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Clinical, neuropsychological and imaging characteristics of Alzheimer's disease patients presenting as corticobasal syndrome

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ABSTRACT

Background: Corticobasal syndrome (CBS) can harbor diverse pathologies, such as corticobasal degeneration (CBD) and Alzheimer's disease (AD). CSF biochemical analysis in CBS patients can confidently distinguish between an AD (CBS-AD) and a non-AD (CBS-nAD) pathology.
Objective: We utilized classical CSF biomarkers to make a distinction between the two groups and examine their clinical, neuropsychological, neuropsychiatric and imaging differences.
Methods: Seventeen patients with a CBS phenotype were included. Detailed clinical history, and neurological examination data were recorded. A thorough neuropsychological and neuropsychiatric test battery was performed, including Goldenberg apraxia test. Simple linear MRI measurements and planimetry data were utilized. CSF biomarkers for AD were ascertained.
Results: Five of seventeen CBS patients had a CSF AD profile. Patients with a CSF AD profile (CBS-AD; n = 5) were older and had a greater age at disease onset compared to CBS-nAD. CBS-AD patients had more frequently alien hand phenomena at examination and greater hippocampi surface asymmetry at MRI. CBS-nAD patients (n = 12) had lower superior colliculi width values.
Conclusion: Clinical, neuropsychological and imaging data cannot confidently differentiate CBS-AD from CBS-nAD patients.

1. Introduction

Corticobasal syndrome (CBS) is a rare clinical phenotype that combines asymmetric extrapyramidal and cortical symptoms and signs, such as rigidity, dystonia, myoclonus, apraxia, alien limb phenomena and cortical sensory deficits [1]. The most common underlying pathology (ranging from 25% to 50%) of CBS patients, is corticobasal degeneration (CBD), a 4R-tauopathy [2–6]. CBD has distinct hyperphosphorylated tau-protein neuropathologic lesions, such as astrocytic plaques, thread-like lesions, coiled bodies and ballooned neurons [7].

The terms CBS and CBD have been used interchangeably in the past. However, clinicopathological studies over the last 20 years have established that there is great clinical-pathological heterogeneity. CBD can not only present with a CBS phenotype, but also as a non-fluent agrammatic primary progressive aphasia, a progressive supranuclear palsy syndrome, a frontal behavioral–visuospatial syndrome and an amnestic syndrome reminiscent of Alzheimer's disease (AD) [1]. CBS on the other hand can harbor diverse pathologies, including CBD, progressive supranuclear palsy (PSP), frontotemporal dementia with tau pathology (FTD-tau) and frontotemporal dementia with TDP-43 pathology (FTD-TDP-43). Most importantly, AD can rarely present with a CBS phenotype [2,3,5,6,8,9].

CSF total tau protein (τ_T), phosphorylated tau ($\tau_{P\text{-}181}$) and amyloid beta ($A\beta_{42}$) analysis can confidently establish an ante mortem diagnosis of underlying AD pathology. For this reason, CSF biochemical profile has been introduced as a biomarker in the most recent, established diagnostic criteria for AD and CBD [1,10,11]. This CSF biochemical profile can discriminate CBS patients into CBS-AD and CBS-non-AD (CBS-nAD) patients [10]. This is of particular importance firstly on a clinical level, for the management of the individual patient; secondly in a research setting, for the correct inclusion of patients in clinical studies of disease-modifying agents.

Previous studies on CBS have mostly relied on post mortem pathology to characterize the underlying pathology [2–6,8,9]. Only a single study has utilized CSF biomarkers to establish an *ante mortem* diagnosis of CBS-AD vs. CBS-nAD [12] to our knowledge. However,

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prospective studies on the subject are lacking. Most studies in the field are retrospective in nature, due to the rarity of CBS [2–6,8,9,12]. Furthermore, most studies have focused on either clinical or imaging correlates of the underlying CBS pathology.

The aim of the present study was: a) to prospectively record all clinical, neuropsychological, neuropsychiatric and imaging characteristics of a well-characterized CBS cohort; b) to examine differences in these fields between CBS-AD and CB-nAD patients, based on their CSF biochemical profile, as it is the most robust tool for *ante mortem* diagnosis of the underlying pathology (AD vs. non-AD).

