



Conventional magnetic resonance imaging key features for distinguishing pathologically confirmed corticobasal degeneration from its mimics: a retrospective analysis of the J-VAC study

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Abstract

Purpose Due to the indistinguishable clinical features of corticobasal syndrome (CBS), the antemortem differentiation between corticobasal degeneration (CBD) and its mimics remains challenging. However, the utility of conventional magnetic resonance imaging (MRI) for the diagnosis of CBD has not been sufficiently evaluated. This study aimed to investigate the diagnostic performance of conventional MRI findings in differentiating pathologically confirmed CBD from its mimics.

Methods Semiquantitative visual rating scales were employed to assess the degree and distribution of atrophy and asymmetry on conventional T1-weighted and T2-weighted images. Additionally, subcortical white matter hyperintensity (SWMH) on fluid-attenuated inversion recovery images were visually evaluated.

Results In addition to 19 patients with CBD, 16 with CBD mimics (progressive supranuclear palsy (PSP): 9, Alzheimer's disease (AD): 4, dementia with Lewy bodies (DLB): 1, frontotemporal lobar degeneration with TAR DNA-binding protein of 43 kDa (FTLD-TDP): 1, and globular glial tauopathy (GGT): 1) were investigated. Compared with the CBD group, the PSP-CBS subgroup showed severe midbrain atrophy without SWMH. The non-PSP-CBS subgroup, comprising patients with AD, DLB, FTLD-TDP, and GGT, showed severe temporal atrophy with widespread asymmetry, especially in the temporal lobes. In addition to over half of the patients with CBD, two with FTLD-TDP and GGT showed SWMH, respectively.

Conclusion This study elucidates the distinct structural changes between the CBD and its mimics based on visual rating scales. The evaluation of atrophic distribution and SWMH may serve as imaging biomarkers of conventional MRI for detecting background pathologies.

Keywords Corticobasal degeneration · Corticobasal syndrome · Magnetic resonance imaging · Asymmetry · Subcortical white matter hyperintensity

Introduction

Corticobasal degeneration (CBD) is a neurodegenerative disorder characterized by the presence of cortical and striatal hyperphosphorylated 4-repeat (4R) tau deposition,

especially astrocytic plaques and thread-like lesions, in the white matter and gray matter, accompanied by neuronal loss in the cortical regions and substantia nigra [1]. In contrast to the tuft-shaped astrocytes observed in progressive supranuclear palsy (PSP), astrocytic plaques are predominantly distributed in the prefrontal and premotor cortices in CBD [2].

As a member of the frontotemporal lobar degeneration (FTLD) spectrum, CBD exhibits diverse clinical phenotypes

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[3]. In addition to classical symptoms like ideomotor and limb-kinetic apraxia, alien limb, limb dystonia, myoclonus, and L-dopa unresponsive rigidity and bradykinesia (i.e., corticobasal syndrome [CBS]), patients with CBD may manifest various clinical manifestations including PSP syndrome, frontal behavioral-spatial syndrome, non-fluent/agrammatic variant of primary progressive aphasia, posterior cortical atrophy syndrome, and Alzheimer's-like dementia [4, 5]. Adding to the complexity, other neurodegenerative disorders such as PSP, Alzheimer's disease (AD), TAR DNA-binding protein of 43 kDa (TDP-43) proteinopathy, and dementia with Lewy bodies (DLB) can present with CBS indistinguishable from that observed in CBD [5–7]. Even with the introduction of new diagnostic criteria, accurately diagnosing CBD remains a challenge [4, 8, 9]. Consequently, the rate of correct antemortem diagnosis of CBD remains low, necessitating neuropathological examination for the accurate diagnosis of this condition.

Considering the diagnostic challenges based on clinical manifestations, the identification of objective biomarkers to differentiate these disorders becomes imperative. For the diagnosis of AD, positron emission tomography (PET) is utilized to detect amyloid- and tau-related pathologies [10, 11]. The detection of amyloid positivity is useful in distinguishing CBS caused by AD pathologies from CBS caused by non-AD pathologies [12]. Cardiac ^{123}I -MIBG scintigraphy is a valuable method for assessing sympathetic denervation in patients with Lewy body disease [13, 14]. However, these methods are expensive and invasive owing to the associated radiation exposure. Furthermore, unlike AD and DLB, useful biomarkers for CBD, PSP, and TDP-43 proteinopathy have not yet been established. Compared with PET and scintigraphy, magnetic resonance imaging (MRI) serves as a readily accessible and noninvasive biomarker in routine clinical practice. MRI aids in the differentiation of neurodegenerative disorders by identifying the characteristic signal changes and atrophic patterns [15]. Therefore, investigating the utility of conventional MRI in discriminating between patients with CBD and those with CBS due to non-CBD pathologies (CBD mimics) is a relevant and important research endeavor. This retrospective study aimed to evaluate the diagnostic accuracy of MRI findings routinely used in clinical practice in patients with pathologically confirmed CBD and CBD mimics.

Materials and methods

This study was conducted as a part of the Japanese validation study of the consensus criteria for CBD diagnosis (J-VAC study) within the framework of the Research Committee of CNS Degenerative Diseases and Research on Policy Planning and Evaluation for Rare and Intractable Diseases, Health, Labour, and Welfare Sciences Research Grants, the Ministry of Health, Labour and Welfare, Japan. A majority of the

participating institutions in the J-VAC study were specialized in managing movement disorders, with the clinical diagnosis made by neurology specialists. Informed consent was obtained from the patients or bereaved families as an opt-out option on the website. The study was approved by the Ethics Committee of the National Hospital Organization Higashinagoya National Hospital (#27–8) and each institute, and was conducted in strict compliance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Study population

The J-VAC study included 32 patients with CBD pathologies and 32 patients with CBS due to non-CBD pathologies (CBD mimics) from 48 institutions between 1996 and 2018 [16]. Patients with CBD mimics met the diagnostic criteria for CBS defined by the Mayo Clinic or the Cambridge [6, 17]. From this cohort, participants who underwent MRI, which included at least T1-weighted image (T1WI) and T2-weighted image (T2WI) scans, were recruited. Patients with insufficient MRI data (e.g., lack of whole-brain coverage) and with destructive lesions (e.g., cerebrovascular disorders and neoplasms), which could cause significant cerebral atrophy and signal changes on MRI scans, were excluded. As it was difficult to evaluate the distribution of atrophic changes, participants who underwent MRI at the advanced stage only were also excluded.

