Table 2 Pathological diagnoses in all cases

Pathological diagnosis	Late-onset schizophrenia and delusional disorders ($n = 23$)	Normal controls ($n = 71$)	Other late-onset psychiatric disorders			
			Depression ($n = 11$)	Bipolar disorders ($n = 2$)	Personality disorders ($n = 6$)	Neurotic disorders ($n = 3$)
Argyrophilic grain disease						
AGD2 + NFT2-4 + SPB	2	–	–	–	–	–
AGD2 + NFT2 + SP0	1	–	1	–	–	–
AGD2 + NFT2 + SPA + TDPlim	–	1	–	–	–	–
AGD1 + NFT3 + SPB	–	1	–	–	–	–
AGD1 + NFT1-2 + SP0-A	2	4	–	–	–	–
Total (n)	5	6	1	–	–	–
Lewy body disease						
LBDdn + NFT5 + SPC + TDPlim	1	–	–	–	–	–
LBDdn + NFT5 + SP0	1	–	–	–	–	–
LBDdn + NFT1-3 + SPC	–	1	1	–	–	–
LBDlim + NFT4 + SPC + TDPlim	1	–	–	–	–	–
LBDlim + NFT1-2 + SPC	1	1	1	–	–	–
LBDbs + NFT1-2 + SPA	2	6	1	–	–	–
Total (n)	6	8	3	–	–	–
Corticobasal degeneration						
CBD + AGD3 + NFT3 + SPC	–	–	–	–	1	–
CBD + AGD1 + NFT1 + LBDbs	–	–	1	–	–	–
CBD + AGD1 + NFT2	1	–	–	–	–	–
CBD + AGD1 + NFT1	–	–	–	–	1	–
Total (n)	1	–	1	–	2	–
Mild to moderate AD pathology						
NFT3-4 + SP0-C	2	1	1	1	–	1
NFT1-2 + SPB-C	1	11	1	–	1	–
NFT1-2 + SP0-A	8	38	4	1	3	2
NFT0 + SPA-C	–	3	–	–	–	–
Total (n)	11	53	6	2	4	3
No degeneration						
Total (n)	–	4	–	–	–	–

NFT1, 2, 3, 4 and 5, Braak NFT stage I, II, III, IV, and V; SPA, B, and C, Braak senile plaque stage A, B, and C; LBDbs, brain stem type Lewy body disease; LBDlim, limbic type Lewy body disease; LBDdn, diffuse neocortical type Lewy body disease; TDPlim, limbic type TDP-43 pathology, AGD1, argyrophilic grain disease stage I; AGD2, AGD stage II, AGD3, AGD stage III; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy

plaques in all LOSD cases were (versus normal controls): 75th percentile 2 (1); median 1 (1); and 25th percentile 0 (0). The Braak Aβ-positive plaque stage was not statistically different between two groups ($P = 0.83$, Mann–Whitney U test).

Frequencies of neurodegenerative changes in LOSD cases with onset age of ≥65 years

Of 11 LOSD cases with onset at ≥65 years of age (median age at death, 79 years), four cases (36.4 %) had AGD, four (36.4 %) had LBD, two (18.2 %) had moderate AD pathology (Braak stage III–IV) alone, and one (9.1 %) had minimal AD pathology (Braak stage I–II) alone (Fig. 4). In contrast, in 36 age-matched normal controls (median age at death, 76 years), three cases (8.3 %) had AGD, seven (19.4 %) had LBD, one (2.8 %) had moderate AD pathology (Braak stage III–IV) alone, and 25 (69.4 %) had minimal AD pathology (Braak stage I–II) alone.

The frequency of AGD was significantly higher in LOSD cases with onset at ≥65 years of age than in normal controls ($P = 0.0424$, Fisher's exact test). LOSD patients with onset at ≥65 years of age had a significantly increased risk of having AGD (odds ratio 6.29; 95 % CI 1.14–34.6) compared to age-matched normal controls.

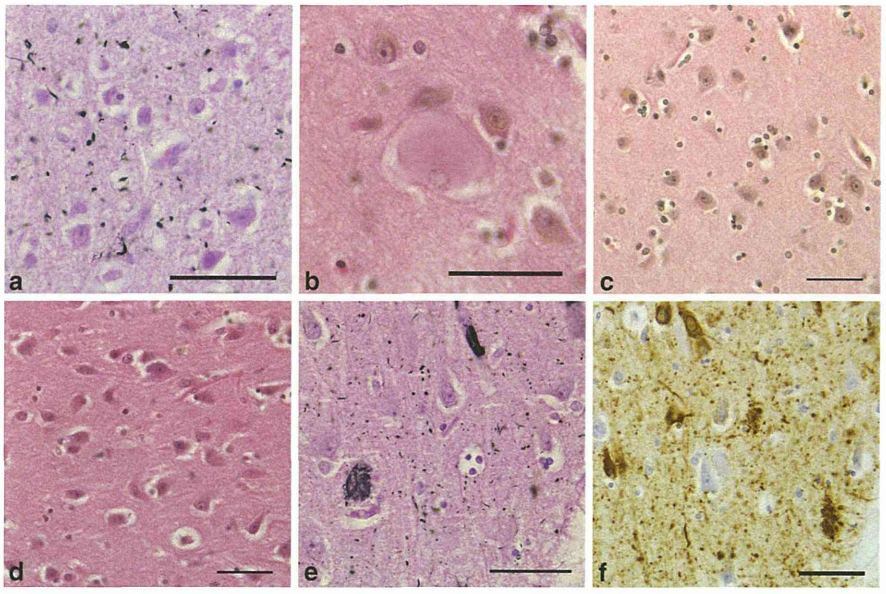

Fig. 1 Pathological findings in a representative argyrophilic grain disease case showing LOSD. Argyrophilic grain disease (AGD) seen in a 79-year-old woman who was diagnosed with senile-onset schizophrenia. She initially showed persecutory delusion and tactile hallucination at 68 years of age. Motor disturbance or dementia was absent throughout the course, and she died suddenly. The brain weighed 1,305 g. **a** Moderate argyrophilic grains in the ambient gyrus. **b** Ballooned neurons in the amygdala. **c** In contrast to the presence of argyrophilic grains, neuronal loss or gliosis is not noted in the amygdala. Pyramidal neurons in the hippocampal CA1 were well spared in number (**d**), but argyrophilic grains were densely distributed in the hippocampal CA1, corresponding to Saito's AGD stage II (**e**). **f** Tau-positive argyrophilic grains with a few neurofibrillary tangles in the hippocampus (Braak stage II). **a**, **e** Gallyas–Braak silver stain, **b**–**d** hematoxylin–eosin stain, **f** AT8 immunohistochemistry. All *scale bars* = 50 μm

Frequencies of neurodegenerative changes in LOSD cases with onset at <65 years of age

Of 12 LOSD cases with onset at <65 years of age (median age at death, 70 years), one had AGD (8.3 %), two (16.7 %) had LBD, and one (8.3 %) had CBD (Fig. 4). Of 59 age-matched normal controls (median age at death, 72 years), three (5.1 %) had AGD, and six (10.2 %) had LBD. The frequency of AGD was not significantly different between LOSD cases whose onset age was <65 years and control cases ($P = 0.53$, Fisher's exact test).

Comparison of severities of neurodegenerative changes between LOSD cases with and without dementia in last stage

The clinical data regarding the presence or absence of dementia in the last stage were available for 19 of 23 LOSD cases, and seven had dementia in the last stage. The Braak NFT stage (LOSD with vs. without dementia, median: 2 vs. 2), Braak Aβ stage (2 vs. 0.5), AGD stage (0 vs. 0), and the frequency of LBD (42.9 vs. 14.3 %) did not significantly differ between LOSD cases with and without dementia in the last stage ($P = 0.54$, 0.27, 0.33, and 0.12, Mann–Whitney U test and Fisher's exact test).

Frequencies of degenerative changes in cases of various psychiatric disorders with onset at ≥40 years of age

We additionally examined pathological changes in 22 patients who developed various psychiatric disorders other than LOSD after 40 years of age (Table 2).

AGD and LBD were found in some depression cases, but not in any case in the other clinical diagnosis groups. The frequencies of AGD (9.1 vs. 8.5 %) and LBD (27.3 vs. 11.3 %) were not statistically different between all depression cases and normal control cases, respectively [$P = 0.56$ and 0.12, Fisher's exact test ($\alpha/2$), Table 2]. Of five depression patients with onset at ≥65 years of age, while no case had AGD, three had LBD. The frequency of LBD was significantly higher in depression patients whose onset age was ≥65 years of age than in normal controls ($n = 56$) (60.0 vs. 10.7 %, $P = 0.0198$, Fisher's exact test). On the other hand, of six depression patients whose onset age was <65 years of age, one had AGD and no case had LBD. The frequency of AGD in this subgroup of depression was not significantly different between LOSD and normal control cases ($n = 21$) [16.7 vs. 14.3 %, $P = 0.66$, Fisher's exact test ($\alpha/2$)].

