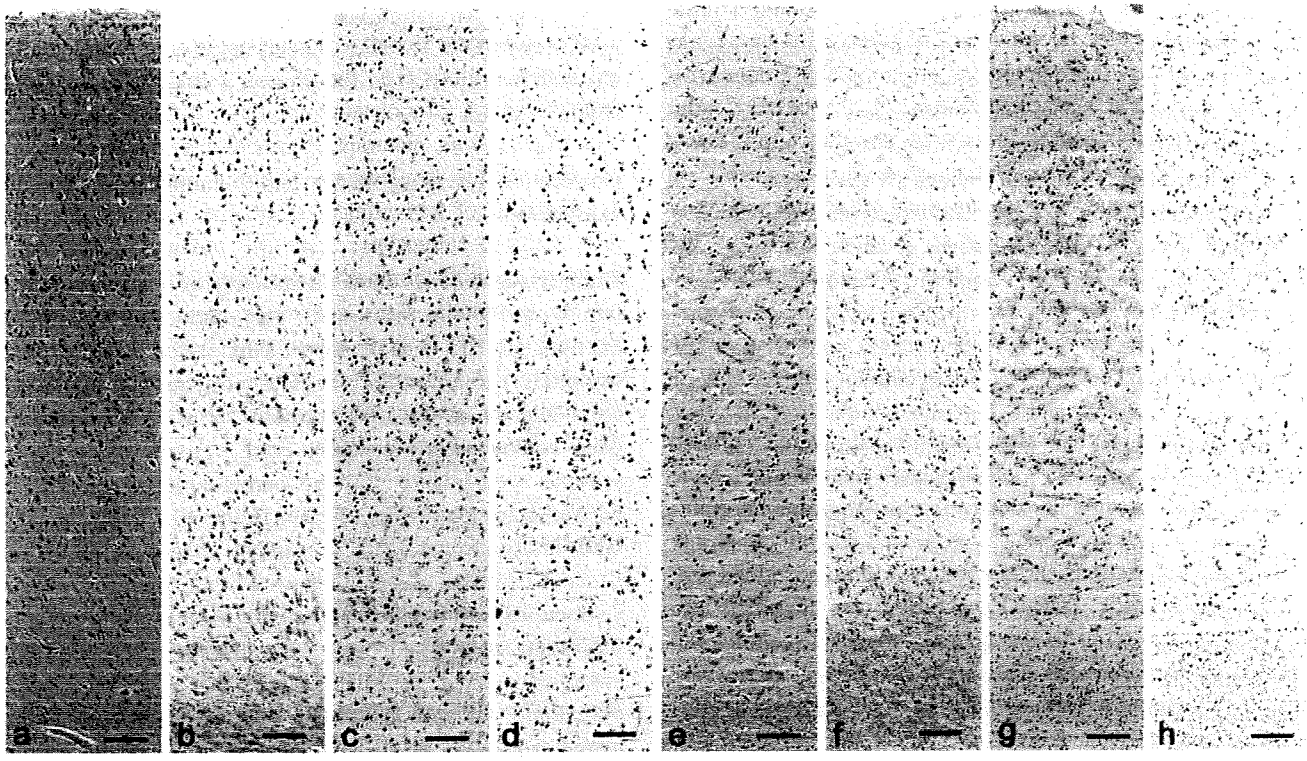


**Fig. 2** Staging of neuronal loss associated with glial proliferation in the cerebral cortex. **a**, **b** Stage 0. In the all cortical layers, the cytoarchitecture is normal and neurons are spared in number. The superior frontal gyrus. FTLD-TDP. **c**, **d** Stage 1. Mild neuronal loss with mild astrocytosis is noted in the cortical layers I and II, but the laminar structure in the deeper cortical layers is almost completely spared. The superior frontal gyrus. FTLD-TDP. **e**, **f** Stage 2. Moderate neuronal loss associated with evident astrocytosis is found in the cortical layers I–III, but neurons in the deep layers are spared in number. The superior temporal gyrus. FTLD-TDP. **g**, **h** Stage 3. In all cortical layers, neurons have almost completely disappeared, and glial proliferation is remarkable. The myelin in the adjacent subcortical white matter is obviously reduced. The inferior temporal gyrus. FTLD-TDP. **a**, **c**, **e**, **g** Hematoxylin–eosin stain, **b**, **d**, **f**, **h** Klüver–Barrera stain. All *scale bars* 100 μm

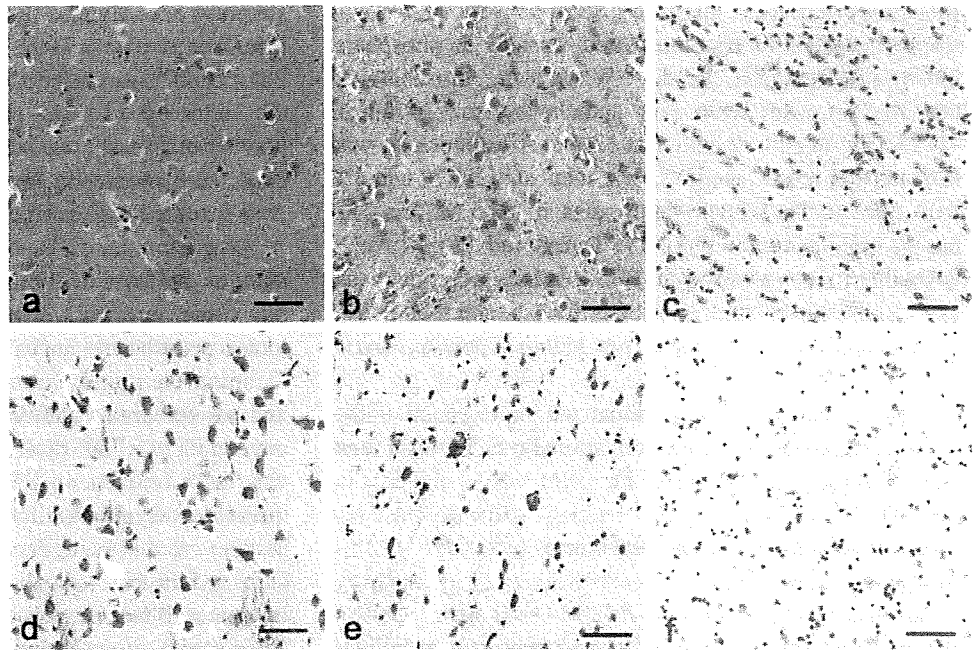


**Fig. 3** Staging of neuronal loss associated with glial proliferation in the putamen. **a, d** Stage 0. Neither neuronal loss nor glial proliferation is noted. A normal control case. **b, e** Stage 2. Moderate neuronal loss with evident gliosis is found, but tissue rarefaction is not seen. FTLD-TDP. **c, f** Stage 3. Severe neuronal loss, remarkable glial proliferation, and tissue rarefaction are found. FTLD-TDP. **a–c** Hematoxylin–eosin stain, **d–f** Klüver–Barrera stain. All *scale bars* 100 μm

et al. [7]: stage 0, no atrophy was noted in the basal ganglia; stage 1, there was minimal atrophy of the basal ganglia, but the structure of the caudate nucleus was not flattened; stage 2, the structure of the caudate nucleus was flattened, leading to dilation of the lateral ventricle; stage 3, the basal ganglia was further degenerated, as evidenced by a concavity of the ventricular surface; and stage 4, the basal ganglia was dramatically reduced in volume, and the ventricle was consequently concave and grossly dilated.

All of these pathological changes were independently evaluated by two investigators (O.Y. and K.T.), and the final grade was determined after discussion when the results were inconsistent.

### Assessment of other pathological changes

Neurofibrillary changes and senile plaques were evaluated by the Braak stage on Gallyas–Braak and methenamine silver-stained sections, respectively [6]. Argyrophilic grains and Lewy pathology were also evaluated on Gallyas–Braak silver-stained sections and α-synuclein immunostained sections, respectively. TDP-43 pathology was classified into types 1–4 according to the recently reported pathological criteria (Figs. 1b–d) [9]. This classification was performed by two researchers (O.Y. and T.A.) who were blind to clinical and pathological diagnoses.

### Statistic analysis

The Chi-square and Mann–Whitney *U* tests were used to analyze the significance of differences in variables, including the demographic data, frequency of each clinical feature, and severity of degeneration in each anatomical region, between the two groups. When the expected frequency was <5 in one or more cells, Fisher's exact test was used. Spearman rank order correlation analysis was applied for univariate correlations between the severity of neuronal loss in representative anatomical regions (i.e., the inferior frontal gyrus, superior temporal gyrus, inferior temporal gyrus, inferior parietal lobule, hippocampus, putamen, substantia nigra, and corticospinal tract at the level of the medulla oblongata) and the development of key clinical symptoms during the course (i.e., apathy, stereotypy, semantic memory impairment, impaired auditory comprehension, impaired speech output, rigidity, pyramidal signs, contracture, and unilateral spatial agnosia) in FTLD-TDP cases and Pick's disease cases, respectively. A value of $P < 0.05$ was accepted as significant. All statistical analyses were conducted using the StatView for Macintosh program version J-4.5.

## Results

### Clinical characteristics in sporadic FTLD-TDP and Pick's disease

The major clinical symptoms and their chronologically evolving patterns in all subjects are shown in the supplementary data.

#### *Demographic data*

Demographic data in sporadic FTLD-TDP and Pick's disease are shown in Table 1. There were no significant

differences between all FTLD-TDP cases and Pick's disease cases with respect to the age at onset, age at death, and disease duration. Among FTLD-TDP cases, FTLD-TDP-PLS(+) cases were over three times as frequent as FTLD-TDP-PLS(−) cases. The disease duration in FTLD-TDP-PLS(+) cases (range 2–21 years) tended to be longer than that in FTLD-TDP-PLS(−) cases (range 4–9 years), and the brain weight in FTLD-TDP-PLS(+) cases tended to be smaller than that in FTLD-TDP-PLS(−) cases.