Neuropathological analysis of CBD and CBD mimics

Formalin-fixed, paraffin-embedded glass slide specimens that were subjected to hematoxylin–eosin staining, Klüver–Barrera staining, Gallyas–Braak (G-B) silver staining, phosphorylated tau (AT8) staining, and amyloid β protein immunohistochemistry were reviewed by a group of well-experienced neuropathologists as previously described [16]. The neuropathological diagnoses of CBD, PSP, FTLTDP, AD, and DLB were made according to the established criteria [1, 18–21].

MRI protocol and visual analyses

Owing to the retrospective nature of this study involving data from various institutions, the MRI protocols employed were not standardized. As a result, the parameters used in the study such as the magnetic field strength, repetition time, echo time, slice thickness, and field of view varied across the database. Therefore, the basic sequences, including T1WI, T2WI, and fluid-attenuated inversion recovery (FLAIR) images, were visually evaluated using the semiquantitative visual rating scales outlined below.

The four-point global cortical atrophy (GCA) scale was utilized to evaluate the degree of atrophy in the frontal, temporal, parietal, and occipital lobes [22]. The score was determined by visually evaluating the axial T1WIs. To assess the degree of atrophy in the hippocampus, the five-point Scheltens' medial temporal atrophy (MTA) scale was evaluated mainly on coronal T1WIs [23]. Using these methods, assessments were conducted separately for each hemisphere, with the final score being the sum of bilateral hemispheres.

In addition to the well-established GCA and MTA scales, newly devised rating scales were utilized to evaluate the presence of midbrain atrophy and asymmetric atrophy. The degree of midbrain atrophy was assessed using a three-point scale (0 = normal, 1 = mild, and 2 = severe) primarily on sagittal T1WIs (Fig. 1). Mild midbrain atrophy indicated a slight reduction in the anteroposterior and/or superoinferior diameters. By contrast, a definitive decrease in these diameters was classified as severe midbrain atrophy. The degree of asymmetry in the frontal, temporal, parietal, and occipital lobes, along with the cerebral peduncle, was assessed using a three-point scale (0 = normal, 1 = mild, and 2 = severe) on axial T1WIs (Fig. 2). Severe asymmetry indicated the definite dilation of the sulcus and/or narrowing of the gyrus between the two hemispheres. Conversely, a case with unremarkable asymmetry was rated as mild.

In addition, the presence/absence of subcortical white matter hyperintensity (SWMH) was visually evaluated on axial FLAIR images [24, 25]. Considering that hyperintensity in the periventricular and deep white matter can be attributed to aging and cerebral small vessel disease (i.e., leukoaraiosis), signal changes confined to the subcortical white matter were exclusively evaluated (Fig. 3).

The aforementioned visual rating scores were independently evaluated by two raters, a neuroradiologist and a neurologist, with 20 years (rater 1, K.S.) and 39 years (rater 2, A.M.T.) of experience in neurodegenerative disorder neuroradiology, respectively. In cases of interobserver disagreement, final decisions were reached by unanimous consensus. Except for the research purpose, these two raters were blinded to the clinical and pathological diagnoses.

Statistical analysis

Statistical analyses were performed using SPSS software (version 24.0; IBM Corp., Armonk, NY, USA). Student's t-test was employed to compare normally distributed data, while the Mann–Whitney U test and Kruskal–Wallis test were employed to compare non-normally distributed data. Fisher's exact test was used for nominal variables. When multiple comparisons showed a significant difference, an unpaired t-test or Mann–Whitney U test was also performed. The resulting *p* values were corrected using the Bonferroni method, and a *p* value of < 0.05 was considered significant.

Results

Participants' data

First, 10 patients with CBD and 12 patients with CBD mimics were excluded from the J-VAC study cohort due to the unavailability of MRI data and the presence of large destructive lesions. Additionally, one patient with CBD mimics comorbid with glioblastoma was excluded. Second, three

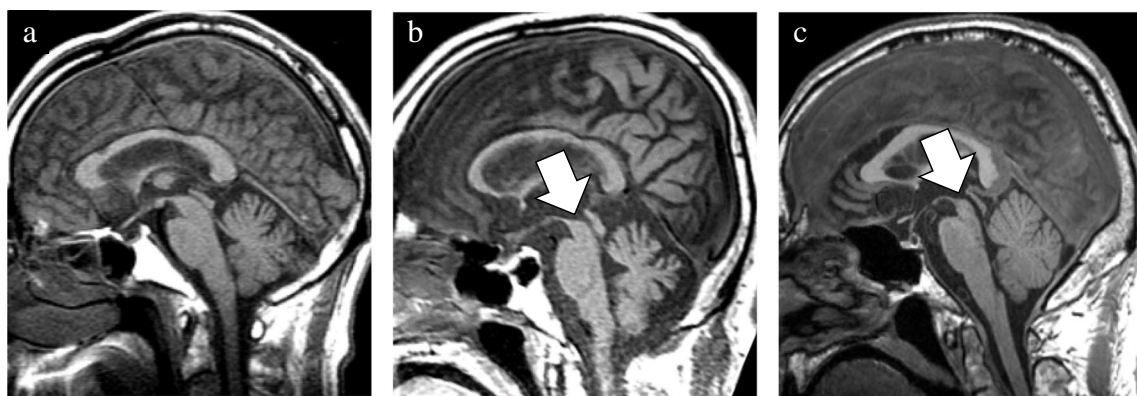


Fig. 1 Visual rating scale of midbrain atrophy. The degree of midbrain atrophy was assessed using the three-point scale (0 = normal, 1 = mild, and 2 = severe). Compared with the normal midbrain in a patient with pathologically confirmed AD (a), mild midbrain atrophy showing a slight decrease in anteroposterior and/or superoinferior

diameters was observed in a patient with pathologically confirmed CBD (b). By contrast, a definite decrease in these diameters was classified as severe midbrain atrophy in a patient with pathologically confirmed PSP (c). AD, Alzheimer's disease; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy

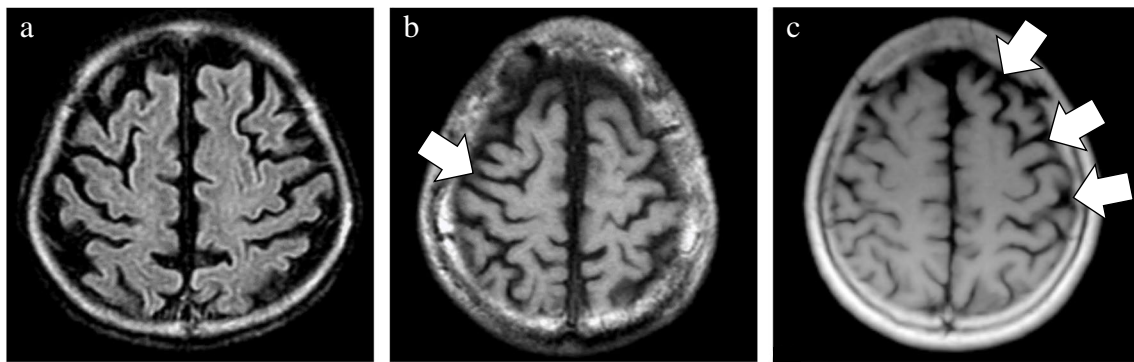


Fig. 2 Visual rating scale of asymmetric atrophy. The degree of asymmetry in the frontal, temporal, parietal, and occipital lobes, and cerebral peduncle was assessed using a three-point scale (0 = normal, 1 = mild, and 2 = severe). In contrast to no obvious asymmetry in a

patient with pathologically confirmed DLB (a), mild asymmetry and severe asymmetry were observed in patients with pathologically confirmed PSP (b) and CBD (c). CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; PSP, progressive supranuclear palsy

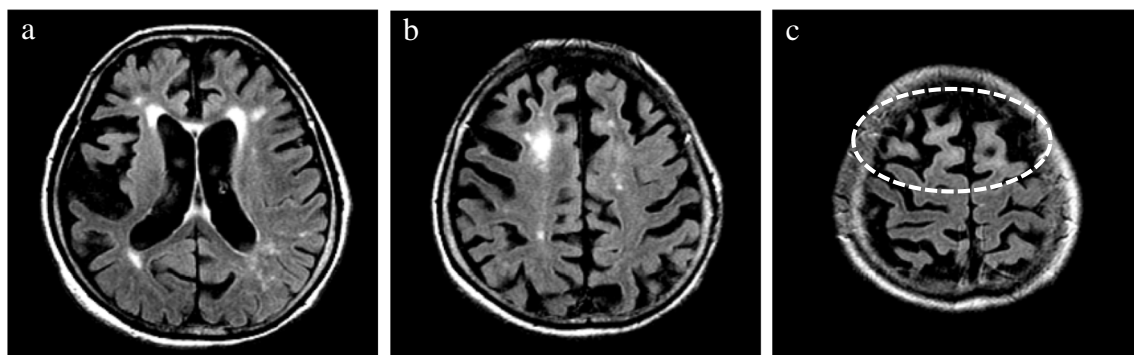


Fig. 3 Evaluation of SWMH. The presence/absence of hyperintensity confined to the subcortical white matter (i.e., SWMH) was evaluated on an axial FLAIR image. In contrast to other lobes at lower convexity level (a, b), distinct SWMH of the bilateral frontal lobes at high

convexity (c) was observed in a patient with pathologically confirmed CBD. CBD, corticobasal degeneration; SWMH, subcortical white matter hyperintensity

patients with CBD and three patients with CBD mimics were also excluded as only MRI data at the advanced stage were available. Ultimately, the study included a total of 19 patients with CBD and 16 patients with CBD mimics (Fig. 4).

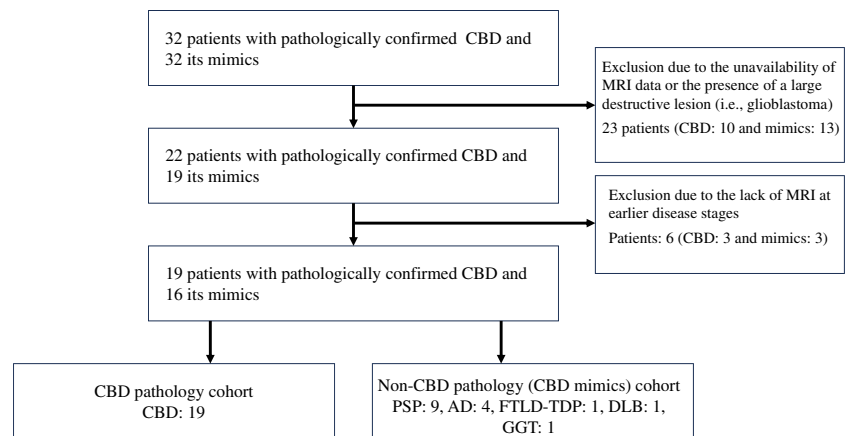
Table 1 displays the pertinent clinicopathological characteristics of all participants. The antemortem clinical diagnosis of the CBD group predominantly included CBD or PSP. Similarly, CBD and CBS were the most prevalent clinical diagnoses in the CBD mimics group. The post-mortem pathological diagnoses of the CBD mimics group comprised PSP (9 patients), AD (4 patients), FTLT-TDP (1 patient), DLB (1 patient), and globular glial tauopathy (GGT, 1 patient). Owing to the retrospective nature of the study, quantifying the participants' neurological findings using advanced scales such as the unified Parkinson's

disease rating scale part III was challenging. Alternatively, the ratio of independent walking at the time of MRI scan was compared between the CBD group and CBD mimics group. No significant differences were observed in sex, age at MRI scan, disease duration at MRI scan, ratio of independent walking at MRI scan, or the time from the MRI scan until death between the CBD group and CBD mimics group.