Pathological changes of CBD were found in one depression case and two cases of presenile-onset

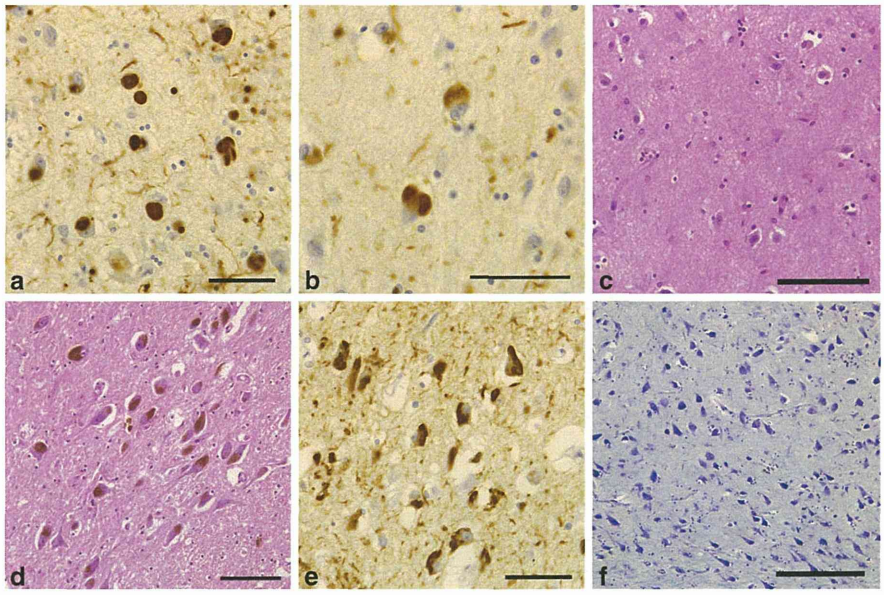

Fig. 2 Pathological findings in a representative Lewy body disease case showing LOSD. Limbic type Lewy body disease seen in a 82-year-old man diagnosed with senile-onset schizophrenia-like psychotic disorder. He initially developed delusion of observation and auditory hallucination at 72 years of age. His intelligence was mildly impaired after 77 years of age, but he did not exhibit dementia throughout the course. Although dysphasia was seen in the terminal stage, muscle rigidity or tremor was absent during the course. He died of pneumonia. The brain weighed 1,150 g. Many α-synuclein-positive Lewy bodies in the entorhinal cortex (**a**) and amygdala (**b**). **c** Moderate neuronal loss with astrocytosis in the amygdala. **d** Neurons in the substantia nigra were well spared in number. **e** Tau-positive neurofibrillary tangles (NFTs) in the hippocampal CA1. This case had NFTs in the insular cortex, corresponding to Braak NFT stage IV. **f** In contrast to NFTs, pyramidal neurons in the hippocampal CA1 were relatively well preserved in number. **a**, **b** Psyn#64 immunohistochemistry, **c**, **d** hematoxylin–eosin stain, **e** AT8 immunohistochemistry, **f** Klüver–Barrera stain. *Scale bars* = (**a**, **b**, **e**) 50 μm, (**c**, **d**, **f**) 100 μm

personality disorder. No psychiatric case had pathological evidence of demyelinating diseases, neoplasms, or infections in the central nervous system.

Comparison of vascular lesions between LOSD cases and psychiatric disease control cases

The severities of vascular lesions in the cerebral cortex in LOSD cases (versus psychiatric disease controls) were: 75th percentile 0.5 (0); median 0 (0); and 25th percentile 0 (0). The severity of vascular lesions in the cerebral cortex was not significantly different between the two groups ($P = 0.42$, Mann–Whitney U test). Likewise, the severities of vascular lesions in the basal ganglia in LOSD cases (versus psychiatric disease controls) were: 75th percentile 1 (1); median 0 (0); and 25th percentile 0 (0). The severity of vascular lesions in the basal ganglia was not significantly different between the two groups ($P = 0.78$, Mann–Whitney U test). The age at death in LOSD cases (the mean age at death 75.1 ± 7.5 years) was not significantly different from that in psychiatric disease control cases (70.5 ± 8.1 years) ($P = 0.082$, Mann–Whitney U test).

Clinical features in pathological diagnosis groups

The demographic data in four pathological diagnosis groups, i.e., AGD (AGD cases lacking LBD or CBD pathology), LBD (LBD cases lacking AGD or CBD pathology), CBD (cases having pathology of CBD), and non-degenerative disease groups (cases having minimal AD pathology of Braak stage I–II/0–A alone) are shown in Table 3. The ages of onset and death in CBD cases were about 10 years lower than those in AGD and LBD cases, respectively. Figure 5 shows the frequencies of clinical symptoms in each pathological diagnosis group. Delusion was significantly more frequent in the AGD group, and disinhibition was significantly more frequent in the CBD group than those in a non-degenerative disease group, respectively [$P = 0.0127$ and 0.0026, Fisher's exact test ($\alpha/3$)].

Discussion

To our knowledge, this is the first study that comprehensively examined the neurodegenerative bases in patients

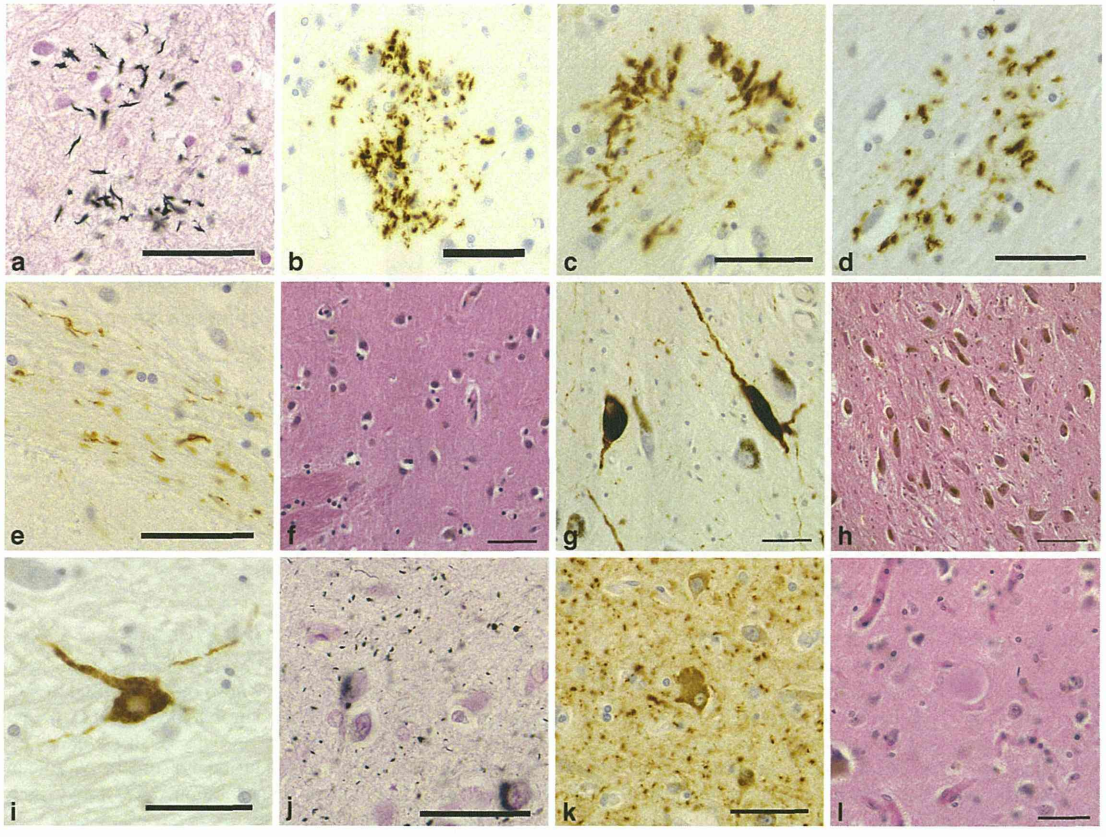

Fig. 3 Pathological findings in a representative corticobasal degeneration case showing LOSD. Corticobasal degeneration (CBD) seen in a 58-year-old man who was diagnosed with late-onset schizophrenia. His initial symptom was apathy at 41 years of age. Auditory hallucination and irritability occurred at 52 years of age. Motor disturbance, aphasia, or dementia was absent throughout the course. He died of chronic obstructive pulmonary disease. The brain weighed 1,480 g. Astrocytic plaques in the superior frontal gyrus (**a**), motor cortex (**b**), caudate nucleus (**c**), and putamen (**d**). **e** A small number of tau-positive threads were seen in the putamen. A small number of tau-positive and Gallyas-positive neurofibrillary tangles and threads were found in the frontal cortex, caudate nucleus, putamen, subthalamic nucleus, substantia nigra (**g**), oculomotor nucleus, pontine nucleus (**i**), and inferior olivary nucleus. Unlike classic CBD cases, neuronal loss with glial proliferation was not seen in the putamen (**f**) or substantia nigra (**h**). **j–l** This case also had Gallyas- and tau-positive argyrophilic grains (**j**, **k**), mild neurofibrillary tangles (Braak stage II), and ballooned neurons (**k**, **l**) in the ambient gyrus and amygdala. However, neuronal loss and gliosis were minimal in these regions (**l**). **a**, **j** Gallyas–Braak silver stain, **f**, **h**, **l** hematoxylin–eosin stain, (**b–e**, **g**, **i**, **k**) AT8 immunohistochemistry. *Scale bars* = (**a**, **c**, **d**, **e–g**, **i–l**) 50 μm, **b** 25 μm, **h** 100 μm

with LOSD and demonstrated a significant relationship between LOSD and AGD. The main findings in the present study were as follows: (1) AGD and LBD had comparably common pathological bases in our LOSD cases (21.7 and 26.1 %), frequencies about 2.5 times higher than those in normal controls (8.5 and 11.3 %). Argyrophilic grains in LOSD cases are almost completely restricted to the limbic system and adjacent temporal cortex. CBD was rarely found in LOSD but never in normal control cases. Consequently, LOSD patients who experienced onset after 40 years of age had about a fourfold increased risk of having either AGD, LBD, or CBD (odds ratio 4.44, 95 % CI 1.62–12.1) compared with normal controls. (2) AGD was significantly more frequent in LOSD patients whose onset occurred at ≥65 years of age than in normal controls, and the LOSD patients had about a sixfold increased risk of having AGD (odds ratio 6.29; 95 % CI 1.14–34.6) compared with normal controls. (3) In a psychiatric case series, the frequency of delusion in AGD cases was significantly more frequent than that in cases having minimal AD pathology alone. These findings suggest that LOSD cases may have heterogeneous pathological backgrounds, including AGD, LBD, and CBD and that mild to moderate argyrophilic grains may play an important role in the occurrence of LOSD, especially in elderly people.

