Jacy Bezerra Parmera

Síndrome corticobasal: estudo prospectivo dos perfis clínicos e de biomarcadores de imagem

Corticobasal syndrome: a prospective study of clinical profiles and imaging biomarkers

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutora em Ciências

Programa de Neurologia
Orientadora: Profa. Dra. Sonia Maria Dozzi Brucki
Coorientador: Prof. Dr. Artur Martins Novaes Coutinho

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São Paulo
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Neurology Program
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*Aos meus pais, **Roberto** (in memoriam) e **Juliana**, dedico este projeto em sua totalidade. Percebo que ele exigiu de mim todos os pilares erguidos na minha educação: a gana de persistir, a ética no lidar com pessoas, a coragem para conquistar os meus sonhos.*

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“Dans la vie, rien n’est à craindre, tout est à comprendre”

— Marie Curie

“Somewhere, something incredible is waiting to be known.”

— Carl Sagan

“O sonho é que leva a gente para frente.”

— Ariano Suassuna

NORMALIZAÇÃO ADOTADA

Esta tese está de acordo com as seguintes normas, em vigor no momento desta publicação: Referências: adaptado de *International Committee of Medical Journals Editors* (Vancouver).

Universidade de São Paulo. Faculdade de Medicina. Serviço de Biblioteca e Documentação. Guia de apresentação de dissertações, teses e monografias. Elaborado por Anneliese Carneiro da Cunha, Maria Julia de A.L. Freddi, Maria F. Crestana, Marinalva de Souza Aragão, Suely Campos Cardoso, Valéria Vilhena. 3ª Ed. São Paulo: Serviços de Biblioteca e Documentação; 2011.

Abreviaturas dos títulos dos periódicos de acordo com *List of Journals Indexed in Index Medicus.*

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ABBREVIATIONS

4R-Tauopathy	Four-repeat tauopathy
AD	Alzheimer's disease
bvFTD	behavioral variant frontotemporal dementia
CBD	corticobasal degeneration
CBS	corticobasal syndrome
CJD	Creutzfeldt-Jacob disease
CSF	cerebrospinal fluid
DLDH	Dementia lacking specific histology
DTI	diffusion tension imaging
fMRI	functional magnetic resonance imaging
FTD	frontotemporal dementia
FTLD-TDP43s	frontotemporal lobar degeneration with TDP-43 inclusion
LBD	Lewy body dementia
MAPT	microtubule-associated protein tau
MND	Motor neuron disease
MRI	magnetic resonance imaging
MSA	multiple system atrophy
NFL	neurofilament light chain
nfvPPA	nonfluent variant primary progressive aphasia
PCA	posterior cortical atrophy
PD	Parkinson's disease
PET	Positron Emission tomography
PIB	Pittsburgh compound-B
PPA	primary progressive aphasia
PSP	progressive supranuclear palsy
PSP-SL	progressive supranuclear palsy- speech-language
SMA	supplementary motor area
SPM	Statistical Parametric Mapping
TMS	transcranial magnetic stimulation
VBM	voxel-based morphometry
WMH	white matter hyperintensities

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Resumo

Parmera JB. *Síndrome corticobasal*: estudo prospectivo dos perfis clínicos e de biomarcadores de imagem [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2021.

Introdução: a síndrome corticobasal (SCB) é uma síndrome parkinsoniana atípica associada a diversas patologias subjacentes. Considerando-se que os agentes modificadores de doença têm como alvo o processo patológico, novos métodos diagnósticos estão sendo desenvolvidos com foco nesse contexto. **Objetivos:** o presente estudo teve como objetivo principal investigar diferenças clínicas no perfil cognitivo, de linguagem e motor nas possíveis variantes patológicas da SCB, identificadas através de biomarcadores de imagem molecular. Avaliou-se também se os padrões individuais de metabolismo através da tomografia com emissão de pósitrons (PET) com [^{18}F]fluorodeoxiglicose (FDG) (PET-FDG) poderiam predizer a positividade na PET com radiotraçador para proteína amiloide [^{11}C]Pittsburgh Compound-B (PET-PIB), marcador relacionado à patologia da doença de Alzheimer (DA). **Métodos:** 45 indivíduos com SCB foram prospectivamente submetidos a avaliações neurológicas e fonoaudiológicas. Todos os pacientes realizaram PET-FDG, e foram divididos em grupos SCB com padrão de metabolismo sugestivo de DA (SCB FDG-DA) e não sugestivo de DA (SCB FDG-nãoDA). Trinta e um indivíduos realizaram PET-PIB num equipamento híbrido de PET-Ressonância magnética (RM) para avaliar a deposição cerebral de peptídeo amiloide. As imagens de PET-FDG e PIB foram classificadas individualmente com base em análises visuais, assistidas por análises semi-quantitativas com o *software* 3D-SSP. Também foram realizadas análises quantitativas de grupo com PET-FDG e PET-PIB com o *software* SPM8, e os padrões de atrofia na RM foram investigados usando morfometria baseada em voxel (VBM). Trinta indivíduos saudáveis foram recrutados como grupo controle para comparações quantitativas dos métodos de imagem. **Resultados:** o grupo SCB FDG-DA (15 pacientes, 33.3%) apresentou pior desempenho cognitivo, sobretudo nos domínios atenção, memória e visuoespacial, assim como apresentou mais mioclonias e alucinações. O grupo SCB FDG-nãoDA (30 pacientes; 67.7%) apresentou mais distonia, alterações de motricidade ocular, perseveração motora e disartria. Todos os pacientes classificados como SCB FDG-DA testaram positivo na PET-PIB, comparados com três entre 20 pacientes do grupo SCB FDG-nãoDA. A classificação individual obtida através da PET-FDG demonstrou 76.92% de sensibilidade, 100% de especificidade e valor preditivo positivo, e 88.5% de acurácia balanceada para detectar positividade na PET-PIB. Indivíduos com resultado de PET-PIB positivo e negativo, demonstraram, respectivamente, hipometabolismo em áreas temporoparietais

posteriores e em tálamo e mesencéfalo, contralateralmente ao lado mais afetado, sendo estas possíveis assinaturas metabólicas das patologias subjacentes. Indivíduos com disartria demonstraram hipometabolismo predominante em região frontal inferior esquerda e córtex pré-motor, além de atrofia cerebral em região opercular frontal e putâmen. **Conclusões:** a SCB é uma entidade com duas principais variantes distintas (associada ou não à DA), possuindo diferentes performances cognitivas e de linguagem, e possivelmente diferentes alterações motoras predominantes. O padrão metabólico através da PET-FDG demonstrou-se útil para retratar os padrões degenerativos específicos de tais variantes, seus perfis clínicos, assim como para predizer positividade no biomarcador para proteína amiloide.

Descritores: Doenças neurodegenerativas; Degeneração corticobasal; Transtornos parkinsonianos; Tomografia por emissão de pósitrons; Tomografia por emissão de pósitrons/métodos; Fluordesoxiglucose F18.

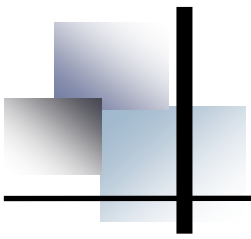
Abstract

Parmera JB. *Corticobasal syndrome*: a prospective study of clinical profiles and imaging biomarkers [thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2021.

Introduction: Corticobasal syndrome (CBS) is an atypical parkinsonian syndrome related to multiple underlying pathologies. Given that disease-modifying agents target the pathologic process, new diagnostic methods are being developed to focus on this context. **Objectives**: the present study aimed to investigate clinical differences regarding cognitive, language, and motor profiles in possible CBS pathological variants identified using molecular imaging biomarkers. Also, we sought to investigate if individual brain [^{18}F]fluorodeoxyglucose-Positron emission tomography (FDG-PET) patterns could distinguish CBS due to Alzheimer's disease (AD) from other pathologies based on [^{11}C]Pittsburgh Compound-B (PIB)-PET. **Methods:** forty-five patients with CBS were prospectively evaluated regarding their clinical and speech-language profiles. They all underwent FDG-PET and were distributed in two groups: likely related to AD (CBS FDG-AD) or likely non-AD (CBS FDG-nonAD). Thirty-one patients underwent PIB-PET on a hybrid PET-Magnetic resonance imaging (MRI) equipment to assess their amyloid status. FDG and PIB-PET images were classified individually based on visual analyses, assisted by semi-quantitative analysis with 3D-SSP software. Quantitative group analyses were performed on FDG-PET and PIB-PET data with the SPM8 software, and atrophy patterns on MRI were investigated using voxel-based morphometry (VBM). Thirty healthy participants were recruited as imaging controls. **Results:** CBS FDG-AD group (15 patients, 33.3%) demonstrated worse cognitive performances, mainly concerning attention, memory, and visuospatial domains, and displayed more myoclonus and hallucinations. The non-AD metabolic group (30 patients, 66.7%) presented more limb dystonia, ocular motor dysfunction, motor perseveration, and dysarthria. All patients classified as CBS FDG-AD tested positive at PIB-PET compared to 3 out of 20 in the non-AD group. The individual FDG-PET classification demonstrated 76.92% sensitivity, 100% specificity and positive predictive value, and 88.5% balanced accuracy to detect positive PIB-PET scans. Individuals with positive and negative PIB-PET showed hypometabolism in posterior temporoparietal areas and thalamus and brainstem, respectively, mainly contralateral to the affected side, disclosing possible metabolic signatures of CBS variants. Moreover, CBS patients with dysarthria had hypometabolism at the left inferior frontal gyrus and premotor cortex and showed brain atrophy patterns mainly at the opercular frontal gyrus and putamen. **Conclusion:** CBS is a clinical syndrome containing two major well-differentiated variants (CBS-AD and CBS non-AD), with different cognitive performances, speech-language

profiles, and possibly different motor features. FDG-PET was useful in depicting their specific degeneration patterns, different clinical features, and brain amyloid deposition.

Descriptors: Neurodegenerative diseases; Corticobasal degeneration; Parkinsonian disorders; Positron-emission tomography; Positron-emission tomography/methods; Fluorodeoxyglucose F18.



INTRODUCTION

1 Introduction

1.1 Evolution of concept

In the vast group of neurodegenerative diseases, corticobasal syndrome (CBS) and corticobasal degeneration (CBD) were first described relatively recently as a unique clinicopathological entity in 1967 and 1968. Rebeiz et al.[1,2] reported clinical and pathological findings of three patients with progressive stiffness and awkward limb movements, dystonic posturing, and gait disorder. They called this entity “corticodentatonigral degeneration with neuronal achromasia”, identified by asymmetrical frontoparietal cortical atrophy and neuronal loss, loss of pigmented neurons in the *substantia nigra*, and swelling of the neuronal cell bodies with achromatic cells[1,2].

Interestingly, the earliest description of CBS dates back to 1925 when Jean L’Hermitte and colleagues described a 72-year-old carpenter presenting with a clumsy, useless arm with rigidity, ideomotor apraxia, abnormal flexed posture, alien limb phenomenon, and cortical sensory dysfunction[3]. There is also speculation that the French composer Maurice Ravel (1875–1937), who developed aphasia, apraxia, and dubious loss of musical creativity, had CBS[4,5].