2. Materials and methods

2.1. Patients

Patients were consecutively and prospectively recruited (between 2011 and 2014), without selection, as part of the Parkinson-plus Registry of our Department. All patients fulfilled latest established criteria for probable corticobasal syndrome [1].

Standard laboratory tests to exclude secondary causes of Parkinsonism were performed in all patients.

2.2. Ethical issues

The study was performed according to the ethical guidelines of the 1964 Declaration of Helsinki, after approval of the Scientific and Ethical Committee of Eginition Hospital. All patients gave written informed consent to participate in the study. In cases of compromised mental capacity, the next of kin carer gave written informed consent.

2.3. Clinical history and neurological examination

All patients were given a semi-structured questionnaire of the presence (yes/no) and time of onset of symptoms. A thorough, structured neurological examination was performed, and signs were assigned as present or absent. All patients were examined independently by two neurologists (PG, CV), with experience in movement disorders. In cases of disagreement, the patient was re-examined by both examiners and a consensus was reached. Clinical evaluation was performed, blinded to CSF results.

2.4. Sample collection and biochemical determination

All patients underwent lumbar puncture, according to latest pre-analytical recommendations [13]. Measurements of $A\beta_{42}$, τ_T, and $\tau_{P\text{-}181}$ also were performed according to strict analytical procedures, as described elsewhere [14]. Analyses were performed in duplicate by double sandwich, enzyme-linked immunosorbent assay (ELISA) as provided by commercially available kits ("Innotest®hTau antigen", "β-amyloid$_{1–42}$" and "phospho-tau$_{181}$" respectively, Fujirebio Europe, Gent, Belgium) according to manufacturer's instructions.

Patients with abnormal values in all three CSF biomarkers (elevated τ_T, $\tau_{P\text{-}181}$ and decreased $A\beta_{42}$ values), according to our laboratory cut-off points (τ_T > 376 pg/ml; $\tau_{P\text{-}181}$ > 56.76 pg/ml; $A\beta_{42}$ < 682 pg/ml) were considered to have a typical CSF AD profile [15] and were designated CBS-AD patients. Moreover, all AD patients had a τ_T / $A\beta_{42\ ratio}$ > 0.6628, according to cut-off limits of our laboratory. All other patients were designated CBS-nAD patients.

2.5. Formal neuropsychological and neuropsychiatric testing

A comprehensive battery of neuropsychological tests was performed in all patients. This included the Mini Mental State Examination (MMSE) [16], Frontal Assessment Battery (FAB), 15-point spontaneous and copy clock drawing test (Clox1 and Clox2), 5-word immediate and delayed recall test, the 1 min semantic fluency (category: animals) and digit span test (backwards and forwards). Neuropsychiatric tests included the 12-item Hellenic version of the Neuropsychiatric Inventory (H-NPI) [17], as well as the 15-item Geriatric Depression Scale (GDS).

Apraxia, a characteristic symptom of CBS, was tested by means of the Goldenberg apraxia test (max: 135). This test comprises: a) a pantomime test (max: 55) with a grip sub-score (max: 20) and a movement/position sub-score (max: 35) and b) an imitation test, which is divided in a hand imitation score (max: 40, 0–20 for each side) and finger imitation test (max: 40, 0–20 for each side) [18,19].

2.6. MRI acquisition

MRI exams were performed on a 3.0-Tesla Philips Achieva 3.0 T (TX) - DS unit when performed in our facility (in six patients). Otherwise the MRI scans provided by the patients were utilized (on various 1.5 Tesla MRI units – nine patients). The sequences utilized included sagittal, axial and coronal T1-weighted images, where available. Two patients had CT scans due to a contraindication for MRI (metal implants).

Atrophy of each lobe (frontal [20], temporal [21], parietal and occipital [22]) and the perisylvian region was graded according to a 5-point visual atrophy scale (0: no atrophy, 1: mild atrophy, 2: medium atrophy, 3: severe atrophy, 4: knife-edge appearance). A total cortical atrophy score was produced by the sum of the sub-scores (max: 40). An atrophy asymmetry index was calculated as the ratio of between – sides atrophy difference divided by the mean atrophy, multiplied by a factor of 100 (max: 200), as a measure of atrophy asymmetry.