It has been reported that some AGD cases with dementia show various psychiatric features, including delusion, hallucination, aggression, irritability, and obsession [31, 34–38]. However, as far as we know, there has been no study that demonstrated a significant relationship between AGD and LOSD in non-demented elderly people. In general, it is difficult to determine whether histopathological

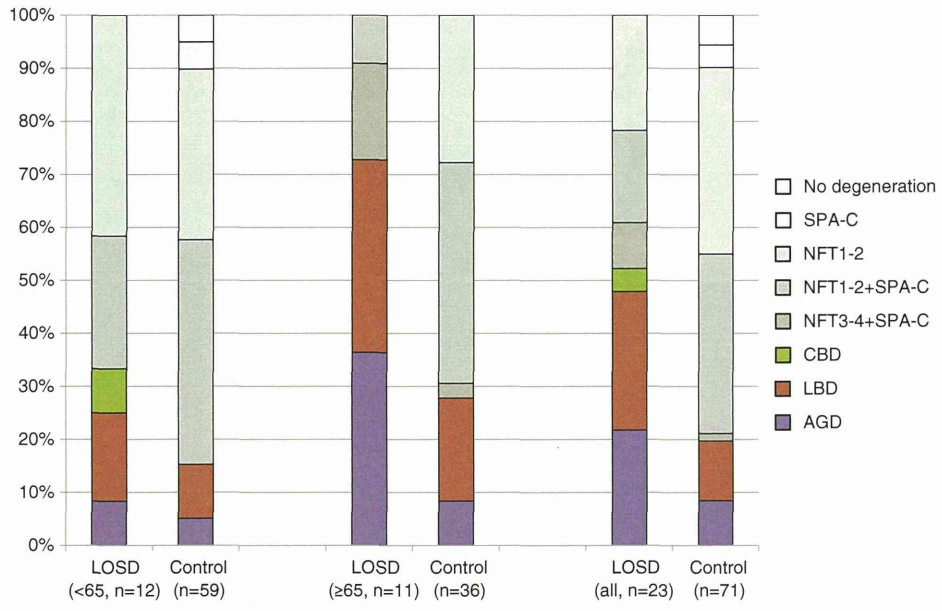

Fig. 4 Distribution of pathological diagnoses in LOSD cases and age-matched normal controls. *Right* A comparison of all LOSD and age-matched normal control cases. The frequencies of AGD and LBD in LOSD cases were about 2.5 times those in controls, and CBD was found only in LOSD cases. The total proportion of AGD, LBD, and CBD was significantly higher in LOSD cases than in controls [$P = 0.0037$, Fisher's exact test ($\alpha/7$)]. *Center* A comparison of LOSD patients ≥65 years of age at onset and age-matched normal controls. The frequency of AGD was significantly higher in LOSD cases than in controls ($P = 0.0424$, Fisher's exact test). *Left* A comparison of LOSD patients whose onset occurred at <65 years of age and age-matched normal controls. The frequency of AGD did not statistically differ between two groups (Fisher's exact test). *LOSD* late-onset schizophrenia and delusional disorders, *NFT* neurofibrillary tangles, *CBD* corticobasal degeneration, *LBD* Lewy body disease, *AGD* argyrophilic grain disease

Table 3 Demographic data by pathological diagnosis in cases with psychiatric disorders

Pathological diagnosis	*n*	Female *n* (%)	Age at onset (years) Mean ± SD	Age at death (years) Mean ± SD	Disease duration (years) Mean ± SD	Brain weight (g) Mean ± SD	Dementia in last stage *n* (%)[g]
Argyrophilic grain disease group[b]	6	4 (67.7)	67.0 ± 12.0	77.8 ± 7.3[f]	10.8 ± 5.9	1,179 ± 138.2	1/4 (25.0)
Lewy body disease group[a]	9	3 (33.3)	70.1 ± 8.3[e]	78.2 ± 5.7[e]	8.9 ± 6.1	1,273 ± 143.2	5/7 (71.4)
Corticobasal degeneration group[c]	4	1 (25.0)	60.5 ± 16.8	66.8 ± 12.4	6.3 ± 7.3	1,315 ± 124.8	2/4 (50.0)
Total	19	8 (42.1)	66.9 ± 11.6	75.7 ± 8.8	8.9 ± 6.1	1,240 ± 133.6	8/15 (53.3)
Non-degenerative group[d]	18	14 (77.8)	59.2 ± 9.4	68.3 ± 5.7	9.7 ± 9.2	1,204 ± 182.2	3/15 (20.0)

LBD Lewy body disease, *AGD* argyrophilic grain disease, *CBD* corticobasal degeneration, *PSP* progressive supranuclear palsy, *SD* standard deviation

[a] Lewy body disease (LBD) cases with variable degrees of Alzheimer's disease (AD) pathology but without argyrophilic grain disease (AGD), corticobasal degeneration (CBD), or progressive supranuclear palsy (PSP) pathology

[b] AGD cases without LBD, CBD, or PSP pathology

[c] All cases diagnosed pathologically as having CBD or PSP

[d] Cases having only minimal AD pathology (Braak NFT stage 0–II and/or Braak senile plaque stage 0–A)

[e] The onset age and age at death in the LBD group were significantly higher than those in the non-degenerative disease group, respectively [median age at onset: 71.5 vs. 61.0 years; median age at death: 77.0 vs. 69.0 years. $P = 0.0090$ and 0.00007. Mann–Whitney U test and Bonferroni correction ($P < 0.016$]

[f] The age at death in the AGD group was significantly higher than that in the non-degenerative disease group [median age at death: 76.0 vs. 69.0 years. $P = 0.0026$, Mann–Whitney U test and Bonferroni correction ($P < 0.016$)]

[g] The proportion of cases that had dementia in the last stage of the course of all subjects whose clinical data in the terminal stage was available

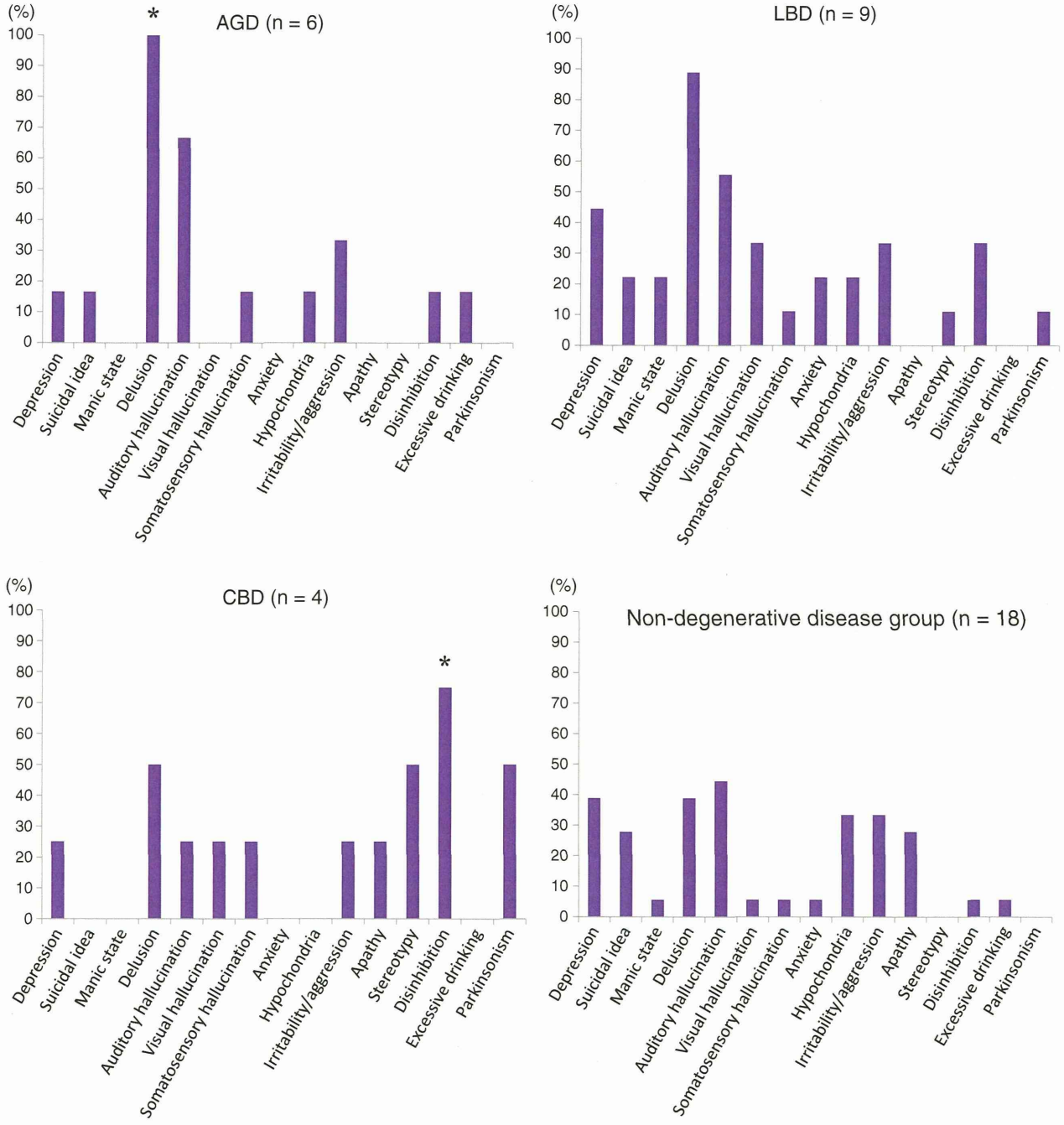

Fig. 5 Frequencies of clinical features by pathological diagnosis group. The frequencies of prominent clinical symptoms in the early stages of LBD ($n = 9$), AGD ($n = 6$), CBD ($n = 4$), and non-degenerative disease groups ($n = 18$). The frequency of delusion in the AGD group was significantly higher than those in a non-degenerative disease group [Fisher's exact test, $P = 0.0162$, Bonferroni correction ($\alpha/3$)]. The frequency of disinhibition in the CBD group was also significantly higher than that in a non-degenerative disease group [$P = 0.0026$, Fisher's exact test and Bonferroni correction ($\alpha/3$)]. See the definition of each pathological diagnosis group in the text. *LBD* Lewy body disease, *AGD* argyrophilic grain disease, *CBD* corticobasal degeneration

changes are causally related to young-onset psychiatric disorders because the initial symptoms usually occur several decades before death, and some major degenerative changes, e.g., argyrophilic grains [32], Lewy bodies [54], NFTs [55], and Aβ deposits [55], increase in frequency with age. However, our study demonstrated that the high frequency of AGD in LOSD cases may not be explained only by the age at death.