Decades after the first comprehensive description, the term “corticobasal degeneration” was coined by Gibb and Marsden in 1989[6], also referred to as corticobasal ganglionic degeneration[7] by some authors.

In the 1990s, within the introduction of immunostaining for tau, the neuronal aggregates in CBD pathology were shown to consist of the microtubule-associated protein tau (MAPT).[8]

Over time, it has become clear that the clinical features described by Rebeiz et al. were associated with various underlying pathologies[9,10], since the clinical presentation reflects the topographic distribution of histopathology more than the specific underlying pathology. Conversely, the topographic distribution of CBD pathology dictates the clinical presentation. Hence, it can be seen in patients presenting other clinical syndromes beyond CBS, some resembling the behavioral variant (bv) frontotemporal dementia (FTD)[11], progressive supranuclear palsy (PSP)[12], nonfluent variant primary progressive aphasia (nfvPPA), and apraxia of speech (AOS)[13], among others[14]. Considering this, Boeve et al.[15] introduced the term “corticobasal syndrome” to embrace the constellation of symptoms leading to the originally described clinical phenotype, while CBD currently denotes the pathological disorder.

Little is known about the epidemiology of CBD and CBS. As CBD is a rare disease with various clinical phenotypes, and CBS can be due to different underlying pathologies, accurate prevalence studies are lacking. A recent study reported a pooled prevalence of FTD, PSP, and CBS as 10.8 per 100.000[16]. Another previous study showed an estimated CBD prevalence of 4.9-7.3 cases per 100.000 individuals[17]. Regarding CBS, a community-based Japanese study found a prevalence rate of 6 per 100.000[18], while a Russian study showed an age-standardized incidence rate of 0.02 cases per 100.000 individuals[19]. Disease onset is typically in the sixth to seventh decades of life, with a mean age of onset at 63.7 years, ranging from 45 to 77.2 years[14,20,21]. No sex bias has been

observed[14]. It is a relentless disease with a poor prognosis, commonly with a shorter duration than other atypical parkinsonian syndromes, such as PSP or multiple system atrophy (MSA)[20].

Before the latest diagnostic criteria, others have been proposed for the diagnosis of CBD and CBS. However, they demonstrated low sensitivity and specificity, mainly reflecting the CBS phenotype[20,22]. In light of the expanding understanding of the disease and its clinicopathologic correlations, a specialist consensus with brain bank cases and a critical literature review developed new diagnostic criteria for CBD/CBS[22]. In this current criteria, probable CBS is characterized by an asymmetric presentation with at least two extrapyramidal dysfunctions of: [a] limb rigidity or akinesia, [b] limb dystonia, [c] limb myoclonus, plus two cortical dysfunctions of: [d] orobuccal or limb apraxia, [e] cortical sensory deficits, [f] alien limb phenomena[22]. (table 1)

Also, these new diagnostic criteria were the first to incorporate phenotypes other than CBS into the CBD phenotypes. They proposed two diagnostic classifications for CBD: (1) “clinical research criteria for probable sporadic CBD” (cr-CBD) and (2) “possible CBD” (p-CBD). In the most specific one, namely cr-CBD, age must be greater than or equal to 50 years, and there should not be a family history. Included phenotypes were probable CBS, nfvPPA, and a frontal behavioral-spatial syndrome. Furthermore, these last two phenotypes must contain CBS clinical components. The p-CBD criteria aimed to be less restrictive with higher sensitivity. There was no minimum age, and positive family history was allowed. In addition, other phenotypes such as possible CBS and PSP phenotypes were included. In both scenarios, the progression must be gradual with insidious onset and a minimum duration of one year[22].

A prior study proposed a “modified Cambridge criteria” after comparing three previous criteria in a group of 40 patients with a clinical diagnosis of CBS. The Cambridge criteria had significantly broader applicability at presentation, almost certainly due to the weight given to cognitive and language dysfunction. Therefore, they suggested a minor modification to capture the high prevalence of aphasia.[23] Table 1 summarizes either the modified Cambridge criteria and the current criteria for CBS.

Despite recent efforts to standardize and refine clinical criteria, validation studies with clinicopathological cohorts demonstrated that there is still poor sensitivity within two years of disease onset, and patients without CBD pathology can fulfill the cr-CBD criteria[24]. Moreover, there is low specificity for distinguishing CBS due to underlying CBD pathology[25].

Additionally, the Movement Disorder Society (MDS) criteria for PSP[26] introduced the category “probable 4-repeat (4R)-tauopathy” for joint clinical diagnosis of PSP and CBD. They included probable PSP, possible PSP with speech and language dysfunction (PSP-SL), and possible PSP in overlap with CBS (PSP-CBS). The two later were included because they are highly specific in predicting PSP or CBD, albeit only moderately specific for PSP pathology. A retrospective validation study[27] compared this proposed criteria with the entire MDS-PSP[26] criteria and the Armstrong criteria[22]. The 4R-tauopathy criteria showed a higher sensitivity for CBD diagnosis than the Armstrong criteria and higher specificity for PSP and CBD compared to the overall MDS-PSP criteria[27].

Table 1 - Proposed clinical criteria for corticobasal syndrome

Modified Bak and Hodges criteria (Cambridge criteria)[23]	**Armstrong et al.** [22]	
Mandatory criteria* • Insidious onset and gradual progression • No sustained response to levodopa treatment	**Probable** •Insidious onset /gradual progression • Asymmetric presentation	**Possible** •Insidious onset /gradual progression • May be symmetric
Major criteria • *Motor features:* Akinetic rigid syndrome •*Cortical motor sensory features:* Limb apraxia • *Cognitive features:* Speech and language impairment	**Cortical dysfunction** At least 2 of: • Orobuccal/limb apraxia • Cortical sensory deficit • Alien limb phenomena	**Cortical dysfunction** At least 1 of: • Orobuccal/limb apraxia • Cortical sensory deficit • Alien limb phenomena
Minor criteria • *Motor features:* Focal or segmental myoclonus Asymmetrical dystonia •*Cortical motor sensory features:* Alien limb phenomenon Cortical sensory loss or dyscalculia • *Cognitive features* Frontal executive dysfunction Visuospatial deficits	**Extrapyramidal dysfunction** At least 2 of: • Limb rigidity or akinesia • Limb dystonia • Limb myoclonus	**Extrapyramidal dysfunction** At least 1 of: • Limb rigidity or akinesia • Limb dystonia • Limb myoclonus

*For a diagnosis of CBS, the patient should satisfy all mandatory criteria, two major criteria, and two minor criteria. *Table adapted from Parmera JB, et al. Dement e Neuropsychol 2016; **10**: 267–75*[28].

1.2 Clinical features

Regarding motor and cortical features in CBS, there is notable asymmetry. CBS is considered an atypical parkinsonian syndrome and usually presents with asymmetric levodopa-resistant akinetic-rigid parkinsonism, dystonia, and myoclonus. Symptoms often start in one limb, which is commonly described as rigid or “clumsy”. Such rigidity, in most case series, is the prevalent motor symptom. Also, it is usually intense and of mixed nature, with aspects of rigidity,

paratonia, and dystonia, associated with marked bradykinesia[15]. The typical scenario is a progressive rigidity and apraxia in one of the upper limbs, then involvement of either the ipsilateral lower limb or the contralateral upper limb, eventually leading to severe generalized disability several years later[15].

Since earlier descriptions, dystonia is considered a classical CBS feature, described in 59%–71% of patients in series mixing CBS and CBD[22,29]. When present, it usually occurs early and without fluctuations, characterized by a focal dystonia with adduction and flexion of the affected arm, forearm, wrist, and metacarpophalangeal joints, and extension of the interphalangeal joints[30]. Other dystonic manifestations include blepharospasm, lower limb dystonia, and cervical dystonia (*anterocollis* and *retrocollis*)[30]. In a recent study involving 296 pathologically confirmed cases of CBD, only 37.5% had dystonia, where upper limb dystonia was the most common pattern (77.4%), followed by cervical dystonia (9.5%) and blepharospasm (8.3%)[31]. Another study sought to investigate the frequency and pattern of dystonia in a group of patients with atypical parkinsonism. The series demonstrated dystonia as a common feature with an overall frequency of 50%, present in 100% of CBS patients[32]. Thus, although included in all sets of criteria for CBS and CBD, dystonia seems to be a less common motor feature than parkinsonism.

Most studies describe myoclonus as a frequent presentation in mixed CBS-CBD series, occurring in 55% to 93% of cases[22,33]. It usually begins as focal, distally confined to one limb, usually in the upper extremity, and may spread proximally or occur in the face. The frequency and amplitude of myoclonic jerks typically increase with tactile stimulation (stimulus-sensitive myoclonus) and action (action myoclonus)[15]. In line with its focal and stimulus-sensitive

presentation, electrophysiological studies demonstrated enhanced direct sensory input to cortical motor areas, suggesting a cortical origin[34].

The tremor in CBS is often a mixture of resting, postural and action tremors. Sometimes, low-amplitude myoclonic jerking (poliminimyoclonus) can be erroneously considered as tremors[20]. Other motor findings described in CBS patients are gait impairment and postural instability, pyramidal signs, and abnormal eye movements. There is no motor feature able to suggest underlying pathology in CBS[35].

Although commonly described as a “Parkinson-plus” syndrome, it is clear that cognitive changes are prominent in the clinical course, affecting the quality of life as much as the motor symptoms. Initially considered an entity with damage to the basal ganglia and the frontal-parietal cortex, with mainly parkinsonism and apraxia, recent investigations have shown variable involvement of frontal, parietal, and temporal cortices, resulting in a combination of other cognitive domains. Higher cortical features include limb or orobuccal apraxia, alien limb phenomena, cortical sensory loss, aphasia, global cognitive impairment, and behavioral changes[28].

Previously, cognitive deficits were considered a late-stage phenomenon[35]. However, it is currently known that these features may be present from the outset of the illness, even in cases with underlying CBD pathology, leading now to their incorporation into most diagnostic criteria (table 1)[28,36].

There is wide variability in the literature regarding the frequency of cognitive dysfunctions in CBS[36]. Multidomain cognitive impairment is extensively reported, and patients can occasionally present memory and executive function impairments, but these symptoms are also commonly seen in other

neurodegenerative diseases. Previous clinicopathologic studies suggested that episodic memory deficits could predict AD pathology in CBS patients[37,38], while the presence of frontal lobe dysfunction (such as nonfluent language deficits and utilization behavior) could predict CBD pathology[37]. Other studies, however, have not demonstrated similar cognitive profiles in CBS cases with underlying AD vs. CBD pathology[39].