MRI analysis data

As the main neuropathology of more than half of the patients in the CBD mimics group was PSP, this group was further categorized into PSP-CBS and non-PSP-CBS subgroups. The MRI findings in the CBD and two CBD

Fig. 4 Flow chart showing the inclusion and exclusion of patients with pathologically confirmed CBD and those with mimics. AD, Alzheimer's disease; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; FTLT-TDP, frontotemporal lobar degeneration with TAR DNA-binding protein of 43 kDa; GGT, globular glial tauopathy; PSP, progressive supranuclear palsy



mimics subgroups are shown in Table 2. Compared with the PSP-CBS subgroup, the CBD group tended to show a higher SWMH ratio (56% vs 0%; $p = 0.060$). In the CBD group, SWMH was exclusively distributed in the frontal or parietal lobe at high convexity. Its sensitivity, specificity and accuracy to diagnose CBD were 56%, 86%, and 69%, respectively. Compared with the non-PSP-CBS subgroup, the CBD subgroup displayed relatively lower temporal GCA score and degree of asymmetry in the temporal and occipital lobes (0.5 [0.3–1.0] versus 1.5 [1.0–2.3], 0.0 [0.0–0.5] versus 1.0 [0.0–1.5], and 0.0 [0.0–0.0] versus 0.0 [0.0–0.0]; $p = 0.073$, $p = 0.073$ and $p = 0.082$, respectively). Confusable SWMH was detected in one patient with FTLT-TDP and one with GGT. Among the CBD mimics subgroups,

the non-PSP-CBS subgroup showed higher frontal, temporal, and occipital lobe GCA scores (1.5 [1.0–2.5] versus 0.5 [0.5–1.0], 1.5 [1.0–2.3] versus 0.0 [0.0–0.5], and 0.5 [0.0–1.0] versus 0.0 [0.0–0.0]; $p = 0.043$, $p = 0.011$, and $p = 0.019$, respectively). By contrast, the degree of mid-brain atrophy was most severe in the PSP-CBS subgroup (2.0 [1.0–2.0] versus 0.0 [0.0–0.3], and 2.0 [1.0–2.0] versus 0.0 [0.0–0.0]; $p = 0.016$ and $p = 0.014$, respectively). The (weighted) kappa of the above-mentioned visual analyses for the interrater reliability of the two raters was high, ranging from 0.77 to 1.00 in this study. The representative MRI findings of patients with pathologically confirmed CBD and CBD mimics are presented in Figs. 5, 6, 7 and 8.

Table 1 Participants' characteristics

	CBD pathology	CBS with non-CBD pathology (CBD mimics)	p value
Number	19	16	N.A
Male/Female	9/10	13/3	0.08 ^a
Diagnosis	Clinical diagnosis	Main neuropathology	N.A
	CBD/CBS 8	PSP 9	
	PSP 7	AD 4	
	FTD 2	FTLT-TDP 1	
	AD 1	DLB 1	
	CVD 1	GGT 1	
Age at MRI scan (y)	69.2 ± 6.9	73.2 ± 8.3	0.13 ^b
Disease duration at MRI scan (y)	2.4 ± 2.0	3.6 ± 2.3	0.13 ^b
Ratio of independent walking at MRI scan ^d	43%(6/14)	50%(6/12)	0.51 ^a
Time from MRI scan until death (y)	5.0 (2.3, 5.8)	3.0 (2.0, 6.0)	0.57 ^c

Data are expressed as absolute number, mean ± standard deviation, or median (1st quartiles and 3rd quartiles)

AD Alzheimer's disease, CBD corticobasal degeneration, CBS corticobasal syndrome, CVD cerebrovascular disorder, DLB dementia with Lewy bodies, FTD frontotemporal dementia, FTLT frontotemporal lobar degeneration, GGT globular glial tauopathy, MRI magnetic resonance imaging, N.A. not applicable, PSP progressive supranuclear palsy, TDP-43 TAR DNA-binding protein-43, y year

^aFisher's exact test; ^bStudent's t-test; ^cMann-Whitney U test; ^dClinical course was not available in five patients with CBD and four patients with CBD mimics