Argyrophilic grains in our LOSD cases tended to be less severe in topographical distribution (i.e., Saito's stage I–II)

compared with those in AGD cases showing dementia reported previously: some previous studies demonstrated that AGD cases with dementia frequently had argyrophilic grains more extensively distributed in the neocortex (i.e., Saito's stage III) [33]. In this context, it seems to be natural that our AGD cases lacking dementia, at least in the early to middle stage of the course, had less severe tau pathology. The impact of such mild to moderate argyrophilic grains on psychological functions, such as mood, anxiety, and thought, has hardly been explored. Our results suggest that LOSD without dementia at the onset may be one of the clinical presentations in elderly people having mild to moderate AGD. It is known that psychosis tends to occur secondarily when the limbic region and temporal cortex are involved in various diseases, such as cerebrovascular disease, traumatic brain injury, and epilepsy [56, 57]. These findings led us to consider that the occurrence of psychotic symptoms in AGD cases may be associated with the initial involvement of the limbic system by tau pathology in AGD [33].

It was reported that some LBD cases show systematized delusion [58]. The frequencies of delusion in LBD cases was reported to be 17–30 % in Parkinson's disease cases with or without dementia [59, 60] and 25–28.6 % in DLB cases [61, 62]. In our study also, although the difference did not reach statistical significance, the frequency of LBD in LOSD cases was about 2.5 times that in normal controls. Further, LBD was significantly more frequent in our depression cases with the onset at ≥65 years of age than in normal controls. On the other hand, AGD was not found in our depression cases. Because the number of cases examined in our study was small, whether the clinical spectrum in LBD cases is different from that in AGD cases cannot be concluded from these results. However, considering that the topographical distribution of degenerative changes, which is usually closely associated with clinical presentation, is different in AGD and LBD, it is plausible that these two degenerative diseases have different neuropsychiatric spectrums. For example, the limbic system and some brain stem nuclei (e.g., the raphe nuclei and locus coeruleus) frequently degenerate in LBD [45, 63], while argyrophilic grains consistently occur in the limbic regions but not in the brain stem nuclei. Dysfunction of the limbic system and brain stem nuclei was reported to be associated with depression [64]. Whether AGD is associated with the occurrence of depression or other psychiatric conditions should be explored by further studies using a larger sample.

In our study, although rare, some LOSD cases had CBD pathology. Several previous studies have also demonstrated that autopsy-confirmed CBD cases rarely showed psychotic symptoms [28–30, 65]. Interestingly, psychiatric symptoms occurred in all of our CBD cases younger than 65 years of age, in contrast to the relatively higher onset age in AGD and LBD cases (Table 3). Given these findings, in psychiatric practice, CBD should be considered one of the possible underlying pathologies in a patient who develops psychiatric symptoms before 65 years of age rather than after. The pathophysiological mechanism in the development of LOSD in CBD cases remains unclear. However, the coexistence of argyrophilic grains observed in all of our CBD cases might contribute at least partially to the occurrence of psychiatric symptoms.

Several previous studies, as well as this study, have consistently demonstrated that LOSD may not be associated with severe AD pathology (i.e., Braak NFT stage V–VI) [24, 25]. However, previous findings regarding the relationship between moderate NFTs in the limbic system and LOSD are not always consistent: while the severity of NFTs in the hippocampal CA1, entorhinal cortex, and temporal cortex was reported to be not significantly different between young-onset schizophrenia and LOSD cases [25], another study demonstrated that moderate NFTs distributed mainly in the limbic system and adjacent temporal cortex (Braak stage III–IV) may be associated with the development of LOSD [24]. In our study, the Braak NFT stage in LOSD cases was significantly higher than that in age-matched normal controls. However, our results cannot be simply compared with previous findings because various histological changes, including AD, LBD, AGD, and CBD pathologies, were not simultaneously evaluated in previous studies. For example, the high Braak NFT stage observed in our LOSD cases may be affected by the high proportions of LBD, AGD, and CBD cases having various severities of NFTs. Interestingly, in our LOSD cases, although the proportion of cases having only moderate NFTs (Braak stage III–IV) is not very large (8.7 %), it tends to be higher than that in normal controls (1.4 %). Considering our results together with previously reported findings, there may be LOSD patients whose onset is explained only by moderate numbers of NFTs distributed mainly in the limbic system; however, the proportion of such cases in all LOSD cases may not necessarily be large.

Limitations of our study are several. First, the sample sizes, especially those in clinical and pathological subgroups, are small. Therefore, our results may not always refute the possibility that LOSD is actually associated not only with AGD but also with LBD, CBD, and PSP. For example, in our study, although statistically not significant, the frequency of LBD in LOSD cases was over double that in age-matched normal controls (26.1 vs. 11.3 %), and CBD was found only in LOSD cases but not in age-matched normal controls. It is also known that LBD is found in some patients with paranoia [27, 59–61] and that clinically diagnosed PSP cases rarely show delusions [66]. Second, because almost all of our LOSD cases were psychiatric hospital inpatients, who probably had more severe clinical symptoms than outpatients, the case selection bias may

affect the frequency of each underlying pathology. Third, vascular lesions of the LOSD and age-matched normal control groups in this study could not be compared because the method of tissue sampling was different between these two groups. The impact of vascular changes on the occurrence of LOSD needs to be examined in the future. Fourth, in general, the immunoreactivity in tissue sections can be reduced by long fixation with formaldehyde, especially when using phosphorylation-dependent antibodies. However, in this study, AGD was explored by not only tau immunohistochemistry using phosphorylation-dependent and phosphorylation-independent anti-tau antibodies but also by Gallyas-Braak silver stain. Further, the fixation time in LOSD cases was longer than that in age-matched normal controls. Therefore, the significantly high frequency of AGD in LOSD cases observed in this study could not be explained by the effect of fixation time. Finally, whether neuronal loss and gliosis occur in AGD cases with LOSD are less severe than that in AGD cases with dementia should be also examined by further studies.

Although the present study demonstrated that LOSD patients have heterogeneous neurodegenerative backgrounds, including AGD, it may be still difficult to predict the underlying pathology in LOSD patients in life. Based on our results, biomarkers for tauopathies [67, 68] and α-synucleinopathies [67, 69], which continue to be developed for the precise clinical diagnosis of neurodegenerative dementias, might be useful to predict the pathogenic background in LOSD patients. Further clinicopathological studies are awaited to provide precise prognostic information to families based on biological findings and to develop novel therapeutic strategies for patients with LOSD.

Acknowledgments We would like to thank Ms. Onbe (Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences) for her excellent technical assistance. This work was supported in part by Grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Nos. 21591517, 23591708), and the Zikei Institute of Psychiatry.

Conflict of interest None.

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PSYCHOGERIATRICS
The Official Journal of the Japanese Psychogeriatric Society

doi:10.1111/psyg.12054 *PSYCHOGERIATRICS* 2014; **14:** 152–164

ORIGINAL ARTICLE

Corticobasal degeneration initially developing motor versus non-motor symptoms: a comparative clinicopathological study

Chikako IKEDA,[1,2] Osamu YOKOTA,[1,2,3] Shigeto NAGAO,[1,2] Hideki ISHIZU,[4] Yumi MORISADA,[5] Seishi TERADA,[1,2] Yoshihiko NAKASHIMA,[6] Haruhiko AKIYAMA[7] and Yosuke UCHITOMI[1]

[1]Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, [4]Department of Laboratory Medicine and Pathology, Zikei Institute of Psychiatry, [6]Department of Psychiatry, Sanyo Hospital, Okayama, [2]Clinical Research Institute, National Hospital Organization Minami-Okayama Medical Center, Hayashima, [3]Department of Psychiatry, Kinoko Espoir Hospital, Kasaoka, [5]Kurashiki Neurological Hospital, Kurashiki and [7]Dementia Research Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan

Correspondence: Dr Osamu Yokota MD PhD, Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan. Email: oyokota1@yahoo.co.jp

Received 17 February 2014; accepted 16 June 2014.

Key words: *corticobasal degeneration, delirium, depression, hallucination, psychosis, tau.*

Abstract

Background: Clinical presentations of pathologically confirmed corticobasal degeneration (CBD) vary, and the heterogeneity makes its clinical diagnosis difficult, especially when a patient lacks any motor disturbance in the early stage.

Methods: We compared clinical and pathological features of four pathologically confirmed CBD cases that initially developed non-motor symptoms, including behavioural and psychiatric symptoms but without motor disturbance (CBD-NM), and five CBD cases that initially developed parkinsonism and/or falls (CBD-M). The age range at death for the CBD-NM and CBD-M subjects (58–85 years vs 45–67 years) and the range of disease duration (2–18 years vs 2–6 years) did not significantly differ between the groups.

Results: Prominent symptoms in the early stage of CBD-NM cases included self-centred behaviours such as frontotemporal dementia (n = 1), apathy with and without auditory hallucination (n = 2), and aggressive behaviours with delusion and visual hallucination (n = 1). Among the four CBD-NM cases, only one developed asymmetric motor disturbance, and two could walk without support throughout the course. Final clinical diagnoses of the CBD-NM cases were frontotemporal dementia (n = 2), senile psychosis with delirium (n = 1), and schizophrenia (n = 1). Neuronal loss was significantly less severe in the subthalamic nucleus and substantia nigra in the CBD-NM cases than in the CBD-M cases. The severity of tau pathology in all regions examined was comparable in the two groups.

Conclusion: CBD cases that initially develop psychiatric and behavioural changes without motor symptoms may have less severe degenerative changes in the subthalamic nucleus and substantia nigra, and some CBD cases can lack motor disturbance not only in the early stage but also in the last stage of the course.

INTRODUCTION

Corticobasal degeneration (CBD) was first reported by Rebeiz *et al.* in 1968.[1] The histopathological hallmarks of CBD were first considered to be neurofibrillary tangles (NFT) and ballooned neurons in the affected cerebral cortex, striatum, and brain stem nuclei. Later, astrocytic plaques were also discovered to be highly specific for CBD.[2] Since the historic report by Rebeiz *et al.*, the core clinical features of CBD have been considered to be asymmetric akinetic-rigid parkinsonism and focal cortical signs such as limb kinetic apraxia and alien hand sign.[3–7] However, subsequent clinicopathological studies have demonstrated that parkinsonism and apraxia are not always observed in the early stage of the course.[8–14]

Currently, it is known that clinical presentations of pathologically confirmed CBD vary, including not only corticobasal syndrome but also Richardson syndrome (a classic clinical presentation of progressive supranuclear palsy characterized by postural

instability, early unexplained falls, vertical supranuclear gaze palsy, symmetric parkinsonism, and dysphagia) (CBD-RS), L-dopa-responsive parkinsonism, pure akinesia and gait failure, frontotemporal dementia (CBD-FTD), progressive nonfluent aphasia, and apraxia of speech.[15] This heterogeneity in the clinical presentation may make the clinical diagnosis of CBD difficult, especially when a patient lacks any motor disturbance in the early stage.