*Early symptoms in sporadic FTLD-TDP and Pick's disease*

The spectrums of early symptoms within 1 year after the onset were obviously different in sporadic FTLD-TDP and Pick's disease cases (Table 2). Frequent early symptoms in all FTLD-TDP cases were naming difficulty (50%), impaired semantic memory (39%), impaired auditory comprehension (22%), reduced speech output (22%), memory impairment (28%), disinhibition (28%), and apathy (28%). The frequency of semantic memory impairment in FTLD-TDP cases was significantly higher than that in Pick's disease cases ($P = 0.008$). Although the number of FTLD-TDP-PLS(−) cases was small, the spectrum of early symptoms in FTLD-TDP-PLS(+) tended to be similar to that in FTLD-TDP-PLS(−) cases.

The most frequent early symptoms in Pick's disease cases were reduced speech output (29%) and disinhibition (29%). Some impairments of speech output (29%), including stuttering and a hesitant quality in utterance, paraphasia, and apraxia of speech, were also frequent in Pick's disease cases. Impaired speech output in the early stage in Pick's disease cases was five times more frequent than in FTLD-TDP cases. Unlike FTLD-TDP cases, none of our Pick's disease cases showed semantic memory impairment or impaired comprehension within 1 year after the onset. Memory impairment (7%) and naming difficulty (14%) were less frequent in Pick's disease than in FTLD-TDP cases.

Gait disturbance [one FTLD-TDP-PLS(+) case], hemiparesis in the right side extremities [one FTLD-TDP-PLS(+) case], and buccofacial apraxia [one FTLD-TDP-PLS(ne) case] were noted only in FTLD-TDP cases. Persecutory delusion and dysarthria were rarely observed in both FTLD-TDP and Pick's disease cases.

*Characteristics of behavioral, language, motor, and other cognitive disturbances during the course of sporadic FTLD-TDP and Pick's disease*

The frequencies of behavioral disturbance, language impairment, motor disturbance, and unilateral spatial agnosia during the course are shown in Table 2. Apathy tended to be more frequent in FTLD-TDP cases and behavioral stereotypy was more frequent in Pick's disease cases. Impairment of semantic memory was noted in 44% of FTLD-TDP cases but not in any Pick's disease case during the course ($P = 0.004$). Impaired auditory comprehension was more frequent in FTLD-TDP than in Pick's disease cases, and impaired speech output was more frequent in Pick's disease than in FTLD-TDP cases.

Approximately 80% of all FTLD-TDP cases developed some asymmetric motor disturbance during the course, over five times as many as in Pick's disease. The asymmetric motor disturbances in FTLD-TDP cases noted in clinical records were rigidity, tremor, pyramidal signs, contracture, and hemiplegia. Asymmetric pyramidal signs were found only in FTLD-TDP-PLS(+) cases, and asymmetric rigidity was more frequent in FTLD-TDP-PLS(−). The total frequency of asymmetric motor disturbances in FTLD-TDP-PLS(+) cases was higher than that in FTLD-TDP-PLS(−) cases (85 vs. 67%). In all FTLD-TDP cases, the motor disturbances often developed in the right-side extremities (nine cases), the prevalence of which was twice as high as that in the left side (five cases). In all FTLD-TDP cases, the mean duration from the disease onset to the development of asymmetric motor disturbances was about 6 years, and the mean duration from the development of asymmetric motor disturbances to death was 2.5 years.

*Evolving patterns of clinical syndrome in sporadic FTLD-TDP and Pick's disease*

The spectrum of evolving clinical patterns in sporadic FTLD-TDP cases hardly overlapped with that in Pick's disease cases (Table 3). The only evolving pattern shared by both FTLD-TDP and Pick's disease groups was the 'FTD alone pattern', which is characterized by early behavioral changes such as disinhibition or stereotypy, gradually increasing apathy, and lack of evident features of other syndromes. However, this pattern was the most frequent course in Pick's disease cases (57%), although it was rare in FTLD-TDP cases (5.6%). The most common first syndrome in Pick's disease cases was FTD (64%), followed by PA (14%).

The most frequent first syndrome in FTLD-TDP cases was SD (39%), followed by FTD (28%). Fifty percent of FTLD-TDP cases showed either SD or impaired auditory comprehension as the first syndrome or the first prominent symptom, and 78% of these cases subsequently developed FTD. Of 14 FTLD-TDP cases having asymmetric motor disturbances, two cases (14%) subsequently developed unilateral spatial agnosia. Unilateral spatial agnosia was not observed in any Pick's disease case. In both cases with unilateral spatial agnosia, the first syndrome was FTD. Unilateral spatial agnosia was noted on the same side as motor disturbance.

**Table 2** Clinical characteristics in FTLD-TDP and Pick's disease

| | FTLD-TDP | | | | Pick's disease ($n$ = 14) | $P$ value[a] |
|---|---|---|---|---|---|---|
| | All FTLD-TDP ($n$ = 18) | FTLD-TDP-PLS(+) ($n$ = 13) | FTLD-TDP-PLS(–) ($n$ = 3) | FTLD-TDP-PLS(ne) ($n$ = 2) | | |
| Early symptoms[b] | | | | | | |
| Naming difficulty [$n$ (%)] | 9 (50.0) | 6 (46.2) | 1 (33.3) | 2 (100.0) | 2 (14.3) | 0.061 |
| Semantic memory impairment [$n$ (%)] | 7 (38.9) | 4 (30.8) | 1 (33.3) | 2 (100.0) | 0 (0.0) | 0.008 |
| Memory impairment [$n$ (%)] | 5 (27.8) | 3 (23.1) | 2 (66.7) | 0 (0.0) | 1 (7.1) | 0.196 |
| Disinhibition [$n$ (%)] | 5 (27.8) | 4 (30.8) | 1 (33.3) | 0 (0.0) | 4 (28.6) | >0.999 |
| Apathy [$n$ (%)] | 5 (27.8) | 3 (23.1) | 2 (66.7) | 0 (0.0) | 2 (14.3) | 0.426 |
| Auditory comprehension deficit [$n$ (%)] | 4 (22.2) | 4 (30.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.059 |
| Reduced speech output [$n$ (%)] | 4 (22.2) | 3 (23.1) | 1 (33.3) | 0 (0.0) | 4 (28.6) | 0.734 |
| Irritability [n (%)] | 3 (16.7) | 1 (7.7) | 2 (66.7) | 0 (0.0) | 0 (0.0) | 0.238 |
| Stereotypic behaviors [n (%)] | 3 (16.7) | 3 (23.1) | 0 (0.0) | 0 (0.0) | 2 (14.3) | >0.999 |
| Dysarthria [$n$ (%)] | 2 (11.1) | 2 (15.4) | 0 (0.0) | 0 (0.0) | 1 (7.1) | > 0.999 |
| Writing impairment [$n$ (%)] | 2 (11.1) | 2 (15.4) | 0 (0.0) | 0 (0.0) | 1 (7.1) | 0.702 |
| Right side hemiparesis | 1 (5.6) | 1 (7.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.492 |
| Gait disturbance [$n$ (%)] | 1 (5.6) | 1 (7.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | >0.999 |
| Buccofacial apraxia [$n$ (%)] | 1 (5.6) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | >0.999 |
| Persecutory delusion [$n$ (%)] | 1 (5.6) | 1 (7.7) | 0 (0.0) | 0 (0.0) | 1 (7.1) | >0.999 |
| Impaired speech output[c] [$n$ (%)] | 1 (5.6) | 1 (7.7) | 0 (0.0) | 0 (0.0) | 4 (28.6) | 0.075 |
| Psychiatric and behavioral symptoms during course | | | | | | |
| Apathy [$n$ (%)] | 14 (77.8) | 10 (76.9) | 3 (100) | 1 (50.0) | 9 (64.3) | 0.453 |
| Behavioral stereotypy [$n$ (%)] | 11 (61.1) | 9 (69.2) | 2 (66.7) | 0 (0.0) | 10 (71.4) | 0.542 |
| Euphoria [$n$ (%)] | 6 (33.3) | 6 (46.2) | 0 (0.0) | 0 (0.0) | 3 (21.4) | 0.457 |
| Oral tendency and pica [$n$ (%)] | 9 (50.0) | 8 (61.5) | 1 (33.3) | 0 (0.0) | 6 (42.9) | 0.857 |
| Language and semantic memory impairment during course | | | | | | |
| Semantic memory impairment [$n$ (%)] | 8 (44.4) | 5 (38.5) | 1 (33.3) | 2 (100.0) | 0 (0.0) | 0.004 |
| Auditory comprehension impairment [$n$ (%)] | 5 (27.8) | 5 (38.5) | 0 (0.0) | 0 (0.0) | 1 (7.1) | 0.138 |
| Impaired speech output[c] [$n$ (%)] | 1 (5.6) | 1 (7.7) | 0 (0.0) | 0 (0.0) | 4 (28.6) | 0.075 |
| Asymmetric motor disturbances and unilateral spatial agnosia during course | | | | | | |
| All asymmetric motor disturbances [$n$ (%)] | 14 (77.8) | 11 (84.6) | 2 (66.7) | 1 (50.0) | 2 (14.3) | 0.001 |
| Rigidity [$n$ (%)] | 8 (44.4) | 5 (38.5) | 2 (66.7) | 1 (50.0) | 2 (14.3) | 0.125 |
| Tremor [$n$ (%)] | 1 (5.6) | 1 (7.7) | 0 (0.0) | 0 (0.0) | 1 (7.1) | 0.854 |
| Upper motor neuron signs [$n$ (%)] | 8 (44.4) | 7 (53.8) | 0 (0.0) | 1 (50.0) | 2 (14.3) | 0.125 |
| Contracture [$n$ (%)] | 5 (27.8) | 5 (38.5) | 0 (0.0) | 0 (0.0) | 1 (7.1) | 0.138 |
| Hemiparesis or hemiplegia [$n$ (%)] | 2 (11.1) | 2 (15.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.198 |
| Limb apraxia [$n$ (%)] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (7.1) | 0.249 |
| Unilateral spatial agnosia [$n$ (%)] | 2 (11.1) | 2 (15.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.492 |