Classically, apraxia is the most recognizable feature and core to all previous criteria concerning CBS and CBD. Apraxia covers a spectrum of disorders that have in common the inability to perform a skilled or learned act that cannot be explained by an elementary motor, sensory or cognitive deficit[40]. Along with the alien limb phenomena, both are archetypical disorders of motor cognition[41]. Apraxia in CBS is often asymmetrical, and the ideomotor type is the most commonly described, although other types such as limb-kinetic, orobuccal, ideational, constructional, and dressing apraxia can also be presented[42].

A previous study investigating cortical dysfunction in CBS apraxia with transcranial magnetic stimulation (TMS) and functional MRI disclosed dysfunction and atrophy in premotor and parietal areas[43]. In the latter stages of the disease, apraxia can be challenging to elicit because of dystonia, bradykinesia, and rigidity in the same limb[15].

The alien limb phenomena are a heterogeneous group of behaviors in which one or more of a patient's limbs, usually an arm, behaves in a manner that appears purposeful or semi-purposeful but is independent of the patient's reported intentions, and is eventually associated with the sensation that a limb is foreign or has a will of its own[22,44,45]. A previous study using functional magnetic resonance imaging (fMRI) in a CBS patient showed that alien hand movements

activated networks from the primary motor cortex, premotor cortex, precuneus, and inferior frontal gyrus[46]. Alien limb phenomena are included in previous and current criteria, even though they are described in only 30% of CBD compiled cases[22].

Another higher cortical feature is cortical sensory loss, presented in approximately 25% of CBD cases[22]. It is characterized by impaired joint position sense, impaired two-point discrimination, agraphesthesia, and astereognosis in the setting of intact primary sensory modalities[15].

Furthermore, language deficits are recognized as a characteristic feature in CBS and CBD[22,28]. In some cases, language dysfunction may be the first symptom, and although estimates vary significantly, probably more than one-third of CBS patients have speech and language disturbances[13]. A large cohort study of 45 patients showed a frequent initial presentation with language impairment (69% of patients) compared to apraxia (29%), unlike most studies that highlight apraxia as the major CBS cognitive sign[47]. The predominant language impairment was coherent with asymmetrical hypoperfusion at the left frontal-parietal and posterior temporal cortices[47]. Additionally, a systematic review showed aphasia in 40% of compiled CBD cases at presentation and 52% over the disease course[22].

Noteworthily, the spectrum of speech-language impairment can range from slight dysarthria to severe aphasia[42]. Most studies have reported reduced verbal fluency, AOS, and also syntactic deficits, mainly when the CBS presentation overlaps with the nfvPPA phenotype[28,36]. Dysarthria is also common in CBS, characterized by a disturbance of the temporal and prosodic aspects of speech[48].

Nevertheless, few studies have thoroughly investigated the profile of speech and language impairments in CBS. Some studies show a pattern similar to the nfvPPA, presenting with agrammatism and AOS[13,48,49]. Conversely, other studies focusing on language assessment reveal a mixed pattern encompassing characteristics of more than one type of PPA[47].

For example, a study using amyloid-imaging with the Positron Emission tomography tracer Pittsburgh compound B (PIB-PET) demonstrated a tendency of greater impairment of sentence repetition in PIB-PET positive cases, a feature also observed in logopenic progressive aphasia[50]. Hence, they suggested that impaired sentence repetition in CBS cases could predict AD pathology[28]. AOS and nfvPPA, otherwise, might be a clinical marker of underlying tau pathology[39,51,52]. This heterogeneity found in the literature on speech-language impairment in CBS may be explained by multiple factors: disease stage at the time of assessment, different underlying pathologies, or lack of consensus on linguistic aspects to be assessed in these patients[49].

Visuospatial and visuoperceptual dysfunctions are well-established components of the presentation and are included in most diagnostic criteria for CBS[23,53,54]. Some patients, who later go on to develop CBS, present PCA in the initial evaluation. They can develop Balint's syndrome or one component of the syndrome (simultanagnosia, oculomotor apraxia, and optic ataxia), and also Gerstmann's syndrome (dyscalculia, dysgraphia, finger agnosia, and left-right disorientation) or visual agnosia[28]. Notably, visuospatial dysfunction is differentially distributed among the atypical parkinsonian syndromes, with the greatest impairment observed in CBS-CBD than PSP or MSA, which can be a useful clinical tool in the differential diagnoses[54].

Concerning underlying pathologies in CBS, a previous cohort demonstrated the existence of Gerstmann's syndrome as a frequent finding in CBS cases related to the presence of AD cerebrospinal fluid (CSF) signature, with considerable sensitivity (75%) and specificity (75%)[47]. Also, another study provided Class II evidence that some subtests of the neuropsychological test Visual Object and Space Perception Battery (VOSP) distinguished the CBS-AD group with 77% specificity and 100% sensitivity from those without AD pathology[55].

Behavioral symptoms similar to those observed in behavioral variant FTD may be present, including apathy, bizarre or antisocial behavior, personality changes, irritability, disinhibition, and hypersexuality[22].

Akin to motor features, there are no cognitive or language manifestations that reliably distinguish underlying pathologies in patients with CBS[28,35].

1.3 Pathology

As mentioned previously, multiple pathological processes have been reported in patients with CBS (table 2). Thus, clinically predicting underlying pathology is difficult, particularly in the first three years of symptoms[35].

In contrast, many patients with a *postmortem* diagnosis of CBD are never suspected of having the disease during life. Accordingly, the sensitivity of clinical findings for predicting underlying CBD pathology ranges from 25% to 56%[22].

Accurate diagnosis of underlying etiologies of CBS is only possible through *postmortem* brain analysis due to the degree of clinicopathological mismatch that exists. Most CBS cases are 4R-tauopathies[27], mainly CBD[28], followed by PSP[5,56]. Also, possible underlying pathologies include Alzheimer's disease (AD)[39,57], FTD

with transactivation response DNA binding protein 43 kDa (TDP-43) inclusions[56], Pick's disease[13], Creutzfeldt-Jacob disease[58], Lewy Body disease[59], among others[11,56,60] (table 2).

A notorious retrospective study at the Queen Square Brain Bank enlightened the multifaceted clinicopathologic correlates in CBS-CBD[5]. Among 21 CBS cases, only five had CBD pathology. Six cases consisted of PSP pathology, five cases showed AD pathology, two cases were Parkinson's disease (PD), two cases were FTD-TDP43, and one case had a non-elucidated pathology. Conversely, among 19 cases of CBD pathology, only five had received an antemortem diagnosis of CBS, eight were diagnosed as PSP, two as PD, one as Pick's disease, one as FTD, one as spastic quadriparesis with myoclonus and one as Gilles de la Tourette's syndrome[5].

The neuronal aggregates in CBD consist of the microtubule-associated tau protein. Tau is an abundant protein, typically found in the cytosol of neurons and glial cells in the central nervous system, and its function is to bind microtubules to stabilize the cell cytoskeleton[61]. In tauopathies, through many insults, the soluble tau protein detaches from microtubules and forms abnormal, fibrillar structures of aggregated, hyperphosphorylated and ubiquitinated tau[62]. The emergence of tau staining over the last decades has dramatically enhanced immunohistochemical characterization of these disorders[35].

In the adult human brain, six isoforms of tau are expressed[61]. They result from alternative splicing of exons two and three and of exon 10 in the MAPT gene[63]. The inclusion of exon 10 generates an isoform with four microtubule-binding domains (4R), while the absence of this inclusion produces an isoform with three microtubule-binding domains (3R)[61].

Table 2 - Pathologic correlations in corticobasal syndrome

Study pathology	Boeve, 2003[64]	Hodges, 2004[65]	Josephs, 2006[11]	McMonagle, 2006[13]	Shelley, 2009[37]	Ling, 2010[5]	Lee, 2011[56]	Total, N(%)
CBS cases, n	34	9	21	19	12	21	40	156(100)
CBD	18	7	10	11	6	5	14	71 (45.5)
PSP	6	0	10	1	0	6	5	28 (18.0)
AD	3	0	0	1	6	5	9	24 (15.4)
Pick's disease	2	0	1	3	0	0	1	7 (4.5)
FTD-TDP43	0	1	0	2	0	1	5	9 (5.8)
FTD- TDP43 + MND	0	0	0	0	0	1	0	1 (0.6)
CJD	3	0	0	1	0	0	0	4 (2.6)
PD	0	0	0	0	0	2	0	2 (1.3)
DLDH	2	1	0	0	0	1	0	4 (2.6)
MST	0	0	0	0	0	0	1	1 (0.6)
Mixed disease	0	0	0	0	0	0	5	5 (3.2)

Mixed cases: 2 PSP, 1 CBD, 1 FTD-TDP, all mixed with intermediate probability of Alzheimer's disease. CBD: Corticobasal degeneration; PSP: Progressive supranuclear palsy; AD: Alzheimer's disease; DLDH: Dementia lacking specific histology; PD: Parkinson's disease; FTD-TDP43: Frontotemporal degeneration with TDP-43 inclusions; MND: Motor neuron disease; CJD: Creutzfeldt- Jacob disease; MST: Multiple system tauopathy without argyrophilia. *Table adapted from Parmera JB, et al. Dement e Neuropsychol 2016; **10**: 267–75*[28].

3R and 4R isoforms are balanced in the healthy adult brain, but in primary tauopathies, either 3R-tau or 4R-tau predominates in the pathological lesions. The different neurodegenerative disorders that can cause CBS are associated with specific tau isoforms. CBD features predominant deposition of 4R-tau, likewise PSP, being both classified as 4R-tauopathies. Otherwise, AD is characterized by the simultaneous presence of 3R and 4R-tau protein, and Pick's disease by 3R-tau[28].

Besides these distinct biochemical features, microscopically, some findings can help to distinguish CBS pathologies. Neuropathological diagnostic criteria for CBD require tau inclusions in neurons and glia with astrocytic plaques and extensive thread-like pathology[66]. PSP has threads in gray and white matter, but in

CBD, the boundary between gray and white matter may be indistinct due to the severity of threads in both compartments[28].

Astrocytic plaques are the hallmark glial lesion of CBD and the most distinguishing histopathological feature between CBD and PSP. They represent tau accumulation in the distal segments of astrocytes with minimal accumulation in the cell body, creating a central clear zone. They are more numerous in the cortex but can also be seen in caudate and putamen and less often in the thalamus and midbrain tectum[28,66,67]. By contrast, in PSP, the characteristic glial lesion is the tufted astrocyte[63]. (figure 1)

Another pathological lesion highly suggestive of CBD is the ballooned neuron (Figure 1). These are swollen cortical neurons, most often found in the third, fifth, and sixth cortical layers, linked to chromatolysis. The cingulate gyrus, amygdala, insular cortex, and claustrum are the most common locations[28,66]. The ballooned neurons are rare or absent in PSP[28]. In addition, the presence of oligodendroglial tau inclusions called coiled bodies are common in CBD but are much more frequent in PSP than CBD[28]. (figure 1) Considering the recent advances in knowledge about tauopathies and the diagnostic challenges of CBS underlying pathologies, the development of specific biomarkers is increasingly necessary.