Maximal hippocampal formation height (A), largest horizontal width between hippocampal formation and brainstem (B), width of choroid fissure (C) and width of temporal horn of lateral ventricle (D) were all measured in the coronal plane, parallel to the commissural - obex reference line, at the level of the hippocampus body. Both hippocampi were graded for atrophy according to Scheltens scale, and hippocampus formation surface was manually measured at the above-mentioned level [23].

Brainstem measures included maximal antero-posterior distance of the midbrain, pons, superior (SC) and inferior colliculi (IC) at the mid-sagittal plane. Furthermore, maximal middle cerebellar peduncle (MCP) width was measured at the axial plane and maximal superior cerebellar peduncle (SCP) width was measured at the coronal plane, at the origin of the SCP [24].

Corpus callosum, midbrain tegmentum, quadrigeminal plate and pons surfaces at the mid-sagittal plane were also measured, as described elsewhere [25]. The corpus callosum was further divided in five segments, according to the method of Hofer et al. [26]. Surfaces of each of the five segments was measured and their relative surfaces were calculated (CC segment surface / total CC surface).

All MRI measurements were performed by CV in a blinded fashion with regard to CSF profile, after MRI anonymization.

2.7. Statistical analysis

Continuous data were checked for normality of distribution and homogeneity of variances by Shapiro Wilk's and Levene's tests respectively. Between group differences were examined by χ^2, independent samples *t*-test and Mann-Whitney test as appropriate, with the significance level set at $p < .05$. Due to the rarity of the syndrome and the exploratory nature of the study, we examined a multitude of signs and symptoms and did not correct for multiple comparisons. All analyses were performed by IBM SPSS Statistics® version 22.0.0.0 (SPSS Inc., Chicago, IL, 2013). All graphs were designed using GraphPad Prism®, version 5.03 (GraphPad Software Inc., La Jolla, CA, 2009).

3. Results

Five of the seventeen CBS patients (29%) had an AD CSF biomarker

Table 1
Demographic, clinical and CSF data of patients.

	CBS-AD	*CBS-nAD*	p-Value
	(n = 5)	(n = 12)	
Demographics			
Age (years)	72.2 (7.36)	65.3 (5.2)	0.044
Sex (m/f)	3/2	6/6	0.707
Age at disease onset (years)	68.7 (7.8)	62.5 (6.1)	0.092
Disease duration (years)	3.6 (1.3)	3.0 (1.7)	0.509
Education (years)	9 (6–16)	6 (6–16)	0.743
CSF profile			
τ_T (pg/ml)	469.1 (102.2)	310.4 (149.8)	0.051
$A\beta_{42}$ (pg/ml)	299.3 (78.6)	860.9 (303.9)	0.002
$\tau_{P\text{-}181}$ (pg/ml)	67.1 (9.7)	48.2 (23.2)	0.105
$\tau_T/A\beta_{42}$	1.75 (1.47–1.77)	0.34 (0.28–0.41)	< 0.0001
$\tau_{P\text{-}181}/\tau_T$	0.15 (0.03)	0.16 (0.04)	0.479
$\tau_{P\text{-}181}/A\beta_{42}$	0.21 (0.18–0.31)	0.06 (0.04–0.07)	< 0.0001

CBS-AD: CBS patients with presumed Alzheimer's disease pathology; *CBS-nAD*: CBS patients with non-Alzheimer's disease pathology; τ_T: total tau protein; $\tau_{P\text{-}181}$: threonine - 181 phosphorylated tau protein; $A\beta_{42}$: amyloid beta.

profile. Two non-AD patients had elevated τ_T and $\tau_{P\text{-}181}$, with normal $A\beta_{42}$. One non-AD patient had low $A\beta_{42}$ and two had marginal $A\beta_{42}$ concentrations (Supplementary Fig. 1). CBS-AD patients were older than CBS-nAD patients by approximately 5 years (72.2 vs. 65.3; p = .044). Age at disease onset was also considerably later in CB-AD patients (68.7 vs. 62.5; p = .092) (Table 1).