*FTLD-TDP-PLS(+)* FTLD-TDP with PLS-like corticospinal tract degeneration, *FTLD-TDP-PLS(–)* FTLD-TDP without PLS-like corticospinal tract degeneration, *FTLD-TDP-PLS(ne)* FTLD-TDP cases of which medulla oblongata or spinal cord tissue could not be histopathologically examined

[a] All FTLD-TDP types versus Pick's disease cases

[b] Early symptoms were defined as all symptoms that developed within 1 year of onset

[c] Apraxia of speech, paraphasia, stuttering, and hesitation in utterances were included

In our series, all patients who showed SD as the first syndrome were classified as FTLD-TDP. Likewise, all of our patients who showed PA or apraxia of speech as the first syndrome were classified as Pick's disease. Although five FTLD-TDP and nine Pick's disease cases showed FTD as the first syndrome, all four patients who subsequently developed asymmetric motor disturbances, including parkinsonism, pyramidal signs, and contracture, were diagnosed as having FTLD-TDP.

**Table 3** Evolving patterns of clinical presentation in FTLD-TDP and Pick's disease groups

| Clinical course | FTLD-TDP ($n$ = 18) | | | Pick's disease ($n$ = 14) | |
|---|---|---|---|---|---|
| | TDP-43 subtype | Macroscopic cerebral atrophy | Clinical diagnosis (year of death) [reference] | Macroscopic cerebral atrophy | Clinical diagnosis (year of death) [reference] |
| (1) SD > FTD > AMD(rt) | 1 | T > F | Pick (1974) | – | – |
| (2) SD > FTD > AMD(rt) | 1 | T > Flt | Pick (2000) | – | – |
| (3) SD > FTD > AMD(rt) | 1 | T > Flt | SPA (2000) [73] | – | – |
| (4) SD > FTD | 1[a] | T > F | VaD (1991) | – | – |
| (5) SD > FTD | 1 | T > F | Pick (1983) | – | – |
| (6) SD | 1[b] | Tlt | Pick (1985) | – | – |
| (7) SD > AMD(rt) | 2[b] | T > Flt | SPA (1998) | – | – |
| (8) IAC > FTD > AMD(lt) | 2 | F > Tlt | Pick (1975) | – | – |
| (9) IAC > FTD > AMD(rt) | 2 | Flt = T | VaD (1977) [37] | – | – |
| (10) Memory impairment > FTD > AMD(rt) | 3[a] | F = Tlt | CBD (2006) | – | – |
| (11) Memory impairment > FTD > AMD(lt) | 1[a] | Trt | Pick (1974) | – | – |
| (12) Gait disturbance > FTD > AMD(lt) | 2 | T > F | Pick (1986) | – | – |
| (13) Delusional state > IAC > FTD > AMD(lt) | 3 | T = F | Pick (1973) [38] | – | – |
| (14) FTD > IAC > AMD(rt) > SA(rt) | 3 | T > Flt | SD? (1995) [53] | – | – |
| (15) FTD > IAC > AMD(lt) > SA(lt) | 1 | F = T | Pick (1979) [38] | - | - |
| (16) FTD > SD > AMD(rt) | 1 | T > Flt | Pick (2003) | – | – |
| (17) FTD > AMD(lt) | 1 | T > F | Pick (1988) | – | – |
| (18) FTD | 3 | F[c] | AD (2000) | F | Depressive state (1992) |
| (19) FTD | – | – | – | F > T | AD (1976) [54] |
| (20) FTD | – | – | – | F > Trt | Pick (1968) [26] |
| (21) FTD | – | – | – | F = T | Pick (1995) |
| (22) FTD | – | – | – | F = T | NA (NA) [69] |
| (23) FTD | – | – | – | F = Trt | Pick (1974) [2] |
| (24) FTD | - | - | - | T > Flt | Pick (1983) |
| (25) FTD | – | – | – | T > Flt | Presenile dem. (1993) [51] |
| (26) FTD > IAC | – | – | – | T > Frt | Pick (1964) [45] |
| (27) Delusional state > FTD > AMD(lt) | – | – | – | T > Flt | Presenile dem. (1993) [24] |
| (28) PA > FTD | – | – | – | Flt = T | Pick (1971) [36] |
| (29) PA | – | – | – | F > Tlt | PPAphasia (NA) [43] |
| (30) AOS > AMD(rt) | – | – | – | F > Tlt | PPApraxia (1994) [15] |
| (31) Schizophrenia (subclinical FTLD) | – | – | – | None | Schizophrenia (1981) |

One FTLD-TDP-PLS(+) case, one FTLD-TDP-PLS(−) case, and five Pick's disease cases were excluded because the clinical information was not adequate. The percentages of 18 FTLD-TDP and 14 Pick's disease cases for which clinical information was available, respectively, are indicated

*T > F* temporal-predominant atrophy, *F > T* frontal-predominant atrophy, *T = F* temporal and frontal lobes were equally atrophic, *lt* left-side predominant atrophy, *rt* right-side predominant atrophy, *FTD* frontotemporal dementia, *SD* semantic dementia, *PA* progressive non-fluent aphasia, *AOS* apraxia of speech, *IAC* impairment of auditory comprehension, *AMD(rt)* right-side predominant motor disturbance, *AMD(lt)* left-side predominant motor disturbance, *SA* unilateral spatial agnosia, *SPA* slowly progressive aphasia, *PPAphasia* primary progressive aphasia, *PPApraxia* primary progressive apraxia, *Pick* Pick's disease, *AD* Alzheimer's disease, *CBD* corticobasal degeneration, *VaD* vascular dementia, *NA* not available

[a] FTLD-TDP-PLS(−) cases

[b] FTLD-TDP-PLS(ne) cases. The other cases of FTLD-TDP were FTLD-TDP-PLS(+)

[c] Microscopically, the frontal and temporal cortices were equally degenerated

## Pathological findings in sporadic FTLD-TDP and Pick's disease

The brain weight in FTLD-TDP cases (range 690–1,450 g) was not significantly different from that in Pick's disease cases (range 530–1,350 g) (Table 1). Minor neurofibrillary changes corresponding to Braak stage I or II were noted in eight FTLD-TDP and five Pick's disease cases. Senile plaques corresponding to Braak stage A were noted in three FTLD-TDP and three Pick's disease cases, stage B in one

Pick's disease case, and stage C in one FTLD-TDP case and one Pick's disease case. One FTLD-TDP case had Lewy bodies in the brainstem nuclei. Argyrophilic grains were not found in any subject.

*Distribution of neuronal loss with gliosis*

There were several significant differences between sporadic FTLD-TDP and Pick's disease cases in the involvement of the temporal cortex, basal ganglia, and motor system (Figs. 4, 5, 6). There were no differences between the distribution and severity of neuronal loss in FTLD-TDP-PLS(+) cases and those in FTLD-TDP-PLS(−) cases, except for the degeneration in the pyramidal tract. In both FTLD-TDP and Pick's disease, the severity of subcortical gliosis was roughly correlated with that of neuronal loss in each adjacent cerebral cortex.

Neuronal loss in all regions of the frontal cortex was more severe in Pick's disease cases than in FTLD-TDP cases, while the temporal cortex was more severely and extensively degenerated in FTLD-TDP cases (Fig. 6). Neuronal loss in the superior temporal gyrus in the FTLD-TDP group was significantly more severe than that in the Pick's disease group ($P = 0.022$). Of 20 sporadic FTLD-TDP cases, 15 (75%) showed temporal-predominant neuronal loss (Fig. 4a–h), and the frontal and temporal cortices were degenerated almost equally in only five cases. No sporadic FTLD-TDP case showed frontal-predominant neuronal loss. In contrast, among 16 Pick's disease cases in which both frontal and temporal tips were available, only seven (44%) showed temporal-predominant degeneration and four (25%) frontal-predominant degeneration (Fig. 5a–f). In five Pick's disease cases (31%), the frontal and temporal cortices were almost equally degenerated (Fig. 5g, h). In three FTLD-TDP (20%) and three Pick's disease (16%) cases, moderate neuronal loss in the parietal cortex was observed, and two of these three FTLD-TDP cases clinically showed unilateral spatial agnosia. In both FTLD-TDP and Pick's disease cases, moderate to severe degeneration was frequently encountered in the insular cortex, cingulate gyrus, subiculum, parahippocampal gyrus, and amygdala. The reduction of pyramidal neurons in the hippocampal CA1 was found in about 40% of both disease groups, respectively.