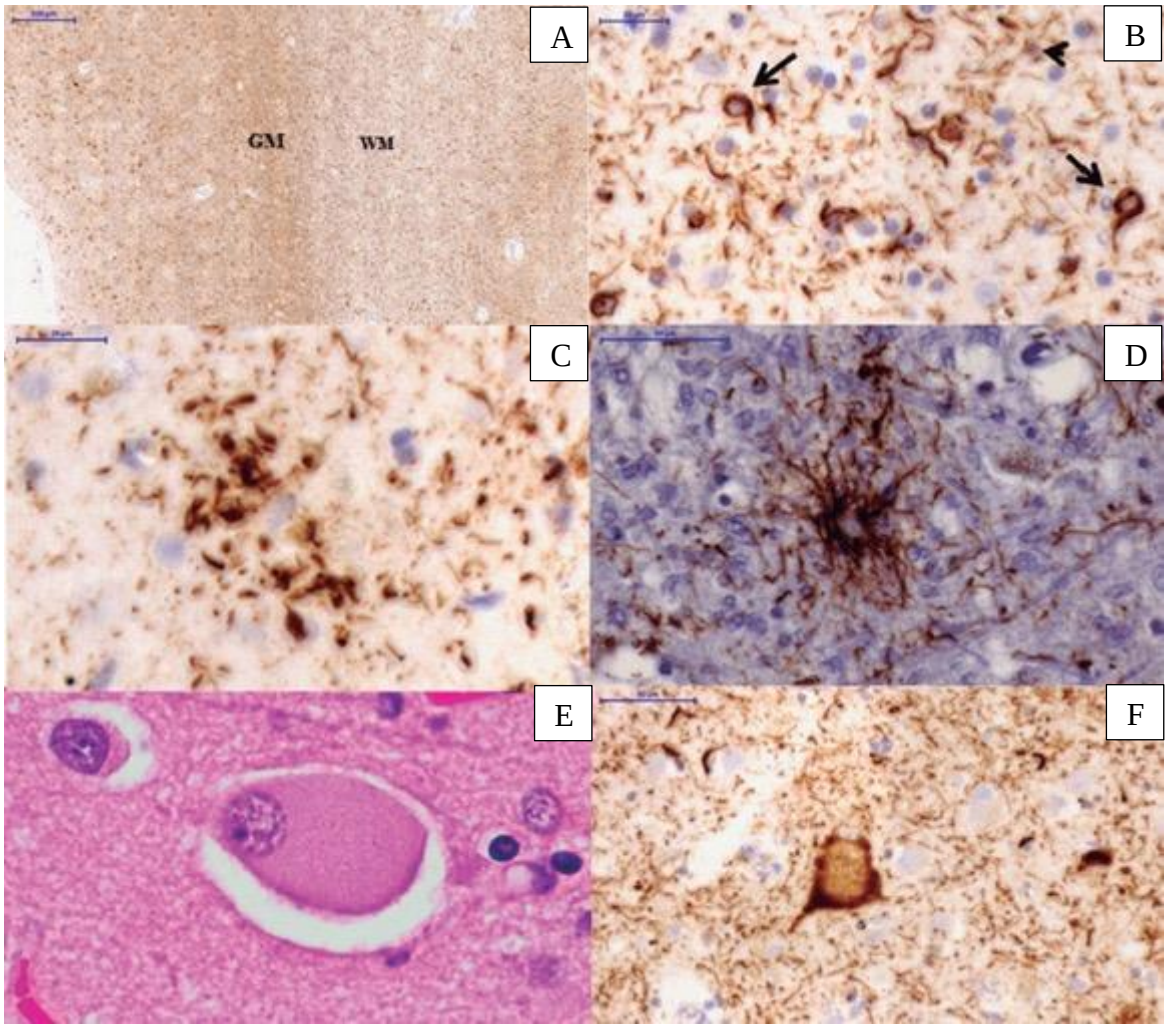


Figure 1 - Microscopic findings in CBD and PSP
[A] boundary between gray matter (GM) and white matter (WM) in the inferior temporal gyrus of a CBD case. [B] oligodendroglial coiled bodies (arrows) and thread-like pathology (arrowhead) in white matter in CBD case (tau immunostain, CP13 antibody); [C] astrocytic plaque, a hallmark of CBD (tau immunostain, CP13 antibody); [D] tufted-astrocyte, the characteristic glial lesion of PSP (tau immunostain, CP13 antibody); [E] ballooned neuron in the temporal cortex (hematoxylin-eosin); [F] tau-positive ballooned neuron in the temporal cortex. Scale bars represent 500 µm in A; 20 µm in B, C; 50 µm in [D, E]; and 10 µm in [F]. *Figure adapted from Parmera JB, et al. Dement e Neuropsychol 2016; **10**: 267–75*[28]

1.4 Biomarkers in corticobasal syndrome

There is growing interest in developing disease-specific biomarkers to aid in predicting pathology in the antemortem diagnosis of neurodegenerative disorders. Tau and Alzheimer's disease pathology-targeted therapies are currently being developed and undergoing clinical trials[68,69].

The main biomarkers under study regarding CBS and CBD include structural imaging modalities such as magnetic resonance imaging (MRI), molecular imaging with functional imaging and specific-ligands using positron emission tomography (PET), single-photon emission tomography (SPECT), and fluid biomarkers such as CSF and serum components[28,63].

Essential insights into the pathophysiological mechanisms related to clinical symptoms and underlying pathology in CBS have been gained by using advanced neuroimaging techniques. Structural and functional neuroimaging studies often show asymmetric cortical and subcortical abnormalities[70].

1.4.1 Structural neuroimaging and fluid biomarkers

Using the voxel-based morphometry (VBM) technique, previous MRI studies showed that CBS is associated with prominent asymmetric atrophy in the frontoparietal regions and basal ganglia[70,71]. A prior study assessed gray and white matter changes using surface-based morphometry and diffusion tensor imaging (DTI)[72]. Cortical thinning, subcortical volume loss, and fiber tract degeneration prominently involved the hemisphere contralateral to the more affected limb. Also, motor severity negatively correlated with the contralateral cortical thinning in the precentral and postcentral gyri and with volumes of putamen and accumbens[72].

Moreover, multimodal MRI studies are searching for specific patterns of structural lesions that may suggest underlying pathology. A case-control study with 24 clinicopathologic analyses suggested that patterns of gray matter loss in CBS differ according to the underlying pathology. CBS patients with a *postmortem* diagnosis of CBD and PSP displayed similar focal atrophy at

premotor and supplementary motor areas, although more severe in CBS-CBD. In contrast, patients with underlying FTD-TDP43 and AD pathology had a more widespread pattern of gray matter loss at the frontotemporal lobe and temporoparietal regions, respectively[73].

A previous multimodal MRI study evaluated whether AD or FTD pathology mediates the disease distribution observed in CBS by comparing gray matter cortical thickness and white matter fractional anisotropy. CBS-FTD had white matter disease in the corpus callosum, corticospinal tract, and superior longitudinal fasciculus, while CBS-AD had reduced temporoparietal gray matter relative to CBS-FTD, including the precuneus and posterior cingulate[74]. In addition to observations from white matter structural changes, a prior study applied network-based and graph-theoretical statistics to construct structural brain networks from DTI and showed that these networks better discriminated CBS-AD from non-AD than gray matter density analysis[75].

Concerning longitudinal analyses, two previous studies reported DTI and VBM changes over a 6-month follow-up period, suggesting that these measures might help to follow the pathological progression in patients with CBS[76,77].

There are no specific tau-based or other protein markers in biofluids to aid CBD diagnosis. CSF analyses are of particular interest given the frequency of AD pathology in CBS cases. It is observed that a high CSF tau/amyloid-b ratio may help distinguish AD from other causes of CBS underlying pathologies[35]. A recent study performed an antibody bead array analysis of CSF from pathologically confirmed cases of CBD and PSP and identified a series of potential CBD protein markers in CSF, which still require proper clinical validation and replication in larger samples.[78]

Another potential fluid biomarker of CBS is the neurofilament light chain (NFL), which release reflects non-specific axonal damage[63]. NFL levels in the serum can distinguish between atypical parkinsonian syndromes and Parkinson's disease, being markedly elevated in the former compared to the latter. However, it cannot distinguish CBD from PSP.[79,80]. Also, NFL is a consistent marker of disease progression and thus may be a helpful end-point in clinical trials of disease-modifying treatments[81].

1.4.2 Functional neuroimaging and specific ligands in corticobasal syndrome

Molecular neuroimaging using PET allows for quantitative visualization of functional processes *in vivo*. [^{18}F]fluorodeoxyglucose (FDG) is the most commonly used radiotracer for the assessment of regional brain glucose metabolism (rBGM) as a marker of neuronal function. By disclosing disease-specific alterations due to synaptic dysfunction, neuronal degeneration, and compensatory network changes, FDG-PET has become an essential part of the diagnostic workup of patients with neurodegenerative diseases[82].

Although disease-specific metabolic patterns in patients with CBS and other parkinsonisms have been known since the early days of PET imaging[83], the valuable role of FDG-PET for differential diagnosis of these entities has been increasingly acknowledged only in recent years[82].

Several studies have shown the applicability of FDG-PET to distinguish PD from atypical parkinsonism[84,85], and that it can assist in early differential diagnosis among the atypical parkinsonian syndromes[85,86]. Some studies used observer-dependent visual reads supported by voxel-based analyses[87,88],

whereas others used observer-independent automated statistical classifications[89,90].

A prior study with histopathological analyses included 20 PD cases, 21 MSA cases, 17 PSP, 10 CBD patients, 15 AD patients, six patients with DLB, and seven FTD patients, and found disease-specific metabolic patterns for each neurodegenerative disease in the Statistical Parametric Mapping (SPM), compared to healthy controls. Concerning CBD patients, they showed cortical hypometabolism contralateral to the affected side, including the prefrontal cortex, temporoparietal regions, motor cortex, cingulate gyrus, caudate nucleus, and thalamus[91]. Another large prospective cohort study with 107 patients showed that the FDG-PET had a higher diagnostic accuracy for the differential diagnosis between Lewy body disease (PD and DLB) versus atypical parkinsonian syndromes (MSA, PSP, and CBD) than striatal dopamine postsynaptic D2/D3 receptor 123-iodobenzamide (IBZM)-SPECT imaging (94% vs. 74%)[85]. This work supported a level I evidence for FDG-PET as an ancillary test in parkinsonism differential diagnosis. Additionally, they found that FDG-PET imaging may perform equally well or even better with a shorter duration of the disease process[85,92].

Moreover, spatial covariance analyses were used to detect abnormal metabolic networks in PD, MSA, and PSP, pointing towards a potential role for correlation with disease severity[82]. Spatial covariance analysis was also applied to CBD, disclosing asymmetric and bilateral metabolic reductions involving the frontal and parietal cortex, thalamus, and caudate nucleus, with more significant impairment contralateral to the most affected body side.[86]

A previous metanalysis addressed this issue and demonstrated that FDG-PET is highly accurate (>90%) at distinguishing between atypical parkinsonism and PD[82]. The specificity obtained in the PET diagnoses for MSA, PSP, and CBD usually exceeded 90%, whereas sensitivity was 77%–96% for MSA, 74%–100% for PSP, and 75%–91% for CBD[82]. Hence, most studies characterize CBD by a usually highly asymmetric hypometabolism of the frontoparietal areas, extending across the sensorimotor cortex and premotor-to-posterior prefrontal areas, striatum, and thalamus, contralateral to the most affected body side[82].