3.1. Symptom prevalence

There were some differences between the two groups in symptom frequency. None of these differences reached statistical significance. CBS-nAD patients had numerically more frequent apraxia (p = .074) and personality change (p = .079). CBS-AD on the other hand reported more frequent myoclonus (p = .074) (Table 2, Supplementary Table 1).

3.2. Neurologic examination

Alien limb phenomena were more frequently observed in CBS-AD patients vs. CBS-nAD (2/5 vs. 0/12 respectively; p = .020). There was a trend towards greater UPDRS III scores in CBS-AD patients (p = .076) (Tables 2, 3, Supplementary Table 1).

3.3. Neuropsychiatric and neuropsychological tests

CBS-nAD patients had higher GDS scores (p = .049), although only two such patients had a score of ≥8/15, indicative of clinical depression (Table 3).

3.4. MRI measurements

CBS-AD patients presented with greater hippocampal surface asymmetry (p = .001), whereas CBS-nAD had lower superior colliculi widths values (p = .09) (Table 4).

4. Discussion

The present study aimed to examine the clinical, neuropsychological, neuropsychiatric and imaging differences of CBS-AD and CBS-nAD patients. Due to the rarity of CBS, few studies have described the clinical and imaging characteristics of patients based on the underlying disease, either by neuropathological confirmation or CSF biomarker profile, with conflicting results [3–5,9,12,27,28].

Our study indicates that CBS-AD and CBS-nAD patients cannot be confidently discriminated on a clinical or imaging basis. However, there are some clinical characteristics which could direct towards an underlying AD pathology in a patient with a CBS phenotype.

Thus, CBS-AD patients in our cohort were older and had a greater age at disease onset, compared to CBS-nAD. This is in agreement with a study by Shelley et al. [5]. However, both no age difference [12] and a younger age for AD patients vs. non-AD patients has been reported elsewhere [3,4,8,9].

Table 2
Clinical symptoms and signs frequency of CBS-AD vs. CBS-nAD patients.

Symptoms (reported)	*CBS-AD*	*CBS-nAD*	p-Value
	(n = 5)	(n = 12)	
Corticobasal syndrome symptoms			
Bradykinesia	100%	66%	0.140
Dystonia	40%	42%	0.949
Myoclonus	60%	16%	0.074
Alien hand	20%	8%	0.496
Apraxia	40%	84%	0.074
Other movement disorders			
Falls	40%	42%	0.949
Writing difficulties	100%	89%	0.439
Tremor	40%	58%	0.490
Levodopa response	0%	33%	0.273
Cognitive symptoms			
Memory difficulties	80%	36%	0.106
Attention deficits	20%	36%	0.513
Language impairment	60%	66%	0.793
Visuospatial dysfunction	25%	0%	0.101
Emotional incontinence	40%	25%	0.536
Personality change	20%	66%	0.079
Various symptoms			
Incontinence	20%	0%	0.110
Urinary urgency	20%	0%	0.126
Dysphagia	0%	8%	0.506
Signs			
Eye examination			
Visual neglect	20%	9%	0.496
Saccades slow speed	20%	41%	0.394
Vertical	20%	41%	0.394
Horizontal	20%	25%	0.825
Hypometric saccades	40%	27%	0.611
Opthalmokinetic apraxia	0%	9%	0.506
Lid opening apraxia	0%	18%	0.383
Procerus muscle sign	0%	25%	0.283
Pyramidal syndrome			
Pyramidal signs (any)	100%	91%	0.506
Maseter reflex	40%	33%	0.793
Hyperreflexia	100%	91%	0.506
Hoffmann sign	40%	41%	0.949
Babinski sign	20%	58%	0.149
Spasticity	40%	17%	0.301
Cerebellar syndrome			
Cerebellar signs (any)	20%	9%	0.496
Dysmetria	0%	9%	0.506
Intention tremor	20%	9%	0.496
Dysdiadochokinesia	0%	0%	NA
Extrapyramidal syndrome			
Cogwheel sign	75%	75%	1.000
Rigidity	50%	75%	0.350
Bradykinesia	100%	75%	0.195
Tremor	40%	25%	0.536
Other motor signs			
Myoclonus	40%	50%	0.730
Limb Dystonia	40%	58%	0.490
Axial dystonia	20%	18%	0.870
Alien limb	40%	0%	0.020
Paratonia	20%	25%	0.825
Sensory examination			
Agraphesthesia	80%	60%	0.439
Astereognosia	60%	60%	1.000
Sensory neglect	60%	30%	0.264
Primitive reflexes			
Grasp reflex	40%	36%	0.889
Suck reflex	33%	18%	0.571
Palmomental reflex	20%	18%	0.931
Pseudobulbar syndrome	0%	36%	0.119