Neuronal loss in the caudate nucleus, putamen, and globus pallidus was significantly more severe in FTLD-TDP than in Pick's disease cases ($P = 0.002$, 0.002, 0.004,

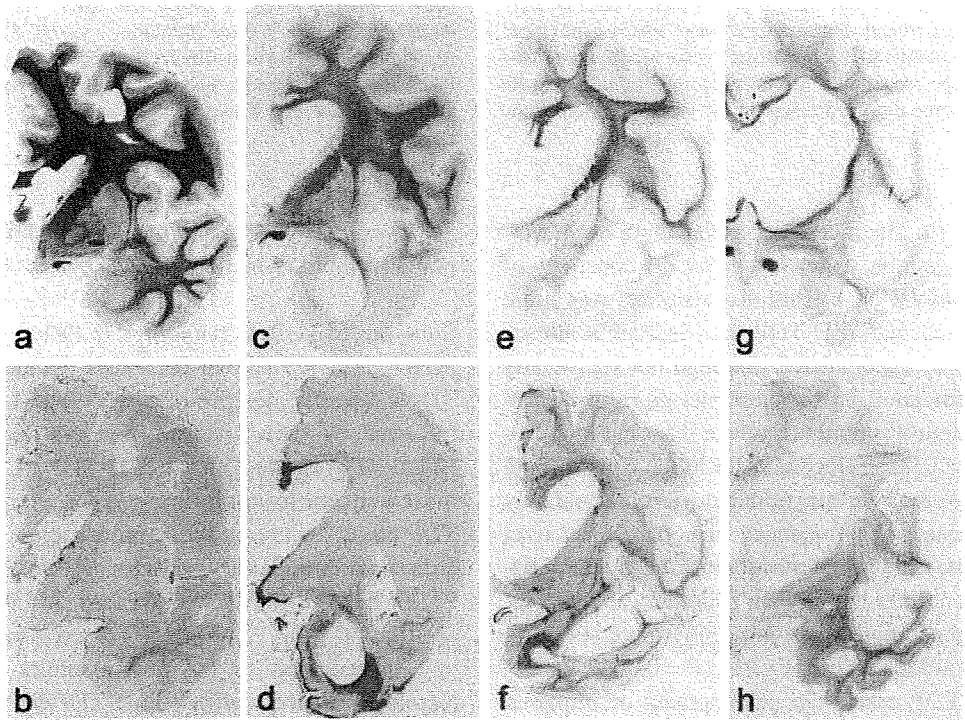


**Fig. 4** Coronal sections of representative sporadic FTLD-TDP cases. Minimal loss of myelin (**a**) and slight gliosis (**b**) in the temporal lobe are noted. However, neither myelin loss nor gliosis is apparent in the frontal lobe. Significant cerebral atrophy is not noted (disease duration: 2 years). Severe loss of myelin (**c**), subcortical gliosis (**d**), and overt cerebral atrophy are noted in the temporal lobe, while these alterations in the frontal lobe are minimal. The caudate nucleus is also atrophic (duration: 11 years). Severe myelin loss (**e**) and evident cerebral atrophy are observed in the temporal lobe. Although subcortical gliosis is noted in the temporal and frontal lobe as well (**f**), gliosis is more severe in the temporal lobe. This case clinically showed impairment of semantic memory in the early stage (duration: 12 years). (**g**, **h**) Severe cortical atrophy and myelin loss associated with gliosis are noted in the frontal and temporal lobes, but the degrees of myelin loss and gliosis are more prominent in the temporal lobe (duration: 21 years). **a**, **c**, **e**, **g** Klüver–Barrera stain, **b**, **d**, **f**, **h** Holzer stain

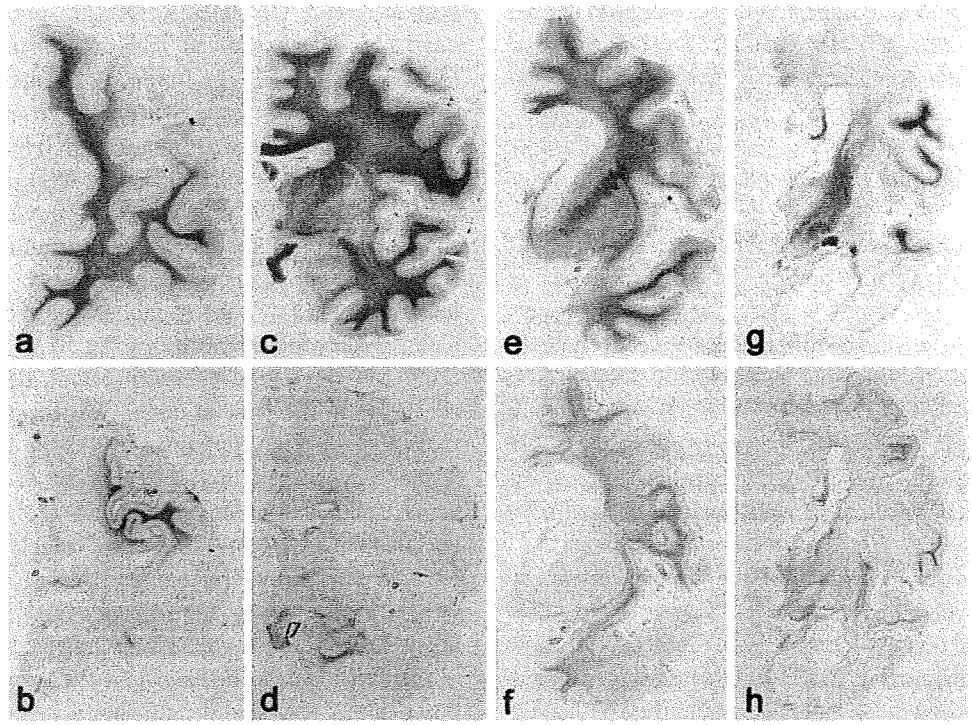


**Fig. 5** Coronal sections of representative Pick's disease cases. Mild myelin loss (**a**) and severe subcortical gliosis (**b**) are observed in the frontal tip, but not in the temporal lobe (**c**, **d**). No evident cerebral atrophy is noticed in the frontal and temporal lobes (disease duration: 1.5 years). Mild loss of myelin is found in the frontal lobe but not in the temporal lobe (**e**). The reduction of the cortical ribbon thickness with subcortical gliosis is the most prominent in the ventral portion of the inferior frontal gyrus (the pars opercularis). This case clinically showed impaired speech output (**f**). The frontal and temporal lobes show similar degrees of cerebral atrophy. The caudate nucleus is slightly reduced in volume (duration: 7 years). Severe loss of myelin (**g**) with subcortical gliosis (**h**) is observed in both frontal and temporal lobes. Both frontal and temporal lobes show severe atrophy (duration 10.7 years). **a**, **c**, **e**, **g** Klüver–Barrera stain, **b**, **d**, **f**, **h** Holzer stain

respectively; Fig. 6). The macroscopic reduction in the volume of the basal ganglia, as evidenced by the concavity of the ventricular surface on the coronal sections, was more frequently observed in FTLD-TDP than in Pick's disease cases (30 and 13%, respectively), although not statistically significant. Degeneration in the substantia nigra in FTLD-TDP cases was significantly more severe than that in Pick's disease cases ($P = 0.003$). Degeneration in the corticospinal tract at the level of the cerebral peduncle was observed only in FTLD-TDP cases. The frequency of corticospinal tract degeneration at the level of the medulla oblongata in FTLD-TDP cases was ten times that in Pick's disease cases (78 vs. 7%), and the degeneration was significantly more severe in FTLD-TDP than in Pick's disease cases ($P = 0.006$).

In all FTLD-TDP cases, the development of impaired auditory comprehension during the course was significantly correlated with the severity of neuronal loss in the inferior frontal gyrus ($r = -0.544$, $P < 0.05$), and unilateral spatial agnosia with that in the inferior parietal lobule ($r = 0.660$, $P < 0.01$). In Pick's disease cases, impairment of speech output was significantly correlated with the severity of neuronal loss in the inferior frontal gyrus ($r = 0.611$, $P < 0.05$).

*Subtypes of TDP-43 pathology and its clinicopathological relationship to sporadic FTLD-TDP and FTLD-MND*

Subtypes of TDP-43 pathology in FTLD-TDP and FTLD-MND cases are shown in Tables 1 and 3. In all FTLD-TDP cases, the most frequent was type 1 histology (55%) followed by type 2 (25%), and type 3 (20%). In both FTLD-TDP-PLS(+) and FTLD-TDP-PLS(−) cases, the most frequent histology was type 1. None of our FTLD-TDP cases, including cases having type 3 histology, had NIIs including lentiform NIIs, a sensitive marker for FTLD-TDP with *PGRN* mutations, in the affected cortex or striatum [40]. No FTLD-TDP case had type 4 histology. In contrast to the heterogeneity of the TDP-43 histological subtypes in FTLD-TDP-PLS(+) and FTLD-TDP-PLS(−), all the FTLD-MND cases examined as a disease control had type 2 histology. Among 7 FTLD-TDP cases showing SD as the first syndrome, six cases had type 1 histology and one had type 2 histology. The most frequent subtype in cases that showed FTD as the first syndrome was type 1 histology (50%), followed by type 3 (33%), and type 2 (17%).