In contrast, the hypometabolism related to CBS shows a more complex set of patterns, eventually involving the posterior parietal and lateral temporal cortex and the cingulate gyrus. The heterogeneity of metabolic patterns found in CBS is most likely due to the variety of underlying pathologies[93]. Therefore, recent studies sought to investigate whether specific patterns of hypometabolism could predict distinctive CBS neuropathologic substrates.

Two previous studies used amyloid-PET as the gold standard for clinical diagnosis and tested the ability of FDG-PET to predict AD pathology in a total of 39 patients with CBS. Sensitivity ranged from 91% to 95%, specificity from 58% to 75%, and accuracy from 73% to 82%[94,95]. Namely, a more prominent temporoparietal than frontal hypometabolism pointed toward an underlying AD pathology in patients with CBS[94]. Hence, a systematic review with a specialist panel consensus considered the evidence supporting the clinical use of FDG-PET for identifying the neuropathology in patients with CBS as “fair”[93,96]. Furthermore, a recent study including 29 CBS cases with *postmortem* neuropathologic examination added robust evidence to this issue and demonstrated that neuropathology modulates metabolism, establishing CBS

metabolic patterns related to CBD, PSP, and AD[97]. The group-level analysis showed that CBS is associated with an asymmetric, frontal, temporal, and parietal pattern of hypometabolism with a common hypometabolic cluster for all pathologic diagnoses at the precentral gyrus. As the underlying pathology significantly modulated FDG uptake distribution, a typical posterior temporoparietal pattern was observed in CBS-AD, a medial–frontal pattern in CBS-PSP, and a frontoparietal cortex, thalamus, and caudate nucleus in CBS-CBD[97].

Specific-pathology ligands, such as the amyloid-PET and tau tracers, are leading the frontiers of neurodegenerative diseases biomarkers with their role in disclosing underlying pathology *in vivo*. The advent of amyloid-PET ligands has enabled the detection and quantification of amyloid neuritic plaques, a core pathologic feature of AD[98].

The first specific tracer to amyloid-beta applied in human studies was the [^{11}C]Pittsburgh Compound-B (PIB)[99], which does not bind to non-amyloid-beta inclusions such as neurofibrillary tangles or Lewy bodies[98]. Later, the second generation of amyloid tracers labeled with longer half-life fluorine-18 have been developed, and named florbetapir, flutemetamol and florbetaben. Noteworthily, amyloid-PET interpretation has some limitations as the fact that it is positive in about 20-30% of cognitively normal individuals and non-AD dementias, especially when older (mostly above 70 years old) or when carrying the ε4 allele of apolipoprotein E[98].

The first study to use amyloid-PET in patients with CBS showed that, among 14 patients, four were positive with high PIB binding (a standardized uptake ratio >1.5), indicating underlying AD pathology. Subtle differences in the

clinical presentation were noted between groups, with greater impairment of visuospatial function, more frequent deficits in sentence repetition, and greater functional decline in PIB-positive cases[50].

Another study using amyloid-PET as a surrogate to AD neuropathology split 25 CBS patients into frontal or temporoparietal variants based on clinical, MRI, and FDG-PET findings. Nine out of the 14 patients classified as having temporoparietal variant were PIB-positive (82% sensitivity and 71% specificity), suggesting that the classification helped to predict the likelihood of underlying AD, even though this requires further refinements. In the same study, one autopsy-proven patient with a positive amyloid-PET scan had the presence of CBD pathology, indicating that the possibility of co-pathology must be considered. Also, greater episodic memory and visuospatial impairment compared to executive dysfunction had the strongest association with PIB status[94]. Currently, amyloid-PET is available for clinical use and is approved by many regulatory agencies worldwide.

Additionally, PET tracers that bind to the microtubule-associated protein tau aggregated as neurofibrillary tangles have been developed. Over the past few years, several promising tau tracers compounds have emerged and consistently demonstrated appropriate brain penetration[98]. Prior studies using the first generation of tau-targeting tracers, as the most widely used ^{18}F-AV-1451 (also known as flortaucipir), showed good correspondence between *in vivo* imaging and *postmortem* evaluation for CBD[100], asymmetrical binding to motor-related subcortical gray and white matter structures in patients with CBS[101], and also a potential to distinguish between CBS and AD or PSP[102].

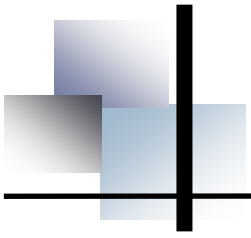
However, as the ultrastructural characteristics of tau filaments differ across diseases, first-generation tau tracers demonstrate more affinity to paired helical filaments found in AD (tau 3R/4R) than straight filaments found in 4R-tauopathies such as PSP and CBD. Accordingly, CBS neuropathologically confirmed cases of Alzheimer's disease show more significant and more widespread ^{18}F-AV-1451 retention and regional atrophy than observed in the amyloid-negative cases[103]. Second generation tau PET tracers such as [^{18}F]PI-2620, otherwise, demonstrated more specificity for 4R-tauopathies and may potentially be useful for a differential diagnosis and monitor disease progression[104].

1.5 Rationale

As previously highlighted, CBS consists of a rare entity with few prospective clinical cohorts investigating biomarkers and their relation to underlying pathologies. Moreover, scarce studies have performed comprehensive clinical protocols addressing simultaneously motor, cognitive, and language profiles. So far, they have mainly focused on cognitive or motor issues or only addressed imaging aspects and their differences due to diverse underlying pathologies. Also, studies with detailed clinical descriptions concerning different CBS pathological substrates are often derived from clinicopathologic retrospective cohorts, which are notoriously accurate regarding pathological descriptions. However, they usually display limitations concerning their retrospective nature.

Furthermore, few studies have explored CBS clinical profile in light of a multimodal imaging approach. Although FDG-PET and amyloid-PET are increasingly recognized to be clinically helpful in this regard, there is still a lack of

evidence supporting FDG-PET in the diagnostic workup depicting CBS pathologies *antemortem*. Considering that amyloid-PET use is often restricted to tertiary and research centers in most countries, FDG-PET might represent an interesting diagnostic tool in the clinical routine if CBS neurodegeneration metabolic patterns become increasingly better understood. Therefore, a prospective clinical evaluation of CBS patients with a multimodal imaging approach should probably aid in the knowledge of this hitherto enigmatic syndrome.



OBJECTIVES

2 Objectives

2.1 Main objective

- To investigate cognitive, language, and motor profiles in a cohort of patients diagnosed with probable CBS according to current criteria, using structural and molecular imaging biomarkers to identify potential features capable of predicting CBS underlying pathologies.

2.2 Secondary objectives

a) To investigate if individual brain FDG-PET patterns could distinguish CBS due to AD from other pathologies based on amyloid-PET.

b) To evaluate CBS clinical features regarding movement disorders, cognitive and language profiles and explore their possible correlations with brain metabolic patterns.

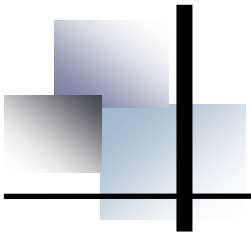
c) To investigate possible differences in CBS clinical features regarding the presence or absence of brain amyloid deposition on PIB-PET.

d) To investigate the metabolic patterns on FDG-PET in CBS patients related to the presence or absence of brain amyloid deposition on PIB-PET.

e) To compare the load of cortical amyloid deposition in CBS patients concerning their individual brain FDG-PET patterns.

f) To compare speech-language deficits in CBS patients related to the presence or absence of brain amyloid deposition on amyloid-PET.

g) To explore metabolic and structural signatures related to the different speech-language profiles observed in CBS patients.



METHODS

3 Methods

3.1 Participants

Forty-five patients meeting the probable CBS criteria[22] were prospectively recruited at the movement disorders and cognitive neurology clinics to prevent selection bias, at the Hospital das Clínicas, University of São Paulo School of Medicine (São Paulo, Brazil) between February 2017 and December 2019.

First, they were classified by assistant doctors at both clinics as having probable CBS. Later, all individuals were further evaluated regarding their clinical profile to perform the study protocol by two neurologists. Inclusion criteria for the patients consisted of presenting a progressive disease course with at least one year and a half duration. They also presented an asymmetric combination of at least two out of three motor features, including akinetic-rigid parkinsonism, dystonia, and myoclonic movements, as well as two out of three higher cortical features, including limb or orobuccal apraxia, alien limb phenomena, and cortical sensory deficits[22].

Exclusion criteria were relevant non-degenerative brain lesions such as stroke sequelae, tumors, hydrocephalus, and remarkable premorbid psychiatric disease. Alternative diagnoses among neurodegenerative diseases were also excluded through clinical history and neuroimaging, such as Creutzfeldt-Jakob disease, other atypical parkinsonian syndromes, Parkinson's disease, typical Alzheimer's disease, among others.

We also included 30 age-matched cognitively healthy participants (NC group) from the community as imaging controls after neuropsychological and neurological evaluations. They were all participants of another prospective research of our group. They matched CBS patients by age (median age 67.0, IQR 62.25-70.0) and scanner type.

3.2 Ethics

The Institutional Review Board of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (CAPPesq) approved the investigation procedure and informed consent under protocol number 67195517.4.0000.0068 (Appendix B). All participants or their caregivers provided written informed consent for the study (Appendix A).

3.3 Clinical assessment

All patients received a standardized predefined clinical evaluation. Global cognitive impairment was assessed with the Addenbrooke's Cognitive Examination – Revised (ACE-R)[53,105,106] and the Mini-Mental State Examination (MMSE)[107], both previously validated in Brazilian cohorts.

The Brief Cognitive Screening Battery (BCSB)[108,109], a visual test able to identify memory impairment in older individuals with different educational backgrounds, was used to assess episodic memory. Attention and working memory were measured with forward and backward digit span tests, respectively. Functional decline was assessed with the Clinical Dementia Rating scale[110] and Functional Activities Questionnaire[111].

Higher cortical functions were clinically evaluated by the presence of limb or orobuccal apraxia, cortical sensory deficits, alien limb phenomena, visual neglect, Balint and Gerstmann syndromes. We characterized the presence of limb apraxia by imitation of meaningful and meaningless gestures and with imaginary tool use, and orobuccal apraxia by meaningless orobuccal gestures[112].

A detailed examination of the motor signs was performed through a neurological examination and evaluated motor signs such as parkinsonism, dystonia, myoclonus, pyramidal signs, postural instability, tremor, ocular motor dysfunction, and elementary motor perseveration. The motor impairment was also categorized by the Hoehn and Yahr scale[113]. Behavioral aspects were evaluated with the Neuropsychiatric Inventory scale (NPI)[114,115].