Table 3
Neuropsychological, neuropsychiatric, apraxia and UPDRS scores in CBS-AD vs. CBS-nAD patients.

	CBS-AD	*CBS-nAD*	p-Value
	(n = 5)	(n = 12)	
Apraxia Scales			
Goldenberg (GB) Total Score (max:135)	72.5 (12.5)	76.8 (22.5)	0.700
GB Immitation Total Score (max:80)	32.0 (12.4)	42.4 (19.1)	0.336
GB Hand Immitation (max:40)	15.6 (6.4)	24.8 (12.9)	0.191
GB Finger Immitation (max:40)	16.4 (6.5)	17.6 (7.3)	0.791
GB Pantomime Score (max:55)	40.2 (6.0)	34.4 (8.0)	0.230
GB Grip (max:20)	12.8 (5.6)	9.6 (3.1)	0.121
GB position/movement (max:35)	27.4 (3.9)	24.8 (5.6	0.416
Neuropsychiatric Scales			
NPI Total Score (max:144)	6 (2 − 12)	12 (4–36)	0.145
NPI Affective Subscore (max:24) (depression & anxiety)	2.2 (3.5)	4.5 (1.5–8.5)	0.222
NPI Psychosis Subscore (max:36) (delus.,hallucin. & night dist,)	0 (0–0)	0 (0–0.5)	0.943
NPI Apathy Subscore (max:24) (apathy & food disturbances)	0 (0–0)	3.5 (0–9)	0.284
NPI Hyperactivity Subscore (max:36) (aggres.,irritab. &disinhib.)	0 (0–2)	2.5 (0–7)	0.524
GDS (max:15)	3.0 (1.6)	6.0 (2.2)	0.049
Neuropsychological Scales			
MMSE (max:30)	22.8 (5.3)	21.8 (5.7)	0.730
Clox1 (max:15)	7.0 (3.5)	5.4 (4.6)	0.495
Clox2 (max:15)	6.0 (4.3)	7.1 (5.4)	0.699
FAB (max:18)	10.8 (3.6)	12.0 (7.3)	0.173
5 Words Immediate Recall Total (max:5)	5 (5–5)	5 (3–5)	0.267
Spontaneous	4 (3–4)	3 (2–5)	0.881
With cue	1 (1–2)	1 (0–2)	0.381
5 Words Delayed Recall Total (max:5)	5 (5–5)	4 (3–5)	0.320
Spontaneous	3 (1–4)	3 (2–4)	0.616
With cue	1 (1–2)	1 (0–2)	0.172
Semantic Fluency	7 (4–10)	4.5 (3–7.5)	0.497
Digit Span (backwards & forwards)	8 (6–8)	6 (4–8)	0.413
UPDRS			
UPDRS III (max:108)	36.2 (15.6)	25 (6.3)	0.076
UPDRS assymetry index (max:200)	33 (0–35)	57 (22 − 120)	0.112
UPDRS bradykinesia subscore (max:64)	13 (12–14)	12 (10–14)	0.606
UPDRS rigidity subscore (max:36)	10 (9–11)	6 (5–9)	0.240
UPDRS stance & gait subscore(max:15)	4 (4–13)	3 (1–5)	0.298
UPDRS tremor subscore (max:32)	2 (0–2)	0 (0–4)	0.606

NPI: Neuropsychiatric Inventory; *GDS*: Geriatric Depression Scale; *MMSE*: Mini Mental State Examination; *FAB*: Frontal Assessment Battery; *UPDRS*: Unified Parkinson's Disease Rating Scale.