The aim of this study was to explore the clinical and pathological features that help predict the underlying CBD pathology in CBD cases lacking motor disturbance in the early stage. To address this, we first demonstrated the clinical and pathological features of four pathologically confirmed CBD cases that initially developed psychiatric or behavioural symptoms without motor disturbance. Then, we compared the distribution and severity of degenerative changes in these CBD cases with those in CBD cases that developed parkinsonism and/or falls as initial symptoms.

MATERIALS AND METHODS

Subjects

We examined four pathologically confirmed CBD cases that developed psychiatric and behavioural changes but lacked motor disturbance as initial symptoms (cases 1–4; mean age at onset: 59.5 ± 16.4 years; mean age at death: 66.3 ± 12.6 years), as well as five pathologically confirmed CBD cases that initially exhibited parkinsonism and/or falls (cases 5–9; mean age at onset: 56.4 ± 9.9 years; mean age at death: 60.0 ± 9.1 years). In this paper, the former cases are called 'CBD initially showing non-motor symptoms without parkinsonism or falls' (CBD-NM), and the latter cases are called 'CBD initially showing motor symptoms (i.e. parkinsonism and/or falls) as initial symptoms' (CBD-M). None of our CBD-NM cases had apraxia during the study period. Limited clinical and histopathological features of case 2 (CBD-NM),[16–18] case 4 (CBD-NM),[19] and case 7 (CBD-M) have been reported previously.[20] The gender distribution, age at onset, age at death, and disease duration did not significantly differ between the two groups.

The pathological diagnosis of CBD was based on the presence of Gallyas- and tau-positive neuronal and glial inclusions such as NFT, threads, coiled bodies, and astrocytic plaques in the frontal cortex, including the primary motor cortex, parietal and temporal cortices, hippocampus, amygdala, caudate nucleus, putamen, globus pallidus, subthalamic nucleus, oculomotor nucleus, substantia nigra, pontine nucleus, inferior olivary nucleus, and dentate nucleus in the cerebellum.[15] In all CBD cases, four-repeat tau rather than three-repeat tau was predominant in accumulated tau-positive lesions.

Six of the nine cases died in psychiatric hospitals, and the remaining three died in general hospitals. Autopsies were carried out after informed consent was obtained from family members. All experiments in this study were approved by the ethics committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (Okayama, Japan).

Neuropathological examination

Brain tissue samples were fixed post-mortem with 10% formaldehyde and embedded in paraffin. Then, 10 μm-thick sections from the frontal, temporal, parietal, and occipital cortices, hippocampus, amygdala, basal ganglia, midbrain, pons, medulla oblongata, and cerebellum were prepared. These sections were stained with haematoxylin–eosin and Klüver-Barrera stains. Sections from representative regions in the cerebrum, cerebellum, and brain stem were stained with Gallyas-Braak silver and modified Bielschowsky silver methods, and they were also immunostained by the immunoperoxidase method using 3,3′-diaminobenzidine tetrahydrochloride. Antibodies used were against phosphorylated tau (AT8, mouse, monoclonal, 1:1000; Innogenetics, Ghent, Belgium), three-repeat tau (RD3: mouse, monoclonal, 1:2000, Upstate, Syracuse, NY, USA) and four-repeat tau (RD4: mouse, monoclonal, 1:100, Upstate), amyloid beta (11–28) (12B2, mouse, monoclonal, 1:100; IBL, Fujioka, Japan), phosphorylated α-synuclein (psyn#64, mouse, monoclonal, 1:5000; Wako Co., Osaka, Japan), phosphorylation-independent α-synuclein (LB509: mouse monoclonal, 1:100; Zymed Laboratories, South San Francisco, CA, USA), phosphorylated transactive response DNA-binding protein of 43kDa (TDP-43) (pS409/410-2, rabbit, polyclonal, 1:5000; Cosmo Bio, Tokyo, Japan), and TDP-43 (anti-TDP-43, rabbit polyclonal, 1:1000; Proteintech, Chicago, IL, USA). When anti-amyloid beta antibodies were used, sections were pretreated with 70% formic acid for 10 min for antigen retrieval. When psyn#64 and pS409/

410-2 were used, sections were autoclaved for 10 min in 10-nM sodium citrate buffer at 120°C.

Semiquantitative assessment of histopathological lesions

Neuronal loss associated with gliosis in the cerebral cortex was assessed on haematoxylin–eosin- and Klüver-Barrera-stained sections according to the grading system used previously:[21] –, no histopathological alteration; +, slight neuronal loss and gliosis only in the superficial layers; ++, obvious neuronal loss and gliosis in cortical layers II and III, often accompanied by status spongiosis and relative preservation of neurons in layers V and VI; and +++, pronounced neuronal loss with gliosis in all cortical layers and prominent fibrillary gliosis in adjacent subcortical white matter. The degree of neuronal loss and gliosis in the basal ganglia and brainstem nuclei was also assessed as follows: –, no histopathological alteration; +, mild gliosis and neuronal loss; ++, moderate neuronal loss and gliosis, but no tissue rarefaction; and +++, severe neuronal loss, severe gliosis, and tissue rarefaction. Degeneration of the corticospinal tract and frontopontine tract at the levels of the cerebral peduncle and medulla oblongata was indicated as follows: –, no degeneration; +, mild degeneration with slight myelin loss and gliosis without atrophy of the tract; ++, moderate degeneration with evident myelin loss and gliosis with slight atrophy of the tract; and +++, severe degeneration with evident myelin loss, gliosis, and severe atrophy of the tract.

Phosphorylated tau-positive NFT and astrocytic plaques were semiquantitatively evaluated using the following staging system on sections immunostained with AT8: –, no lesion; +, one inclusion in each anatomical region; ++, two or more inclusions in each anatomical region but less than one inclusion per ×200 visual field; +++, one inclusion per ×200 visual field; ++++, 2–10 inclusions per ×200 visual field; +++++, 11–20 inclusions per ×200 visual field; and ++++++, 21 or more inclusions per ×200 visual field. The distribution of NFT was also assessed using Braak stages.[22]

The distributions of amyloid beta-positive senile plaques,[22] Gallyas-positive argyrophilic grains,[23] and α-synuclein-positive Lewy body-related pathologies were assessed according to standardized grading systems.[24,25] TDP-43-positive lesions were assessed in the amygdala, entorhinal cortex, hippocampus, frontal and temporal cortices, and hypoglossal nuclei using TDP-43 immunostaining, and the distribution of TDP-43-positive inclusions in the limbic region was classified into three pathological subtypes (i.e. amygdala, limbic, and temporal types) using the grading system reported previously.[26]

Statistical analysis

The Mann–Whitney *U*-test and Fisher's exact test were used to compare the variables between CBD-NM and CBD-M groups. The data were analyzed with Excel 2010 (Microsoft, Redmond, WA, USA). A *P*-value <0.05 was considered statistically significant.

RESULT

Case reports of CBD-NM cases

Case 1 (CBD-FTD)

The patient, a Japanese woman, showed behavioural changes at the age of 58 years. She was late for work, ate lunch during work, and left the office early. At age 59 years, she was admitted to the department of psychiatry of a general hospital. She had no family or past history of neurological or psychiatric disorders. She showed nystagmus and hyperreflexia in all four extremities. Gait disturbance, rigidity, or tremor was not observed. The Mini-Mental State Examination score was 29/30 and Wechsler Adult Intelligence Scale score was 83 (verbal IQ 90, performance IQ 72). Blood examinations, cerebrospinal fluid examination, and electroencephalogram were normal. Head computed tomography scan showed mild atrophy in the frontotemporal lobe. Although mild stereotypic and repetitive behaviours were found, she was able to perform daily living activities and dementia was not observed. She was admitted to a psychiatric hospital. She was euphoric and also indifferent to her own admission to a psychiatric hospital. Although mild repetitive behaviours gradually increased, memory impairment or disorientation was not observed throughout the course. Nine months after admission, liver dysfunction developed; although electroencephalography demonstrated a 9–10-Hz α rhythm, delirium was not observed. Four months later, she died of liver cancer at age 60.

Case 2 (CBD-FTD)

A Japanese woman, an owner of a restaurant, first showed apathy and indifference at the age of 58

years. She did not do housework, and she became indifferent to money. She was first examined at the department of internal medicine of a general hospital. Her cognitive function score was 17 points as evaluated by the Hasegawa Dementia Scale-first version (range: 0–32.5 points; cut–off: 21.5/22), which correlates well with the Mini-Mental State Examination score;[27] this score indicated the stage of 'predementia'. The subject did not have any motor disturbance. Tendon reflexes in the four extremities were decreased, and Babinski reflex was negative. Blood examinations did not reveal any abnormalities that explained her cognitive impairment. Head computed tomography did not reveal any significant cerebral atrophy or vascular lesions. At the age of 60 years, stereotypic behaviours developed (e.g. she bought a lot of same things every day) and she started smoking. At 61 years, her speech output was reduced, and dysphagia occurred. At 62 years, she was in an apallic state, and contractures in all four extremities were observed. Tendon reflexes in the four extremities were decreased, and Babinski reflex was negative. Cerebrospinal fluid examination was normal. Head computed tomography uncovered cerebral atrophy in the frontal lobes. She died of intestinal bleeding 2 months after admission at age 62.

Case 3 (CBD-unclassifiable)

The patient, a Japanese man, first showed abnormal behaviours at the age of 81 years: he stole belongings of other inpatients while hospitalized for surgery for a ureteral polyp. Due to anger and aggression against his family members, especially at night, he was admitted to a psychiatric hospital. At the first examination, however, he conversed politely with medical staff members. Disorientation in time, place, and person, memory impairment, dementia, and gait disturbance were absent. He had a minimal finger tremor, but no rigidity, akinesia, or postural instability. He had no family or past history of neurological or psychiatric disorders. He frequently got angry at night. Behavioural or verbal stereotypy was absent. Blood and cerebrospinal fluid examinations were normal. He had tactile and visual hallucinations, and often wandered about the ward, singing loudly and repeatedly describing bizarre delusions: 'I killed the head of a tribe' and 'A war broke out'. Five months after admission, rigidity in the right upper limb was first observed and gradually worsened. Rigidity was L-dopa unresponsive. His cognitive function and orientation were gradually impaired. Nine months after admission, dysarthria, dysphasia, and oral dyskinesia developed; the subject was 82 years old. Neck rigidity, right side-predominant contracture, increased tendon reflex, and Babinski sign also developed. He became mute and bedridden, and died of pneumonia at 85 years of age.