The neurologists also questioned the participants and caregivers about their first symptoms and, together with major signs at first examination, designated the patient's first symptom as mainly cognitive, language, motor, or behavioral impairment. We also applied the Movement Disorders Society (MDS) criteria for probable 4-repeat (4R)-tauopathies[26].

3.4 Speech and language assessment

A comprehensive speech and language evaluation was performed by two speech-language pathologists, including the Western Aphasia Battery-revised (WAB-R)[116], the American Speech-Language-Hearing Association Functional Assessment of Communication Skills (ASHA-FACS)[117], and verbal fluency tests.

From the WAB-R, the following subtests were utilized: spontaneous speech, verbal comprehension, repetition, naming, and word finding. The aphasia quotient (AQ), a measure of aphasia severity, was derived from those

tests. ASHA-FACS is a scale that measures functional communication. It evaluates the level of assistance that the patient needs to communicate effectively.

The presence of AOS, agrammatism, and dysarthria was also evaluated. AOS was evaluated based on all the speech productions, and the presence of agrammatism was judged based on all oral productions and, when available, written productions.

Dysarthria was characterized as present or absent considering the different manifestations in the motor speech bases (i.e., breathing, phonation, articulation, resonance, and prosody), through the evaluation of reflexes, saliva control, breathing, tonus, and mobility of phonoarticulatory structures, and speech intelligibility.

To characterize the presence of aphasia, the AQ score was compared of each CBS patient to the median value of the AQ of other 24 healthy control subjects with the same age and education level. If this data was not available, aphasia was categorized based on the language score at ACE-R with cut-off scores obtained from a previous Brazilian study, based on age and formal education[105].

For the semantic fluency task, participants were asked to name as many animals as possible in one minute. Participants named words beginning specifically with the letter P for the phonemic fluency task. Based on a previous survey of a Brazilian sample, we determined cut-off scores for semantic fluency of nine for illiterates or individuals with less than eight years of formal education, and 13 for persons with more than eight years of formal education[118]. We determined cut-off scores for phonemic fluency of 13 for illiterates or individuals

with less than eight years of education, and 15 for persons with more than eight years of education[119].

3.5 Neuroimaging data acquisition

Both [^{11}C]Pittsburgh Compound-B (PIB) and [^{18}F]fluorodeoxyglucose (FDG) were produced in an on-site cyclotron (PET trace 880, GE Healthcare) at the Nuclear Medicine Center of the Institute of Radiology (CMN InRad, São Paulo, SP, Brazil) of our Hospital. PIB-PET and MRI images were simultaneously acquired on a hybrid 3.0-Tesla SIGNA PET/MRI scanner (GE Healthcare, Milwaukee, WI). The MRI protocol included volumetric sequences weighted on T1, T2, and T2/FLAIR (fluid attenuation inversion recovery) sequences, as well as diffusion-weighted imaging (DWI) in six and 33 directions, and susceptibility weighted imaging (SWI). All images were visually inspected for the detection of structural lesions of the brain, skull, head and neck lesions, as well as for the assessment of imaging artifacts that could impair imaging processing.

FDG-PET was acquired in a Discovery 710 PET/CT scanner (GE Healthcare, Milwaukee, WI). The radiotracer FDG was injected intravenously in bolus with a mean activity of 5-6 mCi. Before the radiopharmaceutical injection of FDG, the subjects were fasted for at least 6 hours, and their blood glucose level was <180mg/dl. The time interval between injection and scan start was at least 30 minutes, and scan duration was 15 minutes. Each PET scan was corrected for attenuation with CT data. Images were reconstructed using an ordered subset expectation maximization (OSEM) algorithm.

The production of the radiopharmaceutical compound PIB was entirely carried out in the cyclotron of our center and previously validated in our

environment[120]. The images of cortical amyloid deposition were analyzed in the acquisition time of 30 minutes, obtained in rest conditions, between 40 and 70 minutes after intravenous administration of 10-15 mCi of the radiopharmaceutical.

The FDG-PET was performed within one month after clinical examination, and the time between FDG and PIB-PET/MRI varied from 2 days to 6 months.

3.6 MRI visual analysis.

Images were visually inspected by a board-certified neuroradiologist for the detection of structural brain lesions, artifacts that could impair imaging processing, and the assessment of white matter hyperintensities (WMH), according to the Fazekas scale[121].

3.7 FDG-PET and PIB-PET visual analysis and classification

3.7.1 FDG-PET

Visual analysis of FDG-PET images, assisted by the 3D-SSP semi-quantitative software (Cortex ID Suite, GE healthcare) and normalized by at least two different methods (global cortex and pons), was performed by two board-certified nuclear physicians, blinded to each other's interpretation, clinical profile, and PIB-PET status.

The FDG-PET analysis was performed in three steps:

I. Classification in "normal" vs. "abnormal"

II. Classification in "CBS FDG-AD" vs. "CBS FDG-nonAD": based on the FDG-PET findings, the patients were split in two groups, namely “CBS likely related to AD” (CBS FDG-AD), or “CBS likely not related to AD” (CBS

FDG-nonAD), according to patterns of hypometabolism previously described for neurodegenerative diseases[87,88,91,96]. Hypometabolic pattern suggestive of AD included decreased rBGM in the posterior temporoparietal, inferior temporal regions, precuneus, and posterior cingulate gyrus[122,123].

III. A subclassification in different nonAD patterns: we considered the remaining patterns as non-AD group, and performed a subclassification regarding these different patterns into CBD, PSP, Lewy Body dementia (LBD), FTD, and indeterminate (closely related to tauopathies), also according to patterns previously described[91,96]. We evaluated the interrater agreement in the FDG-PET classification and subclassification (II and III steps).

If there was no consensus, a third independent reader rated the exam in order to reach consensus. There was no consensus reading for the non-AD subclassification.

3.7.2 PIB-PET

The same nuclear medicine physicians blindly performed a visual evaluation of the PIB-PET images assisted by a 3D-SSP semi-quantitative software (Cortex ID Suite, GE healthcare). Participants were rated as "CBS-A+" or "CBS-A-" if they were positive or negative, respectively, for the presence of cortical amyloid deposition, according to previously established criteria[124].

Each PIB-PET scan was classified as "amyloid positive" if there was a loss of gray and white matter contrast, with increased uptake in cortical gray matter in at least two of the following six areas: frontal, temporal, lateral parietal,

precuneus, anterior cingulate and posterior cingulate. The image was also classified as positive if only a single large cortical area had a strong tracer uptake. Conversely, the image was rated as "amyloid negative" when there was a clear contrast between gray and white matter, with strong uptake in the white matter and no significant activity in the cortex. Semiquantitative analysis was performed using the 3D-SSP method with standard uptake values ratio (SUVr) of the cortical areas normalized to the cerebellar gray matter. A cutoff point of 1.42 for the SUVr was considered the positivity standard. A previous study from our group observed a high interrater agreement and similar amyloid positivity rates from the literature[125].

3.8. FDG and PIB-PET quantitative group analysis

FDG-PET quantitative group analyses were performed to investigate: 1) which brain areas were more consistently hypometabolic in CBS-A+ and CBS-A- patients 2) which brain areas were more consistently hypometabolic in CBS patients compared to healthy controls; 3) which were the most consistently hypometabolic areas in CBS patients concerning to the difference in speech-language performance; 4) which brain areas were correlated to the scores on phonemic and semantic verbal fluency tests.

PIB-PET quantitative group analyses were performed to investigate: 1) the intensity of cortical amyloid deposition in CBS FDG-AD vs. CBS FDG-nonAD groups; 2) the individual variability of rBGM and amyloid deposition of both groups.

FDG-PET and PIB-PET images were co-registered with their respective MRI images (volumetric T1 sequence) and spatially normalized using the

Statistical Parametric Mapping 8 (SPM8) software (Wellcome Department of Cognitive Neurology, Functional Imaging Laboratory, London, UK) into an anatomic template[126].

To perform the first and second FDG-PET investigations mentioned before, we flipped the images to represent the hemisphere contralateral to the most affected limbs on the right side of the image because of CBS's asymmetric nature. The third and fourth analyses were performed within the images in their original lateralization to evaluate aspects of language hemisphere dominance.

The spatial normalization of FDG-PET scans was performed using a dementia-optimized brain FDG-PET template[126]. PIB-PET images were spatially normalized into an anatomic template generated with Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) algorithm. Scans were smoothed with an 8 mm full width at half maximum Gaussian kernel to reduce misregistration into the template space and improve the signal-to-noise ratio. A default threshold of 0.8 of the mean uptake inside the brain was selected to ensure the analysis only included voxels mapping cerebral tissue. Global uptake differences were adjusted using the "proportional scaling" SPM8 option.

Global uptake differences were adjusted using the “proportional scaling” SPM8 option. For the group analyses, statistical parametric maps were generated with SPM8 threshold at the voxel level at *p* uncorrected (*p* unc) =0.001, with a minimum extension of 100 voxels in the cluster. Statistical results were considered valid when survived correction for multiple comparisons with the familywise error (FWE) or false discovery rate (FDR) methods, (pFWE/FDR<=0.05), or without correction for multiple comparisons with *p* unc <0.001, when a priori regions were observed, according to established patterns

of neurodegeneration[87,91,96,122]. Relevant peak voxels from the statistical parametric maps were identified in the Montreal Neurologic Institute (MNI) coordinates system.

The numeric values representing the mean FDG uptake for each individual (a proxy for rBGM) in the clusters with statistically significant results in the SPM group analyses were obtained with the toolbox MarsBar for SPM (http://marsbar.sourceforge.net/) and later also investigated using GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA, USA).

3.9. Voxel-Based Morphometry analysis

We performed quantitative voxel-based MRI group analyses to investigate: 1) brain atrophy patterns in CBS patients compared to healthy controls; 2) brain atrophy patterns in CBS patients related to the difference in speech-language performance compared to healthy controls.

Like in the FDG-PET quantitative analysis, we flipped the images to represent the hemisphere contralateral to the most affected limbs on the right side in the first step of investigation. The second analysis was performed within the images in their original lateralization to evaluate language hemisphere dominance aspects.

MRI T1-weighted volumetric images were processed using VBM on SPM8 using the SPM toolbox *Diffeomorphic Anatomical Registration using Exponentiated Lie algebra* (DARTEL) algorithm. This algorithm segmented MRI images into liquor, gray matter, and white matter.

3.10 Study design

First, the patients were prospectively selected (3.1) and clinically assessed according to the clinical protocol (3.3). Forty-five patients underwent FDG-PET and were individually classified concerning their metabolic patterns as “CBS FDG-AD” or “CBS FDG-nonAD” (3.7.1). After this, both groups were compared concerning the clinical evaluation, aiming to delineate the clinical variants based on the metabolic patterns.