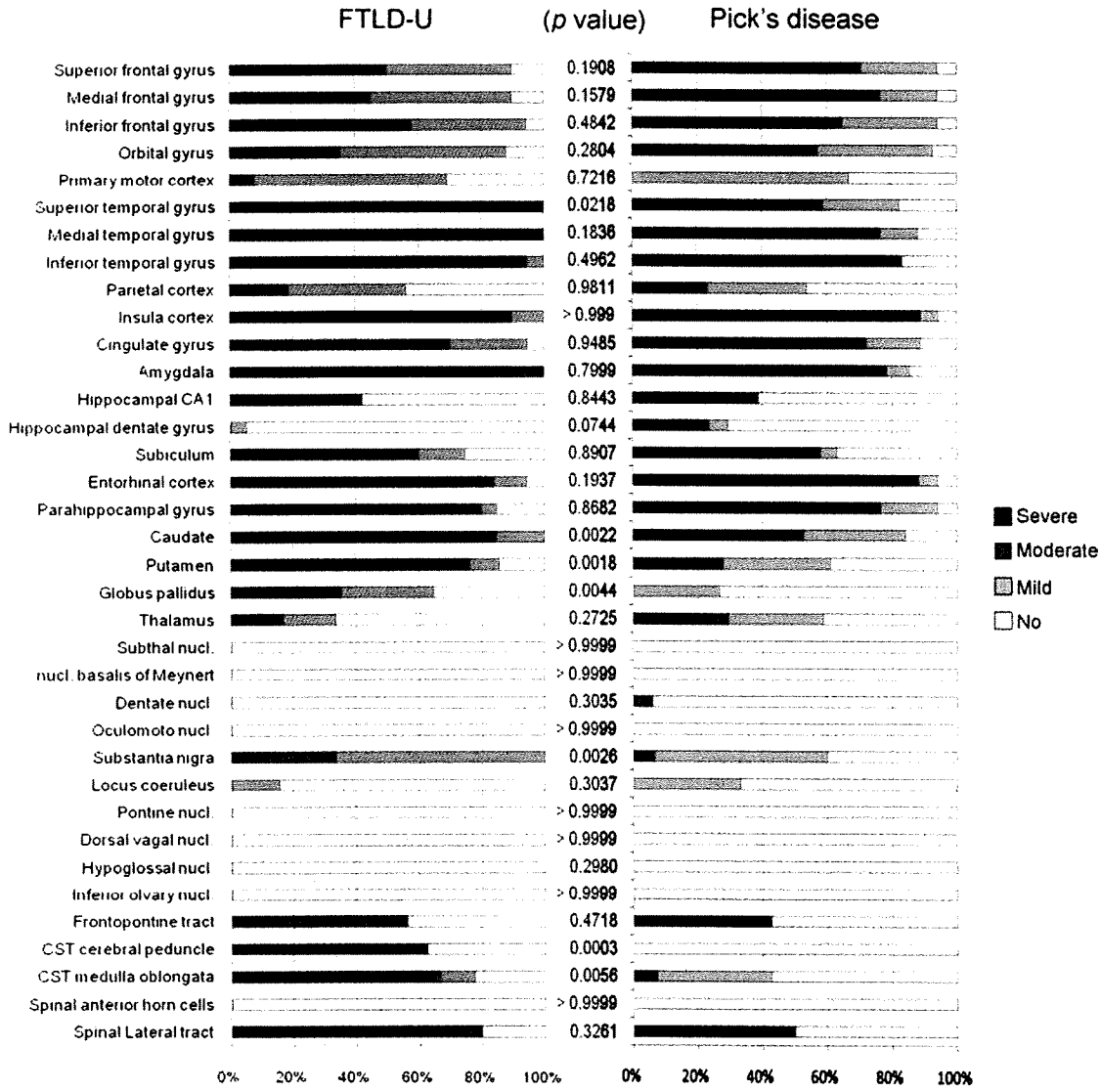


**Fig. 6** Distribution of neuronal loss in FTLD-TDP and Pick's disease. *Black* severe neuronal loss, *brown* moderate neuronal loss, *orange* mild neuronal loss, *white* no neuronal loss

## Discussion

This study demonstrated that the spectrums of clinical features, including early symptoms and evolving patterns of clinical syndromes, differed between our sporadic FTLD-TDP and Pick's disease cases. The clinical course of our FTLD-TDP cases, including FTLD-TDP-PLS(+) and FTLD-TDP-PLS(−) cases, can be summarized as temporal-predominant dysfunction with frequent asymmetric motor disturbances: frequent impairment of semantic memory or auditory comprehension from the early stage, less frequent behavioral problems throughout the course, and frequent asymmetric parkinsonism, pyramidal signs, and/or contracture in the middle to late stage. Asymmetric pyramidal signs were frequent in FTLD-TDP-PLS(+) cases, and asymmetric parkinsonism was frequent in FTLD-TDP-PLS(−) cases. In contrast, the clinical course in our Pick's disease cases can be summarized as frontal-predominant dysfunction with less frequent asymmetric motor disturbance: frequent behavioral symptoms from the early stage, frequent speech output impairment from the early stage, and less frequent asymmetric parkinsonism, pyramidal signs, and contracture throughout the course. Pathologically, degeneration in the temporal cortex, caudate nucleus, putamen, globus pallidus, and corticospinal tract was significantly more severe in sporadic FTLD-TDP than in Pick's disease cases, while the degeneration in the frontal cortex tended to be more severe in Pick's disease cases. Although rare, parietal degeneration was observed in both diseases. Except for pyramidal tract degeneration, there was no evident difference between the distributions of neuronal loss in FTLD-TDP-PLS(+) and FTLD-TDP-PLS(−).

These pathological findings appeared to be in concord with the clinical differences between the two diseases.

Although the available data are limited, it was reported that language disturbance in Pick's disease tended to have a non-fluent nature. Hodges et al. [21] reported that among 20 Pick's disease cases, the most common clinical phenotype was FTD ($n = 11$, 55%), followed by PA ($n = 6$, 30%), and SD ($n = 3$, 15%). Further, among eight PA patients in their series, six cases (75%) had Pick's disease. Thus, Hodges et al. noticed that progressive non-fluent aphasia predicts Pick's disease. Kertesz et al. [33] reported that the first syndromes in six Pick's disease cases included FTD ($n = 3$) and PA ($n = 3$), but not SD. These findings are consistent with the trend in our Pick's disease series. On the other hand, SD is considered one of the representative clinical phenotypes in FTLD-U cases, although its frequency among FTLD-U cases remains controversial [34, 62]. Davies et al. [11] demonstrated that 72% of 18 SD cases (nine sporadic and four familial cases) had FTLD-U, but only 17% had Pick's disease. In our series, as well as in the Manchester series [63], SD as the first syndrome was observed only in FTLD-U (and DLDH in the Manchester series) but not in any Pick's disease cases. Conversely, several studies disclosed that clinical phenotypes in FTLD-U cases are not uniform and that SD is not always the most frequent syndrome. In the Manchester series, the most frequent clinical phenotype in 24 FTLD-U cases was FTD (50%), followed by SD (21%), and PA (21%) [63], although data concerning the family history were not provided in that study. Interestingly, several previous studies demonstrated that FTLD cases with *PGRN* mutations tended to show FTD or PA rather than SD [39, 58, 64, 65], and pathologically, frontal degeneration tended to be equal to or more severe than temporal degeneration in FTLD-U with *PGRN* mutations [30]. These features are in contrast to those in our sporadic FTLD-TDP series showing temporal-predominant involvement, suggesting that the trend in the clinical picture in sporadic FTLD-TDP is not identical to that in *PGRN*-linked FTLD-TDP. It is plausible that the different clinicopathological trends may be associated with relatively clear differences in the nature of language disturbances and evolving clinical patterns between sporadic FTLD-TDP and Pick's disease in our series. If *PGRN*-linked FTLD-TDP cases were included in our study, the frequencies of FTD and PA as the first syndrome might be higher than those presented here.

In our series, asymmetric motor disturbances, in which parkinsonism and pyramidal signs were variably combined and the patients finally showed asymmetric contracture, were significantly more frequent in sporadic FTLD-TDP than in Pick's disease cases. Therefore, although both Pick's disease and FTLD-TDP cases often showed FTD as the first syndrome in our series, the subsequent development of some asymmetric motor disturbance after FTD indicated that the underlying pathology was FTLD-TDP. It was reported that some FTLD-U cases, almost all of which were *PGRN*-linked cases, showed asymmetric parkinsonism or CBD-like asymmetric symptoms [4, 5, 12, 17, 18, 39, 44, 55, 66]. The high frequency of FTLD-TDP-PLS(+) in our FTLD-TDP series was in contrast to the low frequency of it reported in Western countries [13]. Although the reason for the difference is unclear, in Japan, it was reported that FTLD-TDP cases, which were previously regarded as Pick's disease without Pick bodies and later diagnosed as FTLD-TDP, often show evident degeneration of the pyramidal tract without lower motor neuron pathology including Bunina bodies [23, 38]. Dickson et al. [13] noted that motor neuron degeneration in FTLD-U may reflect the greater overall severity of the disease process, and FTLD-U-PLS(+) may have a different pathogenesis from FTLD-MND and ALS. Several trends in our FTLD-TDP series, including the longer disease duration in FTLD-TDP-PLS(+) than in FTLD-TDP-PLS(−), the smaller brain weight in FTLD-TDP-PLS(+) than in FTLD-TDP-PLS(−), the usual occurrence of pyramidal signs in FTLD-TDP from the middle to end stages of the course, and the difference in the distribution of TDP-43 histological subtypes between FTLD-TDP-PLS(+) and FTLD-MND cases appeared to support their hypothesis.

Unilateral spatial agnosia with asymmetric motor disturbance, such as left-side hemineglect with left-side parkinsonism [66] or neglect of use of the right arm with right-side predominant rigidity [64], has been described in a few FTLD-U cases with *PGRN* mutations. Although rare, because unilateral spatial agnosia was observed in FTLD-TDP cases but not in any Pick's disease case in our study, this symptom might indicate sporadic FTLD-TDP rather than Pick's disease. However, considering that the frequency of the evident degeneration in the parietal cortex in Pick's disease cases (17%) was similar to that in FTLD-TDP cases (15%) and that some Pick's disease cases can show apraxia [15, 32, 63], the possibility that the frequency of unilateral spatial agnosia in Pick's disease was underestimated and cannot be excluded.