Table 2 MRI findings

	CBD pathology	CBS with non-CBD pathology (CBD mimics)		
		PSP-CBS	non-PSP-CBS	<i>p</i> value
GCA scale				
Frontal lobe	1.0 (1.0–1.5)	0.5 (0.5–1.0)	1.5 (1.0–2.5) ^f	0.037 ^a
Temporal lobe	0.5 (0.3–1.0)	0.0 (0.0–0.5)	1.5 (1.0–2.3) ^{g,h}	0.013 ^a
Parietal lobe	1.0 (0.5–1.3)	1.0 (0.5–1.0)	1.5 (1.3–2.5)	0.11 ^a
Occipital lobe	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.5 (0.0–1.0) ⁱ	0.020 ^a
MTA scale ^c	1.0 (0.2–2.4)	1.5 (1.4–2.5)	1.5(1.0–1.8)	0.17 ^a
Midbrain atrophy scale ^d	0.0 (0.0–0.3)	2.0 (1.0–2.0) ^{j,k}	0.0 (0.0–0.0)	0.006 ^a
Asymmetry scale				
Frontal lobe	1.0 (1.0–1.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	0.35 ^a
Temporal lobe	0.0 (0.0–0.5)	0.0 (0.0–1.0)	1.0 (0.0–1.5) ^{l,m}	0.003 ^a
Parietal lobe	1.0 (0.0–2.0)	0.0 (0.0–2.0)	2.0 (1.0–2.0) ⁿ	0.007 ^a
Occipital lobe	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0) ^{o,p}	0.002 ^a
Cerebral peduncle	1.0 (0.0–2.0)	2.0 (1.0–2.0)	1.0 (0.0–1.5)	0.27 ^a
SWMH ^e	10/18 (56%) ^q	0/7 (0%)	2/7 (29%)	0.033 ^b

Data are expressed as the absolute number or median (1st quartiles and 3rd quartiles)

Imaging findings showing statistical significance are highlighted in gray color

CBD corticobasal degeneration, *CBS* corticobasal syndrome, *GCA* global cortical atrophy, *MRI* magnetic resonance imaging, *MTA* medial temporal atrophy, *PSP* progressive supranuclear palsy, *SWMH* subcortical white matter hyperintensity

^aKruskal-Wallis test; ^bFisher's exact test; ^cMTA scale was not applicable in nine patients with CBD and one patient with CBD mimics; ^dMidbrain atrophy was not applicable in three patients with CBD; ^eSWMH was not applicable in one patient with CBD and two patients with CBD mimics; ^f*p*=0.043 PSP-CBS subgroup versus non-PSP-CBS; ^g*p*=0.073 CBD versus non-PSP-CBS; ^h*p*=0.011 PSP-CBS versus non-PSP-CBS; ⁱ*p*=0.019 PSP-CBS versus non-PSP-CBS; ^j*p*=0.016 CBD versus PSP-CBS; ^k*p*=0.014 PSP-CBS versus non-PSP-CBS; ^l*p*=0.073 CBD versus non-PSP-CBS; ^m*p*=0.011 PSP-CBS versus non-PSP-CBS; ⁿ*p*=0.005 CBD versus non-PSP-CBS; ^o*p*=0.082 CBD versus non-PSP-CBS; ^p*p*=0.019 PSP-CBS versus non-PSP-CBS; ^q*p*=0.060 CBD versus PSP-CBS; ^{f–p}were evaluated by Mann–Whitney U test with Bonferroni correction; ^qwas evaluated by Fisher's exact test with Bonferroni correction

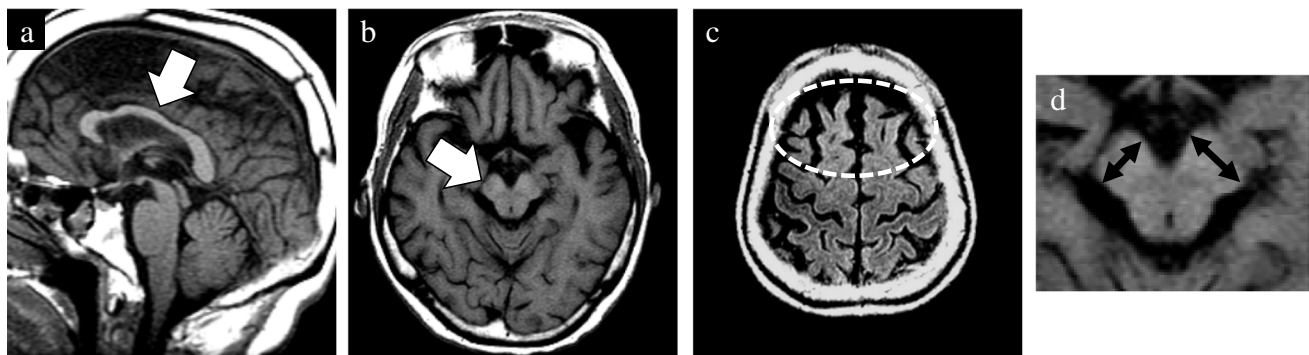


Fig. 5 A representative case of radiologically typical CBD. This 69-year-old female patient obtained an antemortem clinical diagnosis of AD. After the postmortem pathological examination, it was proved that main pathology of this patient was CBD. MRI was performed one year after the symptom onset. In contrast to mild atrophy of the callosal body (arrow, **a**), sagittal T1WI showed relatively preserved midbrain. Axial T1WI and FLAIR image showed right dominant asymmetric atrophy of the cerebral peduncle and frontal lobe (arrow,

b). Additionally, mild SWMH was detected in the frontal lobe at high convexity (circle, **c**). A magnified view was exhibited to emphasize the asymmetry of the short axis in the cerebral peduncles (double sided arrows, **d**). **a**, sagittal T1WI; **b**, axial T1WI; **c**, axial FLAIR image; AD, Alzheimer's disease; CBD, corticobasal degeneration; FLAIR, fluid-attenuated inversion recovery; SWMH, subcortical white matter hyperintensity; T1WI, T1-weighted image