Table 4
Imaging characteristics of CBS-AD vs. CBS-nAD patients.

	CBS-AD	*CBS-nAD*	p-Value
	(n = 5)	(n = 12)	
Hippocampus measurements			
Scheltens Visual R (0–4)	3 (1–3)	1 (1–2)	0.371
Scheltens Visual L (0–4)	2 (1–2)	1.5 (1–2)	0.679
Scheltens Visual mean (0–4)	2.5 (0.5–2.5)	1.25 (1–2)	0.513
Hippocampus Height (mm)	14.0 (1.5)	15.2 (1.6)	0.160
Hippocampus-Brainstem Dist. (mm)	4.8 (1.5)	4.3 (1.6)	0.586
Choroid Fissure Width (mm)	3.6 (1.6)	3.3 (0.6)	0.596
Temporal Horn Width (mm)	4.0 (1.4)	3.1 (1.1)	0.214
Hippocampus Surface L (mm^2)	79.7 (13.4)	79.7 (13.7)	0.997
Hippocampus Surface R (mm^2)	86.1 (25.5)	81.2 (13.4)	0.715
Hippocampus Surface mean (mm^2)	82.9 (19.0)	80.6 (13.4)	0.832
Surface Asymmetry Index (0 − 200)	15.7 (1.7)	4.5 (3.6)	0.001
Cortical atrophy visual scale			
Total (0–40)	20 (19–20)	15.5 (14–21)	0.129
Frontal (0–4)	2.5 (1.5–2.5)	2.5 (2.5–3.0)	0.513
Parietal (0–4)	3.5 (3–3.5)	2.8 (2.5–3.5)	0.254
Temporal (0–4)	2 (1.5–2)	0.8 (0.5–1.5)	0.099
Occipital (0–4)	0 (0–1)	0.3 (0–1)	0.859
Sylvious (0–4)	2.5 (1.5–3)	1.5 (1.5–2.5)	0.129
Atrophy Assymetry Index (0–200)	35 (33–52)	42 (26–48)	0.859
Brainstem distances			
Midbrain (sagittal, mm)	10.8 (0.5)	10.7 (0.7)	0.710
Pons (sagittal,mm)	21.5 (0.5)	22.2 (1.1)	0.188
Superior colliculus (sagittal, mm)	3.5 (0.1)	3.0 (0.3)	0.009
Inferior colliculus (sagittal, mm)	5.0 (0.4)	4.5 (0.9)	0.310
SCP mean (coronal, mm)	3.22 (0.83)	3.22 (0.65)	1.000
MCP mean (axial, mm)	8.4 (1.3)	8.4 (1.4)	0.532
Planimetry measurements			
Midbrain tegmentum (mm^2)	129.3 (12.6)	119.4 (12.4)	0.195
Midbrain quadrigeminal plate (mm^2)	44.3 (8.6)	48.2 (11.5)	0.533
Pons (mm^2)	523.1 (50)	505.3 (50.2)	0.546
Corpus Callosum (mm^2)	515.5 (6.4)	549.9 (146.1)	0.760
Magnetic Resonance Parkinsonism Index	8.2 (−)	8.3 (1.5)	0.969
Corpus callosum segments surface (% of total)			
Segment 1 (prefrontal cortex)	33.8 (0.3)	29.5 (4.4)	0.224
Segment 2 (premotor, supplementary motor cortex)	21.8 (2.1)	22.0 (2.0)	0.937
Segment 3 (motor cortex)	9.5 (0.4)	10.2 (0.9)	0.366
Segment 4 (sensory cortex)	5.5 (0.7)	5.9 (1.2)	0.675
Segment 5 (parietal, temporal, occipital cortex)	35.1 (10.3)	32.4 (2.6)	0.501

SCP: Superior cerebellar peduncle; *MCP*: middle cerebellar peduncle.

Regarding symptom frequency, most studies support that myoclonus is a more frequent manifestation in CBS-AD patients, in agreement to our study [5,27]. Personality changes and apraxia on the other hand were indicative of a non-AD pathology in our cohort.