A limitation in this study was that *PGRN* mutations could not be examined. The lack of lentiform NIIs in our FTLD-TDP series, a sensitive marker for *PGRN*-linked FTLD [30, 40], does not appear to support the possibility that our sporadic FTLD-TDP series included *PGRN*-linked cases. However, although rare, *PGRN* mutations have been noted in a small proportion of FTLD-U cases without a family history [30]. The retrospective nature of our clinical examination might also influence the reported frequencies of clinical symptoms. For example, it is possible that impaired recognition of faces due to semantic memory impairment in some patients examined before the establishment of the

clinical criteria of FTLD [48] was simply described as 'memory impairment'. Thus, the frequencies of semantic memory impairment and SD might be underestimated in this study. Likewise, whether the nature of impaired speech output in sporadic FTLD-TDP was similar to that in Pick's disease is unclear. Therefore, like the results of many pathological studies, the results presented here should be confirmed by prospective studies employing a larger autopsy series.

Finally, although the present study demonstrated clinical differences between sporadic FTLD-TDP and Pick's disease, it is also important to note that, in clinical practice, sporadic FTLD patients may have variable pathological entities such as CBD, PSP, BIBD, NIFID, or Alzheimer's disease with atypical cerebral atrophy as well. Kertesz et al. [33] conducted a comprehensive study of 60 consecutive patients diagnosed clinically with FTD, PA, CBD syndrome, or PSP, and noticed that PA and CBD syndrome presented more frequently with the tauopathies comprising pathological CBD, PSP, and Pick's disease, and that FTD was more frequent in FTLD-U and DLDH. Indeed, the most frequent first syndrome in their FTLD-U series was FTD (78%), which appears to be inconsistent with our findings. However, the frequency of the family history in their FTLD-U cases was not noted, and if it was high, the results are not comparable with those in our study. In addition, in their autopsy series, no patient with SD was included, suggesting a case selection bias different from that in our series. As Kertesz et al. emphasized, the presence of exceptional cases, at present, make it still no simple matter to infer the underlying pathology in FTLD patients based on clinical features in clinical practice. However, considering that in vivo A$\beta$ imaging will soon be put to practical use, further clinical differentiation of pathological subtypes of FTLD besides AD with atypical cerebral atrophy will be needed in the future. Given the results in the present study, (1) when sporadic FTLD patients present with early impairment of semantic memory or auditory comprehension and subsequently develop asymmetric pyramidal signs, parkinsonism, or contracture, clinicians should consider that sporadic FTLD-TDP rather than Pick's disease is a plausible pathology and (2) in sporadic FTLD patients who initially show behavioral symptoms or some impairment of speech output but lack subsequent asymmetric motor disturbances, Pick's disease rather than FTLD-TDP is a plausible pathology. Further, taking the previous findings into consideration, (3) the trend of clinical pictures in sporadic FTLD-TDP may differ from that in FTLD-TDP with *PGRN* mutations, which is clinically and pathologically characterized by frontal-predominant involvement [30, 58]. For more precise prediction of pathologies and the specific pathology-based management in FTLD patients, both further comprehensive studies of consecutive FTLD patients in variable clinical settings and comparative analyses focusing on the clinical differences between pathological entities should be done.

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## References

1. Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, Mann D, Tsuchiya K, Yoshida M, Hashizume Y, Oda T (2006) TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem Biophys Res Commun 351:602–611
2. Arima K, Miyasaka Y (1985) An autopsy case of Pick's disease, with special reference to light and electron microscopical findings of Pick bodies and ballooned neurons. Neuropathology 6:325–339 in Japanese with English abstract
3. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boeve B, Feldman H, Hutton M (2006) Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 442:916–919
4. Beck J, Rohrer JD, Campbell T, Isaacs A, Morrison KE, Goodall EF, Warrington EK, Stevens J, Revesz T, Holton J, Al-Sarraj S, King A, Scahill R, Warren JD, Fox NC, Rossor MN, Collinge J, Mead S (2008) A distinct clinical, neuropsychological and radiological phenotype is associated with progranulin gene mutations in a large UK series. Brain 131:706–720
5. Boeve BF, Baker M, Dickson DW, Parisi JE, Giannini C, Josephs KA, Hutton M, Pickering-Brown SM, Rademakers R, Tang-Wai D, Jack CR Jr, Kantarci K, Shiung MM, Golde T, Smith GE, Geda YE, Knopman DS, Petersen RC (2006) Frontotemporal dementia and parkinsonism associated with the IVS1+1G->A mutation in progranulin: a clinicopathologic study. Brain 129:3103–3114
6. Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82:239–259
7. Broe M, Hodges JR, Schofield E, Shepherd CE, Kril JJ, Halliday GM (2003) Staging disease severity in pathologically confirmed cases of frontotemporal dementia. Neurology 60:1005–1011
8. Cairns NJ, Perry RH, Jaros E, Burn D, McKeith IG, Lowe JS, Holton J, Rossor MN, Skullerud K, Duyckaerts C, Cruz-Sanchez FF, Lantos PL (2003) Patients with a novel neurofilamentopathy: dementia with neurofilament inclusions. Neurosci Lett 341:177–180
9. Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, White CL 3rd, Schneider JA, Grinberg LT, Halliday G, Duyckaerts C, Lowe JS, Holm IE, Tolnay M, Okamoto K, Yokoo H, Murayama S, Woulfe J, Munoz DG, Dickson DW, Ince PG, Trojanowski JQ, Mann DM, Consortium for Frontotemporal Lobar Degeneration (2007) Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta Neuropathol 114:5–22

10. Cruts M, Gijselinck I, van der Zee J, Engelborghs S, Wils H, Pirici D, Rademakers R, Vandenberghe R, Dermaut B, Martin JJ, van Duijn C, Peeters K, Sciot R, Santens P, De Pooter T, Mattheijssens M, Van den Broeck M, Cuijt I, Vennekens K, De Deyn PP, Kumar-Singh S, Van Broeckhoven C (2006) Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 442:920–924
11. Davies RR, Hodges JR, Kril JJ, Patterson K, Halliday GM, Xuereb JH (2005) The pathological basis of semantic dementia. Brain 128:1984–1995
12. Davion S, Johnson N, Weintraub S, Mesulam MM, Engberg A, Mishra M, Baker M, Adamson J, Hutton M, Rademakers R, Bigio EH (2007) Clinicopathologic correlation in PGRN mutations. Neurology 69:1113–1121
13. Dickson DW, Josephs KA, Amador-Ortiz C (2007) TDP-43 in differential diagnosis of motor neuron disorders. Acta Neuropathol 114:71–79
14. Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, Chatterjee A, Hurtig HI, Karlawish JH, Rosen HJ, Van Deerlin V, Lee VM, Miller BL, Trojanowski JQ, Grossman M (2006) Frontotemporal dementia: clinicopathological correlations. Ann Neurol 59:952–962
15. Fukui T, Sugita K, Kawamura M, Shiota J, Nakano I (1996) Primary progressive apraxia in Pick's disease: a clinicopathologic study. Neurology 47:467–473
16. Gass J, Cannon A, Mackenzie IR, Boeve B, Baker M, Adamson J, Crook R, Melquist S, Kuntz K, Petersen R, Josephs K, Pickering-Brown SM, Graff-Radford N, Uitti R, Dickson D, Wszolek Z, Gonzalez J, Beach TG, Bigio E, Johnson N, Weintraub S, Mesulam M, White CL 3rd, Woodruff B, Caselli R, Hsiung GY, Feldman H, Knopman D, Hutton M, Rademakers R (2006) Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. Hum Mol Genet 15:2988–3001
17. Grimes DA, Bergeron CB, Lang AE (1999) Motor neuron disease-inclusion dementia presenting as cortical-basal ganglionic degeneration. Mov Disord 14:674–680
18. Guerreiro RJ, Santana I, Bras JM, Revesz T, Rebelo O, Ribeiro MH, Santiago B, Oliveira CR, Singleton A, Hardy J (2008) Novel progranulin mutation: screening for PGRN mutations in a Portuguese series of FTD/CBS cases. Mov Disord 23:1269–1273
19. Hasegawa M, Arai T, Nonaka T, Kametani F, Yoshida M, Hashizume Y, Beach TG, Buratti E, Baralle F, Morita M, Nakano I, Oda T, Tsuchiya K, Akiyama H (2008) Phosphorylated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Ann Neurol 64:60–70
20. Higaki F, Yokota O, Ohishi M (2008) Factors predictive of survival after percutaneous endoscopic gastrostomy in the elderly: is dementia really a risk factor? Am J Gastroenterol 103:1011–1016
21. Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, Kril JJ, Halliday GM (2004) Clinicopathological correlates in frontotemporal dementia. Ann Neurol 56:399–406
22. Ikeda K (2000) Neuropathological discrepancy between Japanese Pick's disease without Pick bodies and frontal lobe degeneration type of frontotemporal dementia proposed by Lund and Manchester Group. Neuropathology 20:76–82
23. Ikeda K, Akiyama H, Arai T, Ueno H, Tsuchiya K, Kosaka K (2002) Morphometrical reappraisal of motor neuron system of Pick's disease and amyotrophic lateral sclerosis with dementia. Acta Neuropathol 104:21–28
24. Ikeda M, Ikeda K, Endo M, Haga C, Mizutani Y (1994) An autopsied case of slowly progressive Pick's disease. Seishin Igaku (Clinical Psychiatry) 36:1167–1171 in Japanese with English abstract
25. Ikeda M, Ishikawa T, Tanabe H (2004) Epidemiology of frontotemporal lobar degeneration. Dementia Geriatr Cogn Disord 17:265–268
26. Ishino H, Ikeda H (1972) Four autopsy cases of Pick's disease—clinicopathological findings (in Japanese with English abstract). Kyushu Neuro psychiatry 18:82–86
27. Jackson M, Lennox G, Lowe J (1996) Motor neuron disease-inclusion dementia. Neurodegeneration 5:339–350
28. Josephs KA, Holton JL, Rossor MN, Braendgaard H, Ozawa T, Fox NC, Petersen RC, Pearl GS, Ganguly M, Rosa P, Laursen H, Parisi JE, Waldemar G, Quinn NP, Dickson DW, Revesz T (2003) Neurofilament inclusion body disease: a new proteinopathy? Brain 126:2291–2303
29. Josephs KA, Holton JL, Rossor MN, Godbolt AK, Ozawa T, Strand K, Khan N, Al-Sarraj S, Revesz T (2004) Frontotemporal lobar degeneration and ubiquitin immunohistochemistry. Neuropathol Appl Neurobiol 30:369–373
30. Josephs KA, Ahmed Z, Katsuse O, Parisi JF, Boeve BF, Knopman DS, Petersen RC, Davies P, Duara R, Graff-Radford NR, Uitti RJ, Rademakers R, Adamson J, Baker M, Hutton ML, Dickson DW (2007) Neuropathologic features of frontotemporal lobar degeneration with ubiquitin-positive inclusions with progranulin gene (PGRN) mutations. J Neuropathol Exp Neurol 66:142–151
31. Josephs KA, Lin WL, Ahmed Z, Stroh DA, Graff-Radford NR, Dickson DW (2008) Frontotemporal lobar degeneration with ubiquitin-positive, but TDP-43-negative inclusions. Acta Neuropathol 116:159–167
32. Kawamura M, Mochizuki S (1999) Primary progressive apraxia. Neuropathology 19:249–258
33. Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG (2005) The evolution and pathology of frontotemporal dementia. Brain 128:1996–2005
34. Knibb JA, Xuereb JH, Patterson K, Hodges JR (2006) Clinical and pathological characterization of progressive aphasia. Ann Neurol 59:156–165
35. Knopman DS, Mastri AR, Frey WH 2nd, Sung JH, Rustan T (1990) Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. Neurology 40:251–256
36. Kosaka K (1976) On aphasia of Pick's disease—a review of our own 3 cases and 49 autopsy cases in Japan (in Japanese). Seishin Igaku (Clinical Psychiatry) 18:1181–1189
37. Kosaka K, Matsushita M, Oyanagi S, Hato K, Mehraein P (1980) Pick's disease with concomitant traumatic brain damages–Five autopsied cases and a critical review of literatures (in Japanese with English abstract). Seishin Shinkeigaku Zasshi (Psychiatria et Neurologia Japonica) 82:33–47
38. Kosaka K, Ikeda K, Kobayashi K, Hamamoto J, Matsushita M (1985) On pyramidal tract lesions in Pick's disease (in Japanese). Clinical Psychiatry 27:1171–1178
39. Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, Hahn-Barma V, van der Zee J, Clot F, Bakchine S, Puel M, Ghanim M, Lacomblez L, Mikol J, Deramecourt V, Lejeune P, de la Sayette V, Belliard S, Vercelletto M, Meyrignac C, Van Broeckhoven C, Lambert JC, Verpillat P, Campion D, Habert MO, Dubois B, Brice A, French research network on FTD/FTD-MND (2008) Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. Brain 131:732–746
40. Mackenzie IR (2007) The neuropathology and clinical phenotype of FTD with progranulin mutations. Acta Neuropathol 114:49–54
41. Mackenzie IR, Foti D, Woulfe J, Hurwitz TA (2008) Atypical frontotemporal lobar degeneration with ubiquitin-positive, TDP-43-negative neuronal inclusions. Brain 131:1282–1293
42. Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, Kovacs GG, Ghetti B, Halliday G, Holm IE, Ince PG, Kamphorst W, Revesz T, Rozemuller AJ, Kumar-Singh S, Akiyama H, Baborie A, Spina S, Dickson DW, Trojanowski JQ, Mann DM (2009) Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. Acta Neuropathol 117:15–18