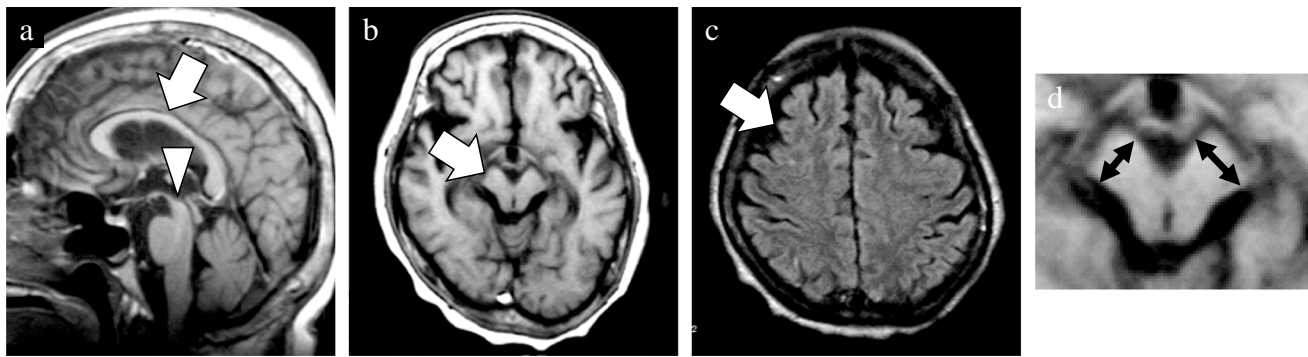


Fig. 6 A representative case of radiologically atypical CBD. This 67-year-old female patient obtained an antemortem diagnosis of CBD. MRI was performed four years after the symptom onset. In addition to atrophy of the callosal body (arrow, **a**), mild midbrain atrophy was also detected on sagittal T1WI (arrowhead, **b**). In contrast to right dominant asymmetric atrophy of the cerebral peduncle and frontal lobe (arrows, **b**, **c**), no obvious SWMH was noted on axial

FLAIR image (**c**). A magnified view was exhibited to emphasize the asymmetry of the short axis in the cerebral peduncles (double sided arrows, **d**). **a**, sagittal T1WI; **b**, axial T1WI; **c**, axial FLAIR image; CBD, corticobasal degeneration; FLAIR, fluid attenuated inversion recovery; SWMH, subcortical white matter hyperintensity; T1WI, T1-weighted image

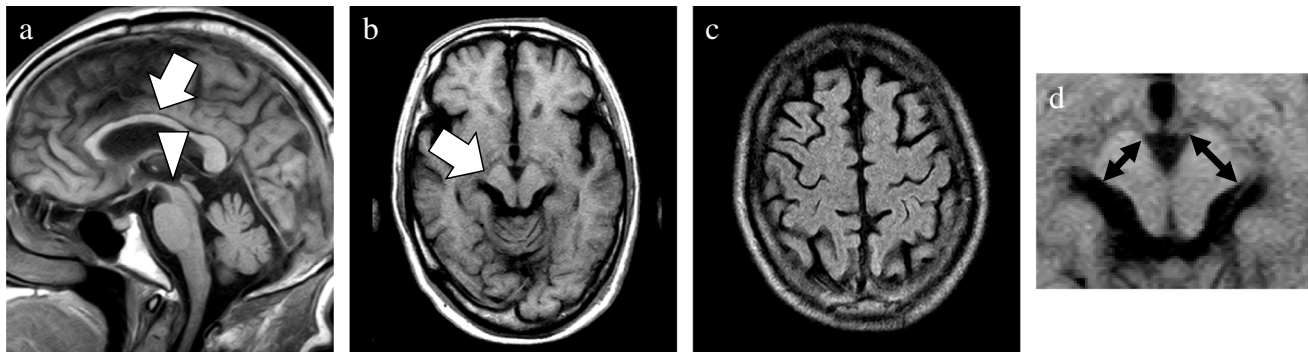


Fig. 7 A representative case of CBD mimics. This 71-year-old male patient obtained a postmortem diagnosis of PSP. MRI was performed two years after the symptom onset. Sagittal and axial T1WI (**a**, **b**), and axial FLAIR image (**c**) showed atrophy of the midbrain and callosal body (arrow and arrowhead, **a**), and right dominant asymmetric atrophy of the cerebral peduncle without obvious SWMH (arrow, **b**). These MRI findings were very similar to those of the patient described in Fig. 6. The case of this patient was exhibited to clarify

the challenges when differentiating CBD without SWMH from its mimics, especially PSP. A magnified view was exhibited to emphasize the asymmetry of the short axis in the cerebral peduncles (double sided arrows, **d**). **a**, sagittal T1WI; **b**, axial T1WI; **c**, axial FLAIR image; CBD, corticobasal degeneration; FLAIR, fluid attenuated inversion recovery; PSP, progressive supranuclear palsy; SWMH, subcortical white matter hyperintensity; T1WI, T1-weighted image

Discussion

This study aimed to differentiate patients with pathologically confirmed CBD from those with CBD mimics using semiquantitative visual rating scales. Various rating scales reflecting the degree of atrophy and asymmetry were not useful for differentiating CBD and its mimics. Conversely, the abnormal subcortical white matter signal on axial FLAIR (i.e., SWMH) was higher in patients with CBD than those with its mimics. Furthermore, severe midbrain in patients with the PSP-CBS subgroup, and severe temporal atrophy and widespread asymmetry in patients with the non-PSP-CBS subgroup were higher than those in patients with CBD.

These results suggest that SWMH and particular atrophic distribution could be a valuable contributor to the differentiation between CBD and its mimics (Fig. 9).