Alien hand phenomena were present in two of the five (40%) CBS-AD patients in our cohort. Interestingly, none of the twelve CBS-nAD patients exhibited this sign. This was the most significant clinical difference in our cohort. Intriguingly, results regarding alien hand phenomena in CBS in the literature are conflicting, with studies reporting greater [9,27], similar [5,6] and lower [4,29] prevalence in CBS-AD compared to CBS-nAD patients.

No AD patient in our cohort presented with lid opening apraxia, procerus muscle sign and opthalmokinetic apraxia, in accordance to the literature [4,6]. Opthalmokinetic apraxia has been reported as a rare late manifestation in AD patients [5].

Surprisingly, CBS-AD patients in our cohort had higher UPDRS-III compared to non-AD pathologies, a view that has been supported elsewhere [9]. Most studies on the subject however support the opposite view [6,8,28], whereas others do not report a difference in the extrapyramidal syndrome [5,29]. Some studies argue that Parkinsonism is present early in the natural course of CBS-AD [4,27].

We could not identify any meaningful difference in the severity or pattern of cognitive dysfunction between the groups. Most studies argue that CBS-AD patients are more impaired, particularly in memory and visuospatial tasks [5,9,12]. Standardized apraxia testing in our cohort did not reveal differences between the two groups.

Regarding MRI measurements, CBS-nAD patients in our cohort had lower superior colliculus width values, which could indicate an underlying PSP pathology. Moreover, CBS-AD patients had greater hippocampus surface asymmetry. All other MRI measurements did not differentiate between AD and non-AD patients.

As in the case of most studies on the subject, due to the rarity of the syndrome, our cohort sample size is modest, and thus underpowered to detect small differences between groups.

Our study lacks neuropathological confirmation, which could further elucidate differences between patients. This is the case particularly in the non-AD group, which comprises patients with heterogeneous pathologies. The association of *ante mortem* CSF biomarkers and neuropathologic changes of AD (amyloid plaques and fibrillary tangles) is well established, with a diagnostic accuracy of 90% [30]. Moreover, CSF biomarkers can confidently differentiate AD from tauopathies, such as PSP and CBD [31–33]. However, a minority of asymptomatic patients can have abnormal CSF biomarkers. These cases may represent patients harboring AD pathology in a pre-symptomatic phase.

Decreased CSF $A\beta_{42}$ may also be a marker of pathologic aging (i.e. presence of senile plaques composed of diffuse, non-neuritic amyloid deposits). These patients by definition lack neurofibrillary degeneration, and are therefore expected to have normal τ_T and $\tau_{P\text{-}181}$ [34]. Lastly, a minority of AD patients may only exhibit abnormal τ_T or $\tau_{P\text{-}181}$ with normal $A\beta_{42}$ or vice versa.

Another issue regarding CSF biomarkers is the presence of two diverse pathologies in the same patient (e.g. CBD and AD) as well as the differentiation of pathologic aging and Alzheimer's disease. To this end, a negative apolipoprotein E (apoE) ε4 status could be indicative of absent concomitant pathologic aging or AD pathology. However, it cannot confidently differentiate between pathologic aging and AD pathology. Furthermore, even patients with a "pure" tauopathy, (i.e. without concomitant AD pathology) may harbor one apoE ε4 allele [34]. Due to these limitations, contrary to CSF biomarkers, apoE4 status has not been included as a biomarker in recent diagnostic criteria [1,10,11].

These limitations notwithstanding, CSF biomarker analysis provide the most robust *ante mortem* diagnosis of AD pathology. Novel biomarkers which would inform us of the specific underlying disease (i.e. 3R-tau, 4R-tau, TDP-43) are essential, in order to reach a precise *ante mortem* etiological diagnosis of these patients. To this end, CSF TDP-43 has already shown promising results [35]. A single study has implemented immune-PCR assays, to determine CSF 3R-tau and 4R-tau. These biomarkers did not differentiate AD from PSP and CBS [36].

5. Conclusions

Clinical, neuropsychological or simple MRI data cannot confidently differentiate between CBS patients with an AD pathology vs. a non-AD pathology. CSF biomarker analysis remains the most accurate means to establish an underlying Alzheimer's disease pathology in a CBS patient.

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Conflict of interest/disclosure statement

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