43. Masaki K, Maeda M, Furuhashi N, Kowa H (1996) Slowly-progressive aphasia and its symptoms—considered in reference to its related literature (in Japanese with English abstract). Kitasato Med 26:397–411
44. Masellis M, Momeni P, Meschino W, Heffner R Jr, Elder J, Sato C, Liang Y, St George-Hyslop P, Hardy J, Bilbao J, Black S, Rogaeva E (2006) Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome. Brain 129:3115–3123
45. Mii T, Sudo K, Hayashi Y (1969) Ein Fall der Pickschen Krankheit (in Japanese with German abstract). Kyushu Neuro-psychiatry 15:106–113
46. Munoz-Garcia D, Ludwin SK (1984) Classic and generalized variants of Pick's disease: a clinicopathological, ultrastructural, and immunocytochemical comparative study. Ann Neurol 16:467–480
47. Munoz DG, Dickson DW, Bergeron C, Mackenzie IR, Delacourte A, Zhukareva V (2003) The neuropathology and biochemistry of frontotemporal dementia. Ann Neurol 54(Suppl 5):S24–S28
48. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51:1546–1554
49. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, McCluskey LF, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretzschmar HA, Trojanowski JQ, Lee VM (2006) Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 314:130–133
50. Obi K, Akiyama H, Kondo H, Shimomura Y, Hasegawa M, Iwatsubo T, Mizuno Y, Mochizuki H (2008) Relationship of phosphorylated alpha-synuclein and tau accumulation to Abeta deposition in the cerebral cortex of dementia with Lewy bodies. Exp Neurol 210:409–420
51. Oda T, Tsuchiya K, Arai T, Togo T, Uchikado H, de Silva R, Lees A, Akiyama H, Haga C, Ikeda K, Kato M, Kato Y, Hara T, Onaya M, Hori K, Teramoto H, Tominaga I (2007) Pick's disease with Pick bodies: an unusual autopsy case showing degeneration of the pontine nucleus, dentate nucleus, Clarke's column, and lower motor neuron. Neuropathology 27:81–89
52. Onari K, Spatz H (1926) Anatomische Beiträge zur Lehre von Pickschen umschriebenen Größhirnrinden Atrophie (Picksche Krankheit). Z Ges Neurol Psychiatr 101:470–511
53. Ota S, Tsuchiya K, Anno M, Akiyama H (2005) An autopsy case of dementia lacking distinctive histologic features showing semantic dementia. No To Shinkei 57:233–238
54. Oyanagi S, Tanaka M, Omori T, Matsuchita M, Ishii T (1979) Regular arrangements of tubular structures in Pick bodies formed in an autopsied case of Pick's disease (in Japanese with English abstract). Shinkei Kenkyū no Shimpo (Adv in Neurol Sci) 23:441–451
55. Paviour DC, Lees AJ, Josephs KA, Ozawa T, Ganguly M, Strand C, Godbolt A, Howard RS, Revesz T, Holton JL (2004) Frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal changes: broadening the clinical picture to include progressive supranuclear palsy. Brain 127:2441–2451
56. Pick A (1892) Ueber die Beziehungen der senilen Hirnatrophie zur Aphasie. Prager Med Wochenschr 17:165–167
57. Pickering-Brown SM (2007) Progranulin and frontotemporal lobar degeneration. Acta Neruopathol 114:39–47
58. Pickering-Brown SM, Rollinson S, Du Plessis D, Morrison KE, Varma A, Richardson AM, Neary D, Snowden JS, Mann DM (2008) Frequency and clinical characteristics of progranulin mutation carriers in the Manchester frontotemporal lobar degeneration cohort: comparison with patients with MAPT and no known mutations. Brain 131:721–731
59. Ratnavalli E, Brayne C, Dawson K, Hodges JR (2002) The prevalence of frontotemporal dementia. Neurology 58:1615–1621
60. Rabinovici GD, Furst AJ, O'Neil JP, Racine CA, Mormino EC, Baker SL, Chetty S, Patel P, Pagliaro TA, Klunk WE, Mathis CA, Rosen HJ, Miller BL, Jagust WJ (2007) 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. Neurology 68:1205–1212
61. Roeber S, Mackenzie IR, Kretzschmar HA, Neumann M (2008) TDP-43-negative FTLD-U is a significant new clinico-pathological subtype of FTLD. Acta Neuropathol 116:147–157
62. Rossor MN, Revesz T, Lantos PL, Warrington EK (2000) Semantic dementia with ubiquitin-positive tau-negative inclusion bodies. Brain 123:267–276
63. Shi J, Shaw CL, Du Plessis D, Richardson AM, Bailey KL, Julien C, Stopford C, Thompson J, Varma A, Craufurd D, Tian J, Pickering-Brown S, Neary D, Snowden JS, Mann DM (2005) Histopathological changes underlying frontotemporal lobar degeneration with clinicopathological correlation. Acta Neuropathol 110:501–512
64. Snowden JS, Pickering-Brown SM, Mackenzie IR, Richardson AM, Varma A, Neary D, Mann DM (2006) Progranulin gene mutations associated with frontotemporal dementia and progressive non-fluent aphasia. Brain 129:3091–3102
65. Snowden J, Neary D, Mann D (2007) Frontotemporal lobar degeneration: clinical and pathological relationships. Acta Neuropathol 114:31–38
66. Spina S, Murrell JR, Huey ED, Wassermann EM, Pietrini P, Grafman J, Ghetti B (2007) Corticobasal syndrome associated with the A9D progranulin mutation. J Neuropathol Exp Neurol 66:892–900
67. Tsuchiya K, Ishizu H, Nakano I, Kita Y, Sawabe M, Haga C, Kuyama K, Nishinaka T, Oyanagi K, Ikeda K, Kuroda S (2001) Distribution of basal ganglia lesions in generalized variant of Pick's disease: a clinicopathological study of four autopsy cases. Acta Neuropathol 102:441–448
68. Tsuchiya K, Ikeda M, Hasegawa K, Fukui T, Kuroiwa T, Haga C, Oyanagi S, Nakano I, Matsushita M, Yagishita S, Ikeda K (2001) Distribution of cerebral cortical lesions in Pick's disease with Pick bodies: a clinicopathological study of six autopsy cases showing unusual clinical presentations. Acta Neuropathol 102:553–571
69. Tsuchiya K, Piao YS, Oda T, Mochizuki A, Arima K, Hasegawa K, Haga C, Kakita A, Hori K, Tominaga I, Yagishita S, Akiyama H, Takahashi H (2006) Pathological heterogeneity of the precentral gyrus in Pick's disease: a study of 16 autopsy cases. Acta Neuropathol 112:29–42
70. Uchihara T, Tsuchiya K (2008) Neuropathology of Pick body disease. In: Duyckaerts C, Litvan I (eds) Handbook of clinical neurology, vol 89 (Third series), Dementias. Elsevier, Amsterdam, pp 415–430
71. Yokota O, Sasaki K, Fujisawa Y, Takahashi J, Terada S, Ishihara T, Nakashima H, Kugo A, Ata T, Ishizu H, Kuroda S (2005) Frequency of early and late-onset dementias in a Japanese memory disorders clinic. Eur J Neurol 12:782–790
72. Yokota O, Tsuchiya K, Oda T, Ishihara T, de Silva R, Lees AJ, Arai T, Uchihara T, Ishizu H, Kuroda S, Akiyama H (2006) Amyotrophic lateral sclerosis with dementia: an autopsy case showing many Bunina bodies, tau-positive neuronal and astrocytic plaque-like pathologies, and pallido-nigral degeneration. Acta Neuropathol 112:633–645
73. Yokota O, Tsuchiya K, Itoh Y, Ishizu H, Akiyama H, Ikeda M, Kuzuhara S, Otomo E (2006) 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. Acta Neuropathol 112:739–749
74. Yokota O, Tsuchiya K, Terada S, Ishizu H, Uchikado H, Ikeda M, Oyanagi K, Nakano I, Murayama S, Kuroda S, Akiyama H (2008) Basophilic inclusion body disease and neuronal intermediate filament inclusion disease: a comparative clinicopathological study. Acta Neuropathol 115:561–575