CBD is a predominantly sporadic 4R tauopathy, clinically classified as one of the atypical parkinsonian syndromes. This condition is characterized by an asymmetrical presentation of akinetic-rigid syndrome, involuntary movements, and signs of cortical dysfunction [26]. However, this clinical feature is not specific to CBD and can be caused by various pathologic conditions, including PSP, AD, FTLD-TDP, and DLB [5–7]. Therefore, the term “CBS” instead of “CBD” was established to encompass the constellation of symptoms associated with this clinical phenotype. The lack of specific clinical symptoms

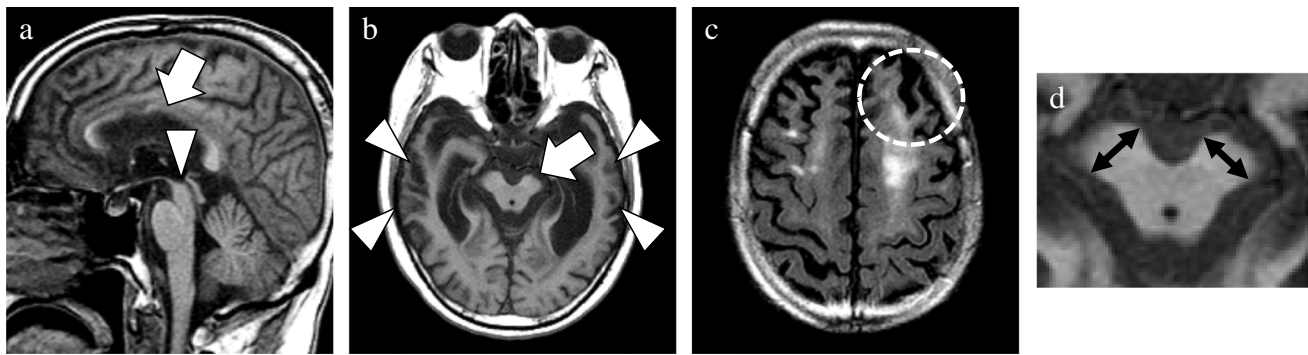


Fig. 8 A representative case of CBD mimics. This 74-year-old male patient obtained a postmortem diagnosis of FTLT-TDP. MRI was performed three years after the symptom onset. The confusable atrophy of the midbrain and callosal body (arrow and arrowhead, **a**), asymmetric atrophy of the left cerebral peduncle (arrow, **b**) and frontal lobe, and SWMH in the left frontal lobe at high convexity (circle, **c**) were detected. The severity of bilateral temporal lobe atrophy (arrowheads, **b**) significantly differed from that of CBD. This patient was exhibited to clarify the different atrophy patterns in the

CBD mimics group, especially the non-PSP subgroup. A magnified view was exhibited to emphasize the asymmetry of the short axis in the cerebral peduncles (double sided arrows, **d**). **a**, sagittal T1WI; **b**, axial T1WI; **c**, axial FLAIR image; CBD, corticobasal degeneration; FLAIR, fluid attenuated inversion recovery; FTLT-TDP, frontotemporal lobar degeneration with TAR DNA-binding protein of 43 kDa; SWMH, subcortical white matter hyperintensity; T1WI, T1-weighted image

and biomarkers contributes to the challenging antemortem diagnosis of CBD.

Asymmetry is a key imaging feature of CBD. Previous studies, evaluating pathologically confirmed patients, have elucidated the presence of asymmetric atrophy in patients with CBD [24, 25, 27]. Voxel-based morphometry (VBM) and volumetry are employed for the objective investigation of this asymmetric atrophy [28–30]. Additionally, distinctive

signal changes in the white matter and subthalamic nuclei have been reported [25, 31]. These results underscore the efficacy of MRI in detecting characteristic structural changes associated with CBD.

However, like a clinical presentation, comparable imaging findings have been documented in both pathologically confirmed CBD and CBS due to non-CBD pathologies. Asymmetric atrophy, which is the most well-known finding

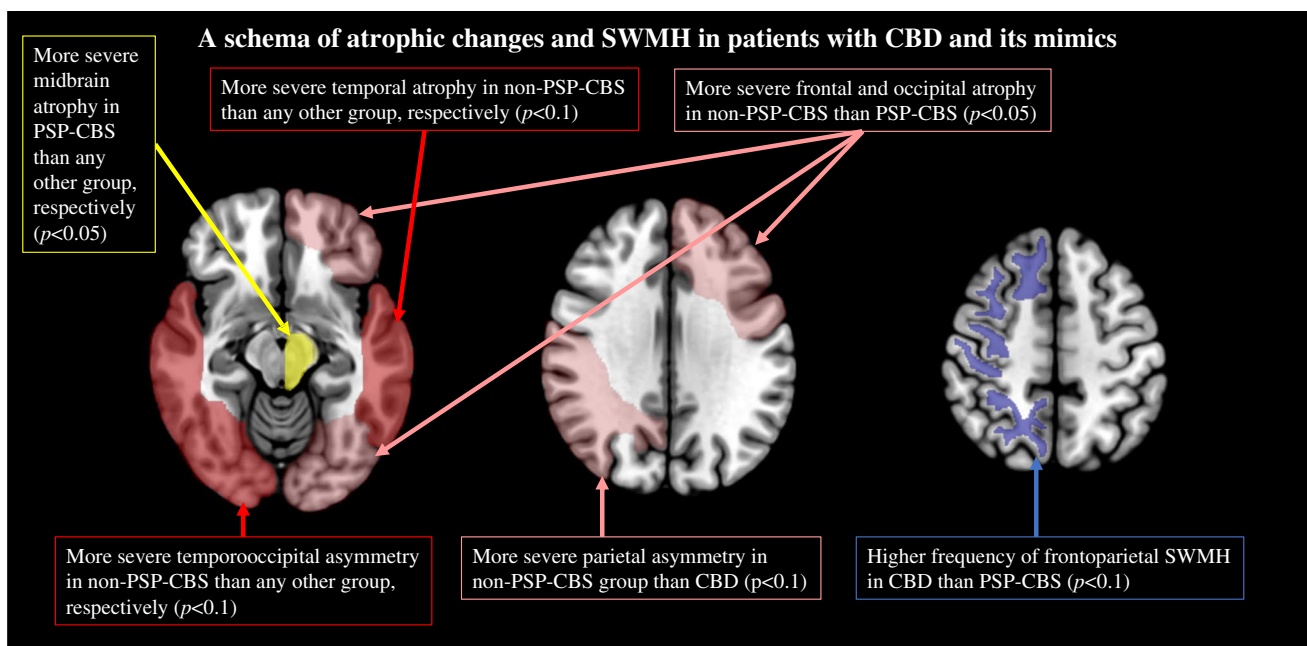


Fig. 9 A schema of atrophic changes and SWMH in patients with CBD and its mimics. In this scheme, asymmetry and signal change were colored in the right hemisphere, and degree of brain atrophy