Thirty patients underwent PET-MRI with [^{11}C]PIB and were classified as CBS-A- and CBS-A+, according to the PIB-PET status (described in section 3.7.2). Diagnostic accuracy for FDG-PET to detect amyloid deposition was evaluated, as well as the clinical profile in patients with positive or negative PIB-PET status. Later, we performed quantitative group analyses as described in sections 3.8. The study design is summarized in figure 2.

3.11 Funding

This work was supported by the São Paulo Research Foundation (FAPESP) in Brazil, reference number 2017/10033–4.

3.12 Statistical analysis

Demographic and clinical analysis was conducted using the appropriate statistical tests with the Statistical Package for Social Sciences software, version 21.0 (SPSS, IBM Statistics, Chicago, IL, USA) and with R program (https://www.r-project.org/).

Categorical variables were expressed as absolute and relative frequencies and compared with Pearson's Chi-square on univariate analysis. Continuous

variables were compared using independent samples Student's t-test or Mann-Whitney test according to data distribution, assessed with Kolmogorov-Smirnov's test. Data with normal distribution were expressed as mean ± standard deviation and data with non-normal distribution as median [Interquartile range (IQR)] or as number [frequency]. All tests were two-sided. Statistical significance was accepted for $p<0.05$.

The sensitivity and specificity of FDG-PET to detect amyloid deposition on PIB-PET were assessed. Positive and negative predictive values, likelihood ratios, overall and balanced accuracy were also calculated. Agreement in visual FDG-PET classification was measured using Cohen´s kappa statistic (κ).

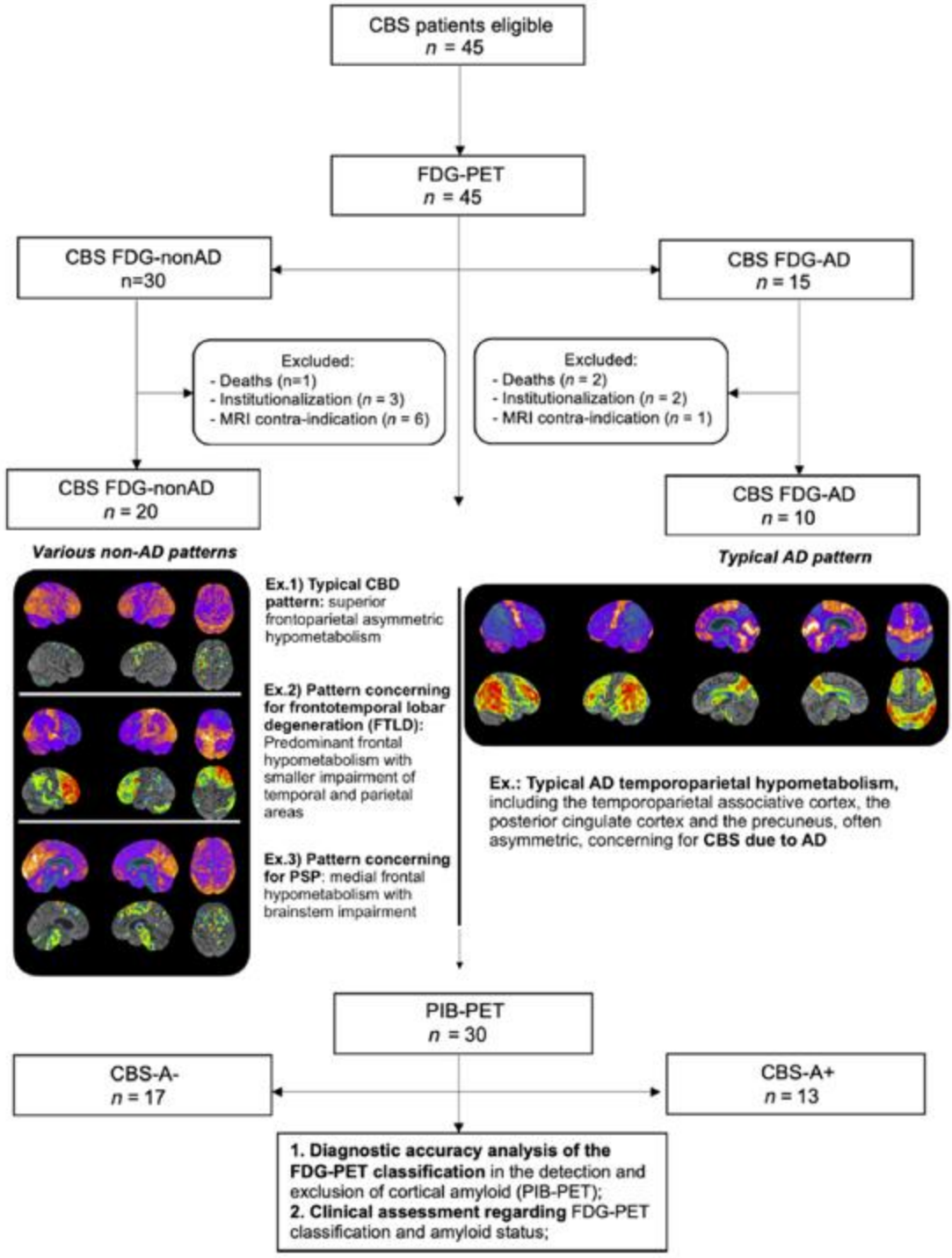


Figure 2 - Study design and flow of participants. Images on the left side depict 3D stereotactic surface projections (3D-SSP) for the CBS FDG-nonAD group, and, on the right side, 3D-SSP projections for the CBS FDG-AD group. Abbreviations: AD, Alzheimer's disease; CBS, Corticobasal Syndrome; FDG-PET, [^{18}F]fluorodexyglucose-PET; PIB-PET, [^{11}C]Pittsburgh Compound-B-PET; CBS FDG-AD, group with a metabolic pattern likely related to AD; CBS FDG-nonAD, group with a metabolic pattern likely not related to AD; CBS-A+, CBS subjects with positive PIB-PET; CBS-A−, CBS subjects with negative PIB-PET. *Adapted from Parmera, Jacy Bezerra et al. Movement disorders. vol. 36,3 (2021): 651-661.*

RESULTS

4 Results

4.1 Demography and clinical features of the whole CBS sample

In total, 45 CBS patients were included and underwent a comprehensive clinical evaluation. Demographic data are summarized in Table 3.

All patients (100%) presented with asymmetric parkinsonism, 30 (66.7%) presented myoclonus, mostly stimulus-sensitive or poliminimyoclonus in upper limbs, and 19 (42.2%) demonstrated upper limb asymmetric dystonia. Seven (15.6%) had cervical dystonia.

Regarding other motor signs, 14 patients (31.1%) had pyramidal signs, 13 (28.9%) had postural instability, and two (4.4%) had upper limb tremor. Eight patients (17.8%) presented ocular motor dysfunction, including vertical supranuclear gaze palsy (two patients) and slowness of vertical saccades (six patients).

Regarding higher cortical dysfunctions, ideomotor apraxia was the most frequent cortical feature, present in 44 (97.8%) patients. Five (11.1%) demonstrated orobuccal apraxia. Eight (17.8%) patients had alien limb phenomena. However, none of these contained intermanual conflict, and were characterized as frontal or parietal variants of alien hand syndrome. Twelve patients (26.7%) had cortical sensory loss, four (8.9%) had Balint syndrome, and three (6.7%) had Gerstmann syndrome.

Concerning speech and language features, among 31 patients who underwent the complete language evaluation, 21 patients (67.7%) had aphasia

according to standard deviations of the AQ at WAB-R test or normative values on language subtest at ACE-R. Most measures obtained from WAB-R showed impairment in naming, sentence comprehension, and spontaneous speech (Table 4). Phonemic and semantic verbal fluency tests were below the normative values in 29 (93.5%) and 26 (84%) patients of the whole sample, respectively. Dysarthria was detected in 11 (35.5%) and AOS in 7 (19.4%). Two patients (6.45%) presented agrammatism.

Frontal and behavioral symptoms were also prevalent, with motor perseveration in 13 cases (28.9%) and visual hallucinations present in 9 cases (20%).

The main initial complaints referred to cognitive (55.6%), followed by motor (40%) and psychiatric issues (4.4%). Cognitive assessment and functional decline of the whole sample of patients with CBS is shown in Table 3. Cortical and motor signs are represented in figure 9, and speech-language features are also represented in figure 10.

Table 3 - Demography, functional decline and cognitive assessment of patients with corticobasal syndrome and comparison according to the FDG-PET metabolic patterns

Demography	**CBS (n = 45)**	**CBS FDG-AD (n = 15)**	**CBS FDG-nonAD (n = 30)**	***p* Value**
Sex, M/F	18/27	6/9	12/18	0.62
Age at symptom onset, y	63.2 (± 8.5)	62.4 (± 7.1)	63.6 (± 9.2)	0.66
Age at main assess, y	67.3 (± 8.5)	66.8 (± 7.7)	67.5 (± 8.9)	0.79
Symptom duration at main assess, y	4.1 (± 2.2)	4.4 (± 1.7)	4.0 (± 2.4)	0.51
Education, y	8.7 (± 5.8)	10.8 (± 6.3)	7.7 (± 5.3)	0.91
First initial symptom	Cognitive: 25(55.6%) Motor: 18 (40%) Psychiatric: 2 (4.4%)	Cognitive:12(80%) Motor:2 (13.3%) Psychiatric:1(6.7%)	Cognitive:13(43.3%) Motor:16 (53.3%) Psychiatric:1(3.3%)	0.073
Functional assessment				
CDR	0.5 13.3% 1.0 4.4% 2.0 51.1% 3.0 31.1%	0.5 0 1.0 6.7% 2.0 40% 3.0 53.3%	0.5 20% 1.0 3.3% 2.0 56.7% 3.0 20%	0.061
Functional Activities Questionnaire	20.4 (± 8.2)	23.6 (± 7.5)	18.7 (± 8.2)	0.062
Hoehn &Yahr	2.9 (± 1.2)	2.6 (± 1.1)	3.1 (± 1.2)	0.14
Cognitive Assessment				
ACE-R Total	39.8 (± 22.8)	26.6 (± 18.5)	45.6 (± 22.4)	**0.019[a]**
ACE-R Attention	10.2 (± 4.1)	7.1 (± 3.3)	11.6 (± 3.7)	**0.003[a]**
ACE-R Memory	8.7 (± 6.7)	3.9 (± 3.8)	10.9 (± 6.6)	**0.002[b]**
ACE-R Fluency	2.8 (± 2.9)	1.9 (± 2.1)	3.2 (± 3.1)	0.22
ACE-R Language	15.4 (± 6.7)	13.0 (± 7.8)	16.5 (± 6.0)	0.16
ACE-R Visuospatial	5.8 (± 3.7)	2.9 (± 2.2)	7.0 (± 3.6)	**0.001[b]**
MMSE	15.4 (± 7.4)	9.4 (± 6.5)	18.7 (± 5.7)	**< 0.001[b]**

continue

Delayed Recall (BCSB)	3.4 (± 2.8)	1.7 (± 2.0)	4.1 (± 2.9)	**0.030[a]**
Verbal Fluency (letter)	3.3 (± 2.9)	3.1 (± 2.6)	3.5 (± 3.1)	0.71
Verbal Fluency (animals)	6.2 (± 4.2)	5.0 (± 3.3)	6.8 (± 4.6)	0.23
Digit Span Forwards	5.7 (± 2.1)	4.7 (± 2.1)	6.3 (± 1.8)	0.30
Digit Span Backwards	1.7 (± 1.7)	1.2 (± 1.8)	2.1 (± 1.7)	0.14
NPI	17.1 (± 13.6)	20.0 (± 16.3)	15.4 (± 11.8)	0.32

finale

Abbreviations: AD, Alzheimer's Disease; CBS, Corticobasal Syndrome; FDG, [^{18}F]fluorodeoxyglucose; CBS FDG-AD, group with a metabolic pattern likely related to AD; CBS FDG-nonAD, group with a metabolic pattern likely not related to AD; CDR, Clinical Dementia Rating; MMSE, Mini-mental State Examination; ACE-R, Addenbrooke Cognitive Examination-Revised; BCSB, Brief Cognitive Screening Battery; NPI, Neuropsychiatric Inventory scale. Data reported as mean ± SD; P is significant at the .05 level. Comparison analysis was performed between CBS FDG-AD and CBS FDG-nonAD with **a.** Student's t-test and **b.** Mann-Whitney test.