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ORIGINAL PAPER

# Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction

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**Abstract** The two current major staging systems in use for Lewy body disorders fail to classify up to 50% of subjects. Both systems do not allow for large numbers of subjects who have Lewy-type α-synucleinopathy (LTS) confined to the olfactory bulb or who pass through a limbic-predominant pathway that at least initially bypasses the brainstem. The results of the current study, based on examination of a standard set of ten brain regions from 417 subjects stained immunohistochemically for α-synuclein, suggest a new staging system that, in this study, allows for the classification of all subjects with Lewy body disorders. The autopsied subjects included elderly subjects with Parkinson's disease, dementia with Lewy bodies, incidental Lewy body disease and Alzheimer's disease with Lewy bodies, as well as comparison groups without Lewy bodies. All subjects were classifiable into one of the following stages: I. Olfactory Bulb Only; IIa Brainstem Predominant; IIb Limbic Predominant; III Brainstem and Limbic; IV Neocortical. Progression of subjects through these stages was accompanied by a generally stepwise worsening in terms of striatal tyrosine hydroxylase concentration, substantia nigra pigmented neuron loss score, Mini Mental State Examination score and score on the Unified Parkinson's Disease Rating Scale Part 3. Additionally, there were significant correlations between these measures and LTS density scores. It is suggested that the proposed staging system would improve on its predecessors by allowing classification of a much greater proportion of cases.

**Keywords** Parkinson's disease · Parkinsonism · Dementia with Lewy bodies · Alzheimer's disease · Incidental Lewy bodies · α-synuclein · Olfactory bulb · Amygdala · Limbic · Brainstem · Neocortex

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## Introduction

It has been almost two centuries since the first description [73, 74] of Parkinson's disease (PD) and almost one century since the subsequent discovery of its characteristic microscopic lesion, the Lewy body [47, 61, 82]. The intervening years have provided a wealth of detail on its clinical manifestations and pathology. The presenting syndromes are dementia, motor parkinsonism or both. Since Kosaka's delineation of "diffuse Lewy body disease" associated with dementia in 1976 [55], followed by the alternative concepts of "senile dementia of the Lewy body type" [78] and "Lewy body variant of Alzheimer's disease" [41], those presenting with dementia are now termed dementia with Lewy bodies (DLB), the definition of which has undergone two major iterations [66, 67]. In both PD and DLB, aggregation, phosphorylation and nitration of α-synuclein, an abundant synaptic protein, have been

suggested to be critical processes leading to Lewy body formation and clinical symptomatology [3, 29, 36, 38, 80].

Investigations that have mapped the topographical distribution and density of Lewy bodies and their associated abnormal neurites have indicated that these are spread much more widely throughout the neuraxis than formerly appreciated [22, 30, 31, 39, 46, 49, 50, 57, 69, 80, 81]. The SN, for so long believed to be the epicenter of PD, is neither the earliest nor the most severely affected region. More caudal brainstem structures are now recognized as involved prior to the SN while the amygdala and associated limbic structures may be struck first and hardest in some cases [11, 40, 63, 65, 75, 84, 85]. Furthermore, it is also now more clearly apparent that Lewy body pathology frequently extends to the spinal cord and peripheral nervous system [9, 10, 15–17, 24, 44, 54, 72, 86].

Much effort has been expended by numerous investigators to devise staging systems that might be used, as in neoplastic disease, to define and categorize the progression of Lewy body disorders in terms of microscopic appearance and regional presence [13, 65–67, 81]. These endeavors have not only provided more precise descriptions of disease extent, they have also given an improved understanding of disease progression. It is hoped that this will lead to useful clues regarding disease pathogenesis.

However, it has become apparent that the current staging systems fall short of adequately describing the full histopathologic range and variability of Lewy body disorders. There are two major competing systems, both of which have been determined to some degree inadequate by several recent and comprehensive investigations and/or reviews [34, 51, 52, 59, 62, 76]. These two schemes have been differentially conceived, one for PD and the other for DLB [10, 12, 66, 67]. Both of these have been reported to provide insufficient guidance, especially when applied outside of their initial focus, so that up to 50% or more of cases are unclassifiable [51]. The recent redefinition of DLB has left many cases, mainly those harboring Alzheimer's disease (AD) and limbic lobe-restricted Lewy bodies, without a diagnostic label entirely [67, 85]. Undoubtedly, contributing to the confusion are large differences between laboratories in the sensitivity of immunohistochemical methods for α-synuclein, along with variability in sampling sites, tissue processing and inter-observer assessment [2, 20, 70].

We undertook this investigation in an attempt to construct, from the valuable foundation already achieved, a unified staging system that could be applied to all of the major Lewy body disorders, including not only PD and DLB but also incidental Lewy body disease (ILBD) and Alzheimer's disease with sparse, predominantly limbic Lewy bodies (ADLB). A sensitive immunohistochemical method for α-synuclein was used to stain sets of brain sections from more than 600 autopsied subjects. The densities and frequencies of occurrence of Lewy-type α-synucleinopathy (LTS) in ten standard brain regions were tabulated and correlated with diagnostic category as well as measures of nigrostriatal degeneration, cognitive impairment and motor dysfunction. The results are presented in this manuscript.

## Materials and methods

### Human subjects

Brain tissue was obtained from Sun Health Research Institute (SHRI), located in the Sun Cities retirement communities of northwest metropolitan Phoenix, Arizona. Brain necropsies were performed on elderly subjects who had volunteered for the SHRI Brain Donation Program [5]. The majority of Brain Donation Program subjects are clinically characterized at SHRI with annual standardized test batteries that include functional, neuropsychological and neuromotor components, including the Mini Mental State Examination (MMSE) and Unified Parkinson's Disease Rating Scale (UPDRS). Additionally, private medical records are requisitioned and reviewed for each subject and the postmortem Dementia Questionnaire [32] is administered to subject contacts to help determine the presence or absence of dementia for those subjects lacking standardized antemortem evaluations. The Brain Donation Program has been approved by the SHRI Institutional Review Board.

Subjects were chosen by searching the Brain Donation Program database for all cases with a completed neuropathologist's examination, a full set of paraffin blocks (defined as blocks having all ten regions as defined in the histologic methods) and diagnoses of a Lewy body disorder, including PD, DLB, ILBD, and ADLB. Comparison groups were composed of subjects without evidence of dementia or parkinsonism (normal elderly subjects) and subjects with AD but no Lewy body pathology (ADNLB).

Subjects received standardized neuropathological examinations. Specific diagnostic criteria were used for AD [19], PD [37], and DLB [66]. For both AD and DLB, cases received the diagnosis if they were classified as "intermediate" or "high" probabilities in their respective classification schemes. Cases with LTS but not meeting these diagnostic criteria were designated as either ILBD, if they had no clinical history of parkinsonism or dementia, or ADLB if they had Alzheimer's disease and Lewy bodies in any brain region but failed to meet criteria for DLB.

Gross and microscopic neuropathologic assessments were made by a single observer (TGB) without knowledge of the clinical history or clinical diagnosis; subsequently the clinical history was reviewed in order to make an appropriate clinicopathologic diagnosis. Subjects with Lewy body