was colored in the left hemisphere, respectively. CBD, corticobasal degeneration; CBS, corticobasal syndrome; PSP, progressive supranuclear palsy; SWMH, subcortical white matter hyperintensity

of CBD, can be observed in patients with PSP, AD, and FTLT-DTP [30, 32–34]. Hence, the degree and distribution of atrophy were also evaluated in this study. Visual rating scales delineate distinct atrophic profiles among the CBD and CBD mimics subgroups. Compared with the CBD and PSP-CBS subgroups, the non-PSP-CBS subgroup showed more severe asymmetric atrophy, especially in the temporal lobe. This discrepancy aligns with the findings of a previous VBM study, demonstrating more extensive asymmetric temporal, parietal, and occipital atrophy in AD and FTLT-DTP than in CBD and PSP [28]. Actually, the non-PSP-CBS subgroup in this study comprised patients with AD and FTLT-DTP. The pathological changes of these disorders can frequently impair the temporal region. Consequently, severe asymmetric atrophy, particularly involving the temporal region, may become a key feature for distinguishing CBD from its non-PSP-CBS mimics.

Midbrain atrophy, a well-known imaging finding of PSP, has been reported in patients with pathologically confirmed CBD [25, 35]. In this study, the degree of midbrain atrophy is more severe in patients with PSP than in those with CBD. However, the degree of midbrain atrophy depends on the background pathologies and clinical phenotypes [36]. Patients with atypical PSP may exhibit mild midbrain atrophy indistinguishable from that of patients with CBD and vice versa.

Compared with the above-mentioned atrophic changes, changes in white matter signal have not garnered much attention as an imaging feature of CBD. However, some studies have reported white matter signal changes in patients with pathologically confirmed CBD [24, 25, 31]. Notably, just over half of the patients with CBD showed SWMH, and this ratio was relatively higher than that of patients with PSP-CBS in this study. Furthermore, consistent with the result of a previous study comparing patients with pathologically confirmed CBD and those with PSP, none of the patients with PSP showed SWMH [25]. SWMH was not also observed in patients with AD and DLB. In CBD brains, tau-positive fine threads extensively distribute in the cerebral cortices, subcortical white matter, basal ganglia, thalamus, and brainstem. These threads cause not only atrophic changes but also loss of myelin beneath the subcortical white matter including U-fibers. This subcortical white matter degeneration seems to cause MRI signal changes (i.e., SWMH) in patients with CBD. In contrast, such pathological changes are not generally observed in PSP and AD brains, which constitute the majority of CBD-mimics. Considering the pathogenesis of the signal change, this finding can be useful for the differentiation of CBD and other disorders. Thus, SWMH can serve as a clue for the diagnosis of CBD, but caution is warranted when interpreting this finding. First, considering the nonspecific signal changes (i.e., leukoaraiosis) observed in the periventricular and deep white matter,

signal changes localized to the subcortical region should be evaluated. Second, patients with non-CBD pathologies may exhibit confusable subcortical white matter signal changes [34, 37]. In this study, two patients with CBD mimics (one who developed FTLT-DTP and another who developed GGT) were judged as having a positive SWMH. In diagnosing patients with asymmetric atrophy and SWMH, not only CBD but also FTLT-DTP and GGT should be considered as one of the differential diagnoses.

The application of semiquantitative visual rating scales in patients with pathologically confirmed cases represents a notable strength of this study. A previous study has already clarified the close correlation between the regional gray matter atrophy on VBM and visual assessment on visual rating scales [38]. Therefore, it is plausible to consider that visual assessment by experienced raters has diagnostic capabilities similar to VBM. Semiquantitative visual rating scales provide a clear delineation of the varying degrees and distributions of atrophy and asymmetry between the CBD and CBD mimics subgroups without the need for specialized software. Nonetheless, some limitations are associated with the retrospective nature of this study. First, the number of participants was relatively small, especially those with AD and FTLT-DTP. The visual rating scale scores demonstrated more pronounced atrophy and asymmetry of the temporal lobe in the non-PSP-CBS subgroup, aligning with the findings of the VBM study [28]. However, the non-PSP-CBS subgroup included those with nonuniform conditions, and the number of participants in this group was relatively small. A larger number of cases is necessary to accurately assess the atrophic and asymmetric findings in the non-PSP-CBS. Second, inconsistent MRI protocols made it impossible to perform more sophisticated analyses such as VBM and diffusion tensor imaging. It should be noted that even using semiquantitative visual rating scales, it is not easy to detect subtle imaging abnormalities for inexperienced raters. Considering the difficulty to detect the subtle SWMH and asymmetric atrophy by visual assessment, establishment of supplementary techniques such as VBM, volumetry, and deep learning to support visual assessment is a future challenge for the imaging diagnosis of CBD. The exploration of MRI parameters such as FLAIR to detect subtle SWMHs remains challenging. Therefore, a large multicenter prospective cohort study with a uniform MRI protocol is required to further investigate the imaging differences between the CBD and CBD mimics.

Conclusion

This study clarifies the different structural changes between the CBD and its mimics based on visual rating scales. The evaluation of atrophic distribution and SWMH may serve as imaging key features in conventional MRI.

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Data availability The data used for MRI and pathological analyses are available from the authors and may be provided upon reasonable request to the corresponding author.

Declarations

Ethic approval We declare that this study has been approved by the Ethics Committee of the National Hospital Organization Higashinagoya National Hospital (#27–8) and each institute, and has therefore been conducted in strict compliance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patients or bereaved families as an opt-out on the website.

Competing interests The authors declared that they have no competing interests.

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