Case 4 (CBD-unclassifiable)

The patient was a Japanese man who was 58 years old at the time of death. He had no family history. He began to miss work repeatedly without notice at the age of 41 years. At the age of 51, he began to be regarded with suspicion in his neighbourhood because he often invited several primary school children to his apartment to watch television with him. At age 53, he was admitted to a psychiatric hospital because he repeatedly shouted at night and kicked the door of his apartment. His appearance was bizarre: he wore a cap and sunglasses even during examinations. He had auditory hallucinations, but the thought disorder and blunted affect common in young-onset schizophrenia were mild. Memory impairment or disorientation in time, place, and person was not observed. Neither rigidity nor tremor was found, and tendon reflex in four extremities was normal. Blood and urine examinations, as well as electroencephalography, did not demonstrate any abnormal findings. Auditory hallucination was ameliorated with the use of atypical antipsychotics, although his bizarre behaviours were not changed. Ten months after admission, he was discharged and admitted to a long-term care facility. Thereafter, chronic obstructive pulmonary disease was found, and domiciliary oxygen therapy was initiated. Spasms of the neck began at 54 years and gradually increased in frequency; a dystonic posture, with his head orientated to the right, developed at 55 years of age. Despite respiratory dysfunction, his cognitive function was normal, and he could walk for a short time. He was able to perform activities of daily living sufficiently to remain independent. Parkinsonism or apraxia was absent. He died of gastrointestinal bleeding at 58 years old.

Clinical summary of CBD-NM and CBD-M cases

Two CBD-NM cases were retrospectively included in the CBD-FTD category because these cases devel-

oped behavioural disturbance consistent with FTD (e.g. disinhibition and stereotypy) in the early stage of the course (Table 1).[15] The remaining two CBD-NM cases showed evident psychiatric and behavioural changes without motor disturbance in the early stage, but these could not be classified in any non-motor symptom-predominant clinical subtype reported previously, such as CBD-FTD, CBD- progressive nonfluent aphasia, or CBD-apraxia of speech. Therefore, in this paper, these cases were classified in unclassifiable type (CBD-unclassifiable).

Among the five CBD-M cases, two were classified as CBD-corticobasal syndrome based on unilateral or asymmetrical rigidity, dystonia, apraxia, and cortical sensory signs in the early stage. The remaining three CBD-M cases exhibited Richardson syndrome, which is a classic clinical picture of progressive supranuclear palsy that is characterized by falls and unsteady gait, postural instability, symmetrical axial rigidity, abnormal posture of the neck, bradykinesia, and impaired eye movements; these three cases were classified as CBD-RS. However, one CBD-RS case showed asymmetric parkinsonism (i.e. tremor in the right hand from the early stage), had evident axial rigidity, and repeatedly fell, and another CBD-RS case showed left side-predominant asymmetric cerebral atrophy on magnetic resonance images (Fig. 1).

Among the four CBD-NM cases, none showed gait disturbance in the early stage, and three lacked asymmetric parkinsonism until the middle stage. Two CBD-NM cases lacked contracture and could walk without any support even in the last stage. In contrast, all CBD-M cases showed contracture in all four extremities and eventually became bedridden.

Comparison of pathological findings between CBD-NM and CBD-M cases

Macroscopically, frontal-predominant cerebral atrophy, rather than temporal-predominant cerebral atrophy, was observed in all cases for which data were available (Table 2). Asymmetrical cerebral atrophy was found in three CBD-NM and two CBD-M cases. Brain weight was not statistically different between CBD-NM and CBD-M cases (1241 ± 209 g vs 1198 ± 209 g), but CBD-M cases tended to have more evident atrophy in the frontal lobe, basal ganglia, and corpus callosum than CBD-NM cases (Fig. 2). Histopathologically, neuronal loss with gliosis in the subthalamic nucleus in CBD-M cases (median: 2.0 (25th–75th percentile: 2.0–2.0)) was significantly more severe than that in CBD-NM cases (1.0 (0.5–1.0)) (P = 0.009; Mann–Whitney U-test) (Table 3, Fig. 4). Likewise, the severity of neuronal loss in the substantia nigra in CBD–M cases (3.0 (3.0–3.0)) was significantly higher than that in CBD-NM cases (2.0 (1.75–2.25)) (P = 0.028; Mann–Whitney U-test) (Fig. 4). Although statistically not significant, the severity of neuronal loss in the parietal cortex (2.0 (1.5–2.0)), caudate nucleus (2.0 (2.0–3.0)), putamen (2.0 (2.0–2.0)), and globus pallidus (3.0 (3.0–3.0)) in CBD-M cases tended to be higher than those in CBD–NM cases (0 (0–0.25), 1.0 (1.0–1.5), 1.0 (0.75–1.25) and 1.5 (0.75–2.25), respectively; Mann–Whitney U-test) (Fig. 3).

Tau-positive neurofibrillary changes in the caudate nucleus (median: 1.0 (25th–75th percentile: 1.0–1.0)), subthalamic nucleus (1.0 (0.5–1.0)) and pontine nucleus (1.0 (1.0–1.0)) in CBD-M cases tended to be more severe than those in CBD-NM cases (0.35 (0.15–0.625), 0.2 (0.15–0.4) and 0.35 (0.15–0.625), respectively) (Table 4, Figs 3,4). However, the differences did not reach statistical significance (Mann–Whitney U-test) (Table 4). Astrocytic plaques were frequently observed in the frontal cortex, caudate nucleus, putamen, and globus pallidus in both groups (Table 4). The severity of astrocytic plaques of the two groups was comparable (Mann–Whitney U-test).

The coexistence of argyrophilic grain disease (AGD) was seen in all CBD cases. The severity of AGD was not significantly different between CBD-NM and CBD-M cases (Table 2). Braak NFT stage and Braak senile plaque stage of the two groups were also comparable. One CBD-M case had TDP-43 pathology (limbic type), and another CBD-M case had minimal Lewy body-related pathology (brain-stem type). A small lacuna was observed in two CBD-NM cases (cases 3 and 4), while no case of CBD-M case had a vascular lesion in the cerebral cortex, basal ganglia, or brain stem nuclei.

DISCUSSION

This is the first study to demonstrate that the neuronal loss in the subthalamic nucleus and substantia nigra in CBD-NM cases, which initially developed psychiatric and behavioural symptoms without motor disturbance, may be less severe than that in CBD-M cases, which initially developed motor disturbance, such as parkinsonism, gait disturbance, and falling as initial symptoms. Of the four CBD-NM cases, all lacked

Table 1 Clinical features in all subjects

	CBD-NM cases with psychiatric or behavioural onset				CBD-M cases with motor symptoms onset				
Case	1	2	3	4	5	6	7	8	9
Clinical diagnosis	Pick's disease	Pick's disease	Senile-onset psychosis with delirium	Schizophrenia	PSP	AD with aphasia	CBD	PSP	PSP
Sex	F	F	M	M	M	F	M	M	M
Age at onset (years)	58	58	81	41	55	62	65	60	40
Age at death (years)	60	62	85	58	58	66	67	65	45
Duration of illness (years)	2	4	5	18	4	5	2	5	6
Family history	–	–	–	–	–	–	–	–	–
Initial symptoms	Self-centred behaviours, decline in personal hygiene	Apathy, forgetfulness	Delirium-like irritability and aggression at night	Social withdrawal, apathy	Repeated falls, gait disturbance, dysarthria, forgetfulness, tremor and weakness in right hand	Bradykinesia, speech difficulty	Difficulty using right hand, speech difficulty	Bradykinesia, delirium, falls, tremor, depression	Repeated falls, reduced speech output, forgetfulness depression
Clinical symptoms at the first examination									
Duration from onset	11 m	2 m	5 m	11 y	2 y	1 y	10 m	4 y	4 y
Rigidity	–	–	–	–	Axial and limb rigidity	Limb rigidity (R)	Axial and limb rigidity (R > L)	–	Axial and limb rigidity
Tremor	–	–	±†	–	+ (R)	–	–	–‡	–
Gait disturbance	–	–	–	–	+	–	+	+	+
Postural instability	–	–	–	–	+	–	+	+	+
Eye movement impairment	n.d.	–	n.d.	–	Vertical gaze palsy	n.d.	Vertical gaze palsy, akinesia	Vertical gaze palsy	Vertical gaze palsy
Other symptoms	Hyperreflexia	–	–	Auditory hallucination, decline in personal hygiene	Dysarthria, tremor in right arm, akinesia		Babinski signs (R, L), limb kinetic apraxia (R > L)	Apathy	Hypersexuality
Clinical symptoms during course									
Rigidity	–	–	+ (R > L)§	–	+	+ (R)	+	–	+
Tremor	–	–	+ (R > L)		+	–	–	+	–
Gate disturbance	–	+	+	–	+	+	+	+	+
Eye movement impairment	–	–	n.d.	–	Vertical gaze palsy	+¶	Supranuclear gaze palsy (upward, left)	Vertical gaze palsy	Vertical gaze palsy
Hyperreflexia	+	–	+	–	–	–	+	–	–
Babinski sign	n.d.	–	+	n.d.	–	n.d.	+ (R, L)	n.d.	–
Asymmetry in motor disturbances	–	–	+	–	+	+	+	–	–
Effectiveness of L-dopa	n.u.	n.u.	–	n.u.	–††	n.d.	+	+	–
Dementia	–	+‡‡‡	+§§	–	+	+§§	+	+	+§§
Other symptoms	Disinhibition, stereotypy, euphoria	Disinhibition, stereotypy	Aggression, visual hallucination	Auditory hallucination	Palmomental reflex	Depression	Aggression	Depression	Forced grasping, palmomental reflex, disinhibition stereotypy depression
Clinicopathological classification of CBD	CBD-FTD	CBD-FTD	CBD-unclassifiable	CBD-unclassifiable	CBD-RS	CBD-CBS	CBD-CBS	CBD-RS	CBD-RS

†Minimal finger tremor was seen after neuroleptic treatment to ameliorate remarkable aggression. ‡Tremor disappeared after anti-Parkinson's drug prescribed by another physician. §Rigidity was observed 10 months after onset. ¶A total vertical and horizontal gaze palsy was observed 3 years after onset. ††Cognitive function and dysarthria, but not other motor disturbances, were improved after L-dopa use. ‡‡Dementia occurred prior to motor disturbance. §§Dementia developed with motor disturbance. –, absent; +, present; AD, Alzheimer's disease; CBD, corticobasal degeneration; CBD-M, corticobasal degeneration initially showing motor symptoms as initial symptoms; CBS, corticobasal syndrome; F, female; FTD, frontotemporal dementia; L, left; M, male; m, month; n.d., not described; n.u., not used; NM, initially showing non-motor symptoms without parkinsonism or falls; PSP, progressive supranuclear palsy; R, right; RS, Richardson syndrome; y, year.