4.2 FDG-PET individual classification and comparison to PIB-PET status

All patients underwent FDG-PET and showed hypometabolism predominantly asymmetrical, contralateral to the most affected side. At the visual classification, assisted by semi-quantitative analyses, thirty (66.7%) patients had a non-AD metabolic pattern (CBS FDG-nonAD group), and 15 (33.3%) showed an AD pattern (CBS FDG-AD group). A subset of 30 patients underwent PIB-PET examinations. Fifteen patients, however, did not undergo because of distinct reasons mentioned in figure 2. Regarding the 30 patients who underwent PIB-PET, 10/30 (33%) were blindly classified as belonging to the CBS FDG-AD group, and 20/30 (67%) to the CBS FDG-nonAD group.

Interrater agreement regarding the AD and non-AD FDG-PET classification was high, reaching a 98% inter-observer agreement (κ = 0.95). There was only one divergent classification, which the third independent reader blindly rated the scan as FDG-AD.

The subclassification concerning non-AD patterns disclosed CBD pattern in 50% by reader 1 and 58.1% by reader 2; PSP pattern in 20% by reader 1 and 12.9% by reader 2; FTD in 3.3% by both readers; LBD in 3.3% by reader 1 and 6.6% by reader 2, and indeterminate in 20% by reader 1 and 16.1% by reader 2. The interrater agreement regarding this subclassification was more modest, reaching 73.3% agreement (κ = 0.58). Patterns of individual FDG-PET classification are depicted at figures 3, 4, 5 and 6.

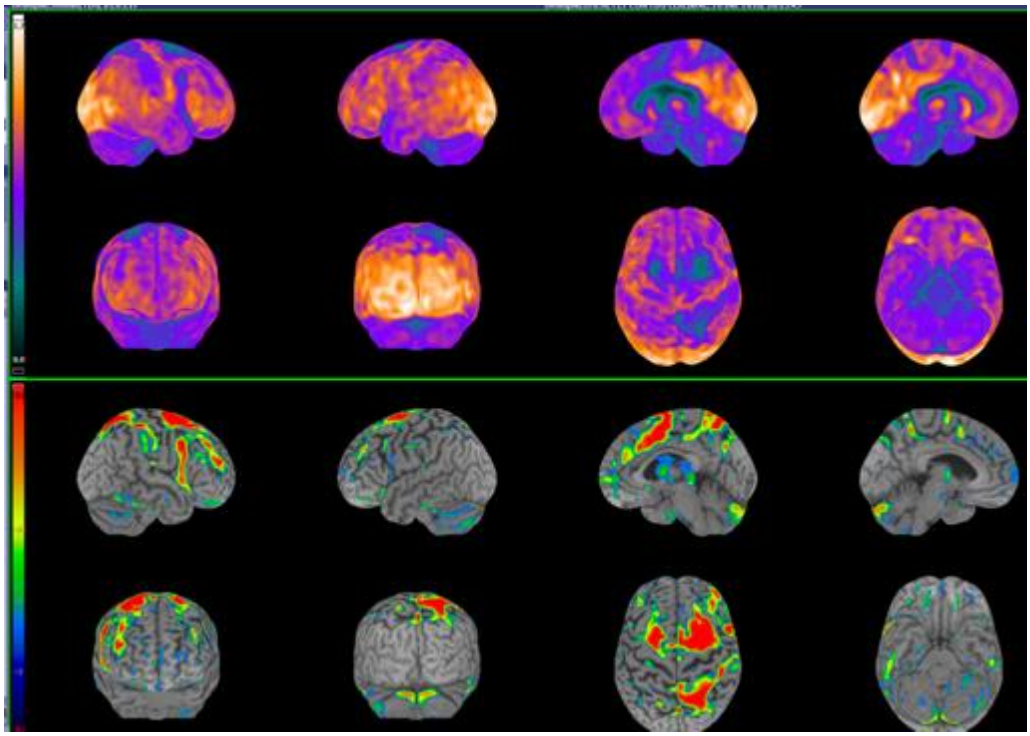


Figure 3 - FDG-PET disclosing CBD hypometabolic pattern
Upper row: FDG-PET 3D-stereotactic surface projection (3D-SSP, software Cortex ID Suite, GE Healthcare): asymmetric hypometabolism at frontoparietal areas, extending across the sensorimotor cortex and prefrontal areas, striatum, and thalamus. Lower row:Three-dimensional standardized projection (3D-SSP) on the individual comparison z-score map metabolic pattern in relation to age-matched normal individuals.

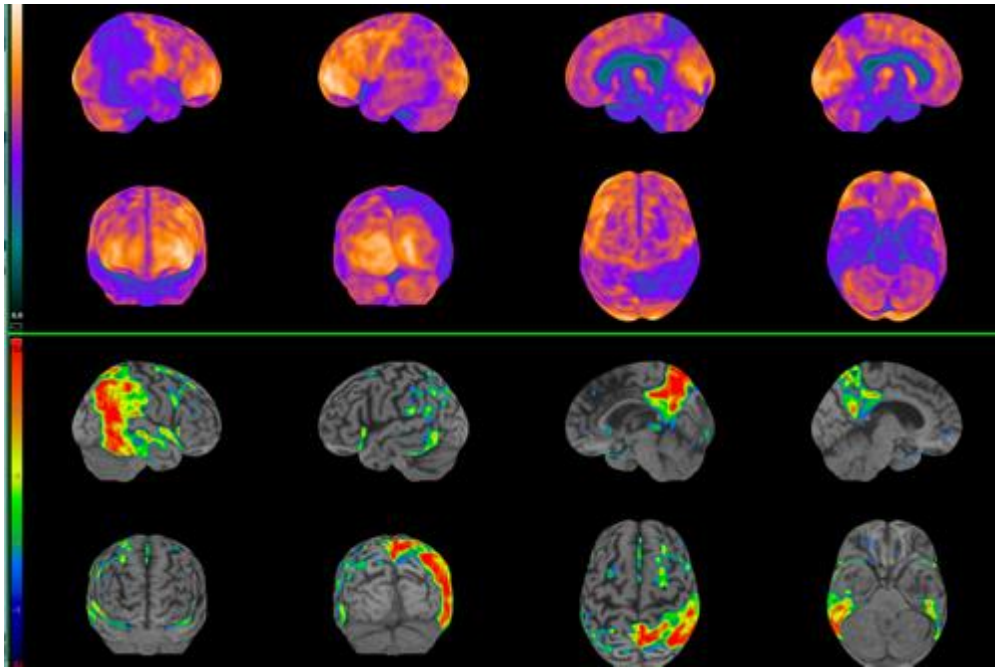


Figure 4 - FDG-PET disclosing AD hypometabolic pattern
Upper row: FDG-PET 3D-stereotactic surface projection (3D-SSP, software Cortex ID Suite, GE Healthcare): asymmetric AD pattern of posterior temporoparietal hypometabolism, with involvement of the posterior cingulate region and precuneus. Lower row:Three-dimensional standardized projection (3D-SSP) on the individual comparison z-score map metabolic pattern in relation to age-matched normal individuals.

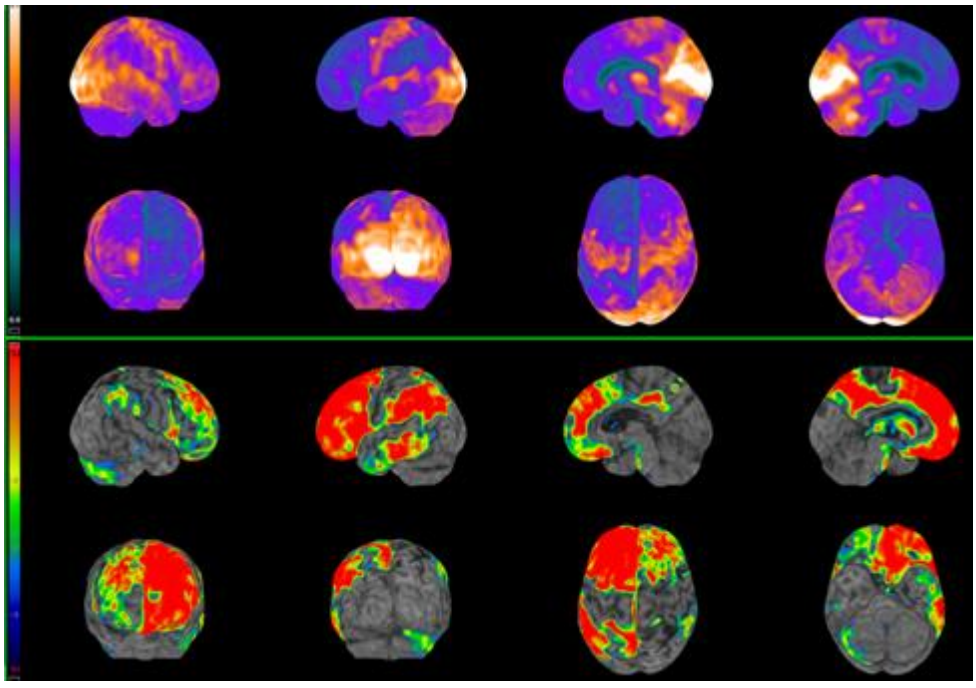


Figure 5 - FDG-PET disclosing FTD hypometabolic pattern
Upper row: FDG-PET 3D-stereotactic surface projection (3D-SSP, software Cortex ID Suite, GE Healthcare): predominantly asymmetrical anterior hypometabolism, mainly frontal and temporal regions. Lower row: 3D-SSP projections on the individual comparison z-score map metabolic pattern in relation to age-matched normal individuals.