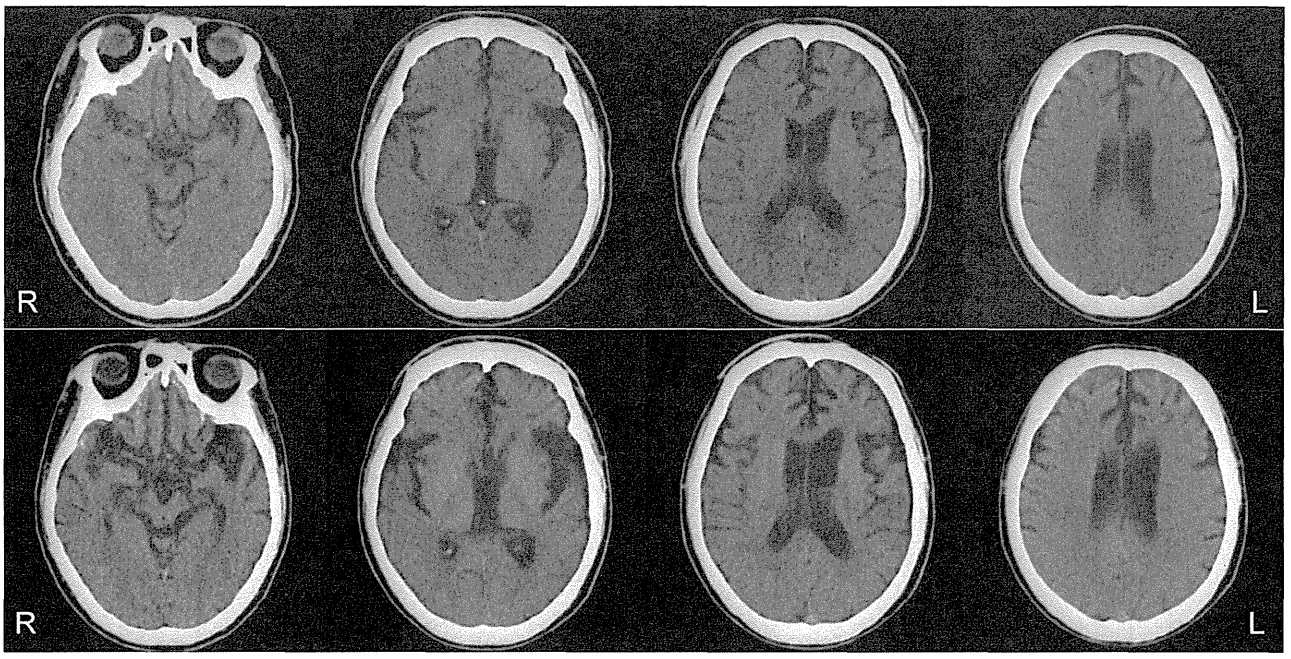

Figure 1 Brain computed tomography scan images in a CBD-M case (case 9) that was clinically diagnosed with PSP 4 years (the upper layer) and 5 years after onset (the lower layer). Left side-predominant frontotemporal atrophy and dilation of the third ventricle are seen. Cortical atrophy is more severe in the frontal lobes than in the temporal lobes. The midbrain was also evidently atrophic (the lower layer). CBD-M, corticobasal degeneration initially showing motor symptoms as initial symptoms; L, left; PSP, progressive supranuclear palsy; R, right.

parkinsonism, gait disturbance, or postural instability in the early stage, three lacked asymmetric parkinsonism until the middle stage, and two lacked contracture and could walk without support even in the last stage. These features contrasted with the fact that all of the CBD-M cases presented with contractures of all four extremities and became bedridden. The difference in these clinical and pathological features between CBD-NM and CBD-M cases could not be explained by disease duration because it did not significantly differ between the two groups. Recent studies demonstrated that pathological CBD cases do not always exhibit asymmetric parkinsonism or limb kinetic apraxia as an initial symptom, but they may have various clinical presentations, including Richardson syndrome, a representative clinical syndrome of progressive supranuclear palsy.[15] Our results suggest that the distribution of degenerative changes may differ between CBD cases with and without early motor disturbance and that some CBD cases can lack motor disturbance not only in the early stage but also in the last stage of the course.

In our study, the neuronal loss in the substantia nigra and subthalamic nucleus in CBD-M cases was significantly more severe than those in CBD-NM cases. These findings suggest that neurons in the substantia nigra and subthalamic nucleus may be relatively spared in number throughout the course of CBD cases that lack motor disturbance at least in the early stage. Considering that these nuclei are closely associated with motor functions (e.g. parkinsonism), minimal involvement of these regions may be concordant with the absence of motor disturbance in three of the four CBD-NM patients, even in the middle of the course. In contrast, our study did not demonstrate a significant difference between CBD-NM and CBD-M cases in the severity of tau pathology in any region examined. This discrepancy may be explained by the small sample size and the ceiling effect of severe tau pathology. In various proteinopathies, including tauopathies, the development of clinical symptoms is often more closely associated with the severity of neuronal loss rather than with the accumulation of abnormal proteins, which may be downstream in the neurodegenerative process.[21,28,29] Indeed, our results were consistent with the view that the abnormal accumulation of tau precedes loss of neurons in each anatomical region (Tables 3,4, Figs 3,4).

Table 2 Pathological features in all subjects

	CBD-NM cases with psychiatric or behavioural onset				CBD-M cases with motor symptoms onset					
Case	1	2	3	4	5	6	7	8	9	*P*-value
Brain weight Macroscopic atrophy	1320 g F (R > L)	987 g F (R > L)	1180 g F (L > R)	1480 g F (mild)	1260 g F	1000 g F > T, Bs (L > R)	1300 g F (L > R)	1280 g n.a	1150 g F > T, Bs	0.624
Depigmentation in the substantia nigra	+	n.a.	n.a.	–	+	+	+	n.a.	+	
Braak NFT stage	1	1	3	2	1	3	3	1	2	0.694
Braak senile plaque stage	0	A	C	0	0	A	0	0	0	0.305
Argyrophilic grains	1	1	3	1	1	3	1	1	2	0.769
Lewy body-related pathology	–	–	–	–	–	–	–	Brain stem type	–	1.000
TDP-43 pathology	–	–	–	–	–	–	–	–	Limbic type	1.000

Bs, brain stem; CBD-M, corticobasal degeneration initially showing motor symptoms as initial symptoms; CBD-NM, corticobasal degeneration initially showing non-motor symptoms without parkinsonism or falls; F, frontal lobe; n.a., not available; NFT, neurofibrillary tangles; P, parietal lobe; T, temporal lobe; transactive response DNA-binding protein of 43kDa; TDP-43.

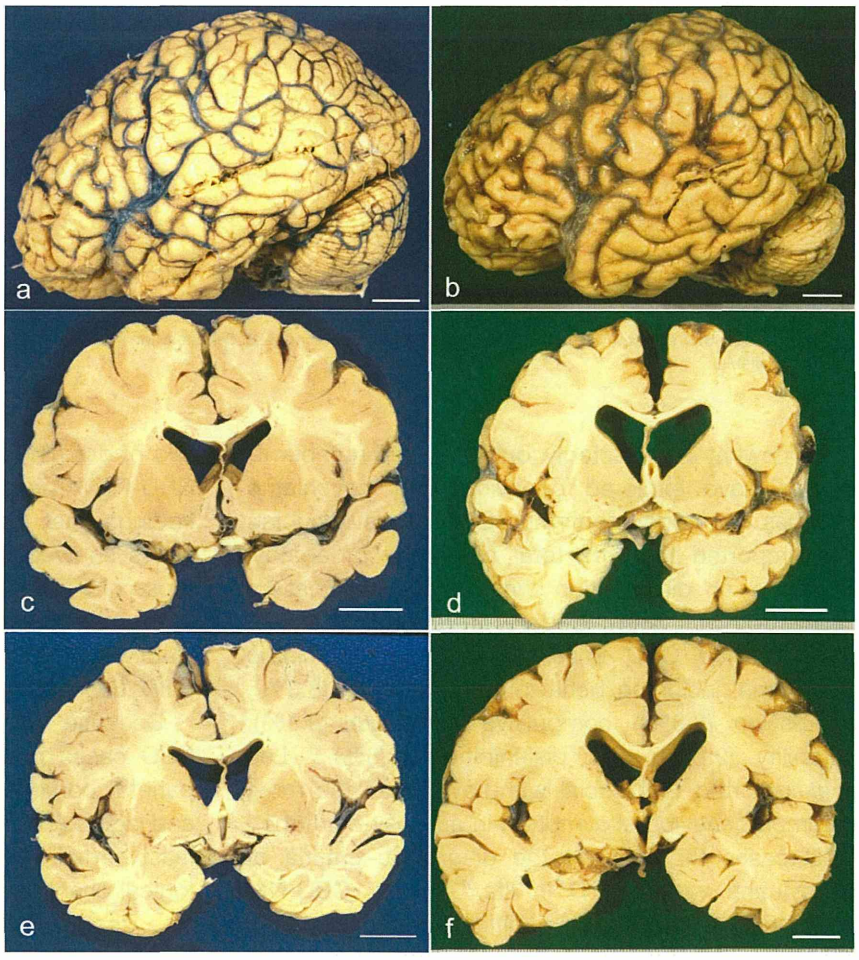

Figure 2 Macroscopic findings in cases of (a,c,e) CBD-NM (case 1) and (b,d,f) CBD-M (case 6). (a,c,e) In this CBD-NM case, (a) frontal atrophy is mild, and (c) the corpus callosum and (e) striatum are also spared in volume. (b,d,f) Evident atrophy in the frontal cortex, including (b) the precentral gyrus, (d) corpus callosum, and (f) striatum is seen in a CBD-M case. All scale bars: 2 cm. CBD-M, corticobasal degeneration initially showing motor symptoms as initial symptoms; CBD-NM, corticobasal degeneration initially showing non-motor symptoms without parkinsonism or falls.

Table 3 Distribution of neuronal loss with gliosis in all subjects

	CBD-NM cases with psychiatric or behavioural onset				CBD-M cases with motor symptoms onset					
Case	1	2	3	4	5	6	7	8	9	*P*-value
Superior frontal gyrus	+	++	+	–	+	++	++	+	++	0.227
Middle frontal gyrus	+	++	+	–	–	++	+++	+	++	0.372
Inferior frontal gyrus	+	++	+	–	–	++	+	n.a.	+	1.00
Motor cortex	n.a.	++	–	–	+	++	+	+	+	0.69
Superior temporal gyrus	+	–	–	–	+	–	–	+	–	0.654
Middle temporal gyrus	+	–	–	–	+	+	+	+	–	0.119
Inferior temporal gyrus	+	–	–	–	+	+	+	–	–	0.322
Parietal cortex	–	+	–	–	–	++	++	n.a.	++	0.082
Occipital cortex	–	–	–	–	–	–	–	–	–	
Hippocampal CA1 and subiculum	–	–	–	–	–	–	–	–	–	
Amygdala	+	+	+++	++	++	++	++	++	+++	0.342
Caudate nucleus	+	+++	+	+	++	+++	+++	++	++	0.121
Putamen	+	++	+	–	++	++	++	+	++	0.100
Globus pallidus	+	+++	++	–	++	+++	+++	+++	+++	0.079
Thalamus	+++	+	++	++	++	+++	+++	++	+	0.694
Subthalamic nucleus	+	n.a.	+	–	++	++	++	++	++	0.009*
Oculomotor nucleus	+	+	–	–	+	+	+	+	–	0.371
Substantia nigra	++	+++	++	+	+++	+++	+++	+++	+++	0.028*
Frontopontine tract at level of cerebral peduncle	–	+	–	–	+	+	–	n.a.	+	0.185
Locus coeruleus	+	–	+	–	+	+	+	++	–	0.273
Pontine nucleus	+	–	–	+	–	–	–	–	–	0.091
Dorsal vagal nucleus	–	–	–	–	–	–	–	–	–	
Inferior olivary nucleus	+	–	–	–	++	–	–	+	–	0.558
Corticospinal tract										
At level of cerebral peduncle	–	–	–	–	–	–	–	–	–	
At level of medulla oblongata	–	–	–	–	–	+	–	–	–	0.371
Dentate nucleus in cerebellum	+	+++	+	–	++	++	–	++	++	0.518
Cerebellar cortex	–	+	–	–	–	–	–	–	–	0.263

*$P < 0.05$.

–, no neuronal loss; +, mild neuronal loss; ++, moderate neuronal loss; +++, severe neuronal loss; CA1, cornu ammonis 1; CBD-M, corticobasal degeneration initially showing motor symptoms as initial symptoms; CBD-NM, corticobasal degeneration initially showing non-motor symptoms without parkinsonism or falls; n.a., not available.

Somewhat unexpectedly, only a limited number of studies have explored behavioural or psychiatric changes in autopsy-confirmed CBD cases. Wenning *et al.* reported that the total frequency of apathy, irritability, or disinhibition was 58%, and that of depression was 38%.[5] Geda *et al.* reported that 8 of 36 autopsied CBD cases (22%) had psychiatric symptoms, including behavioural dyscontrol (8.3%), depression (8.3%), compulsive behaviour (8.3%), irritability (2.8%), and disinhibition (2.8%).[30] Lee *et al.* reported that social withdrawal was the most common behavioural symptom in autopsy-confirmed CBD cases that fulfilled the diagnostic criteria of behavioural variant FTD in life.[31] In our CBD-NM and CBD-M cases, disinhibition, stereotypy, and depression were the most frequent psychiatric symptoms, followed by aggression, apathy, self-centred behaviour, social withdrawal, and euphoria. Therefore, two of our nine CBD cases (22%) were classified as CBD-FTD. These findings are consistent with previous findings that some pathologically confirmed CBD cases showed behavioural changes consistent with those of FTD:[5,10–12,14,30–34] Ling *et al.* reported that only 1 of 19 autopsied CBD case (5%) showed FTD,[14] and Lladó *et al.* noted that three of eight autopsy cases of CBD (38%) showed FTD.[33]

Because tau pathology in the cerebral cortex in CBD cases preferentially occurs in the frontal and parietal cortices, the personality change, irritability, and aggression observed in CBD cases may be at least partially explained by the distribution of histological changes in the cerebral cortex. However, it is also known that AGD, which initially occurs in the amygdala and adjacent limbic cortex, often coexists with CBD pathology. Indeed, all of our CBD cases had various degrees of AGD associated with neuronal loss

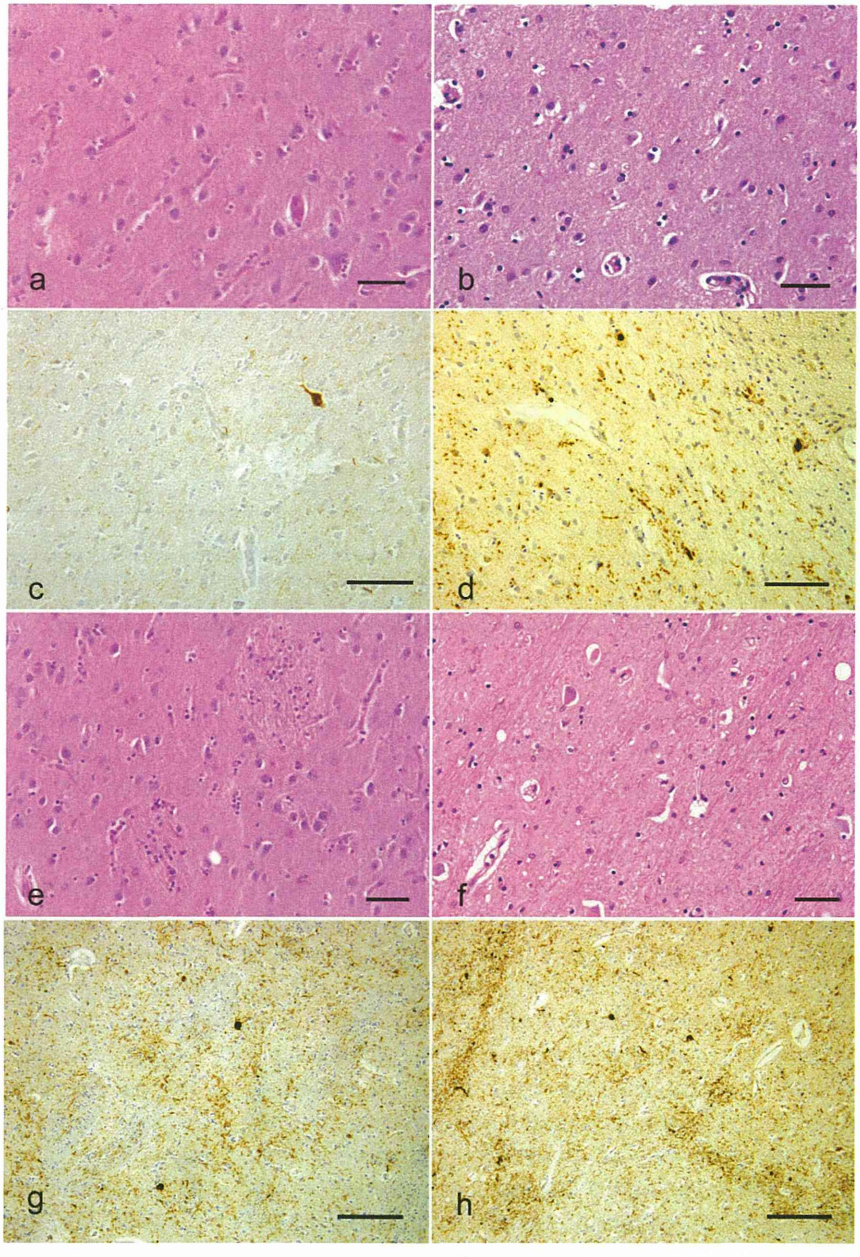

Figure 3 (a–d) Microscopic findings in the caudate nucleus in (a,c) a CBD-NM case (case 3) and (b,d) a CBD-M case (case 5). In the CBD-NM case, (a) neuronal loss was minimal, and (c) tau pathology was mild. In the CBD-M case, (b) neuronal loss with gliosis and (d) tau pathology were moderate. (e–h) Microscopic findings in the putamen in (e,g) a CBD-NM case (case 3) and (f,h) a CBD-M case (case 5). (g,h) Although tau pathology was comparably severe in both cases, neuronal loss with gliosis was less severe in (e) the CBD-NM case than in (f) the CBD-M case. (a,b,e,f) Haematoxylin–eosin stain. (c,d,g,h) AT8 immunohistochemistry. All scale bars: 50 μm. CBD-M, corticobasal degeneration initially showing motor symptoms as initial symptoms; CBD-NM, corticobasal degeneration initially showing non-motor symptoms without parkinsonism or falls.

in the amygdala. Previous studies have demonstrated that some AGD cases having dementia show characteristic psychiatric symptoms, including irritability and aggression.[35] Therefore, it is likely that, besides CBD pathology, the coexistence of argyrophilic grains in the limbic systems, including the amygdala, may be associated with the occurrence of psychiatric and behavioural symptoms in CBD cases. The relationship between AGD, neuronal loss in the limbic region, and the occurrence of psychiatric and behavioural features in CBD cases should be explored in further clinicopathological studies.

Previous studies have demonstrated that visual and auditory hallucinations and delirium may be rare in CBD cases.[14,34,36] Therefore, it is noteworthy that two of our four CBD-NM cases had hallucinations and delusions. In case 3, emotional lability and irritability with remarkable aggression, mainly at night, were observed from the early stage. Because neither L-dopa nor psychotropic drugs had been used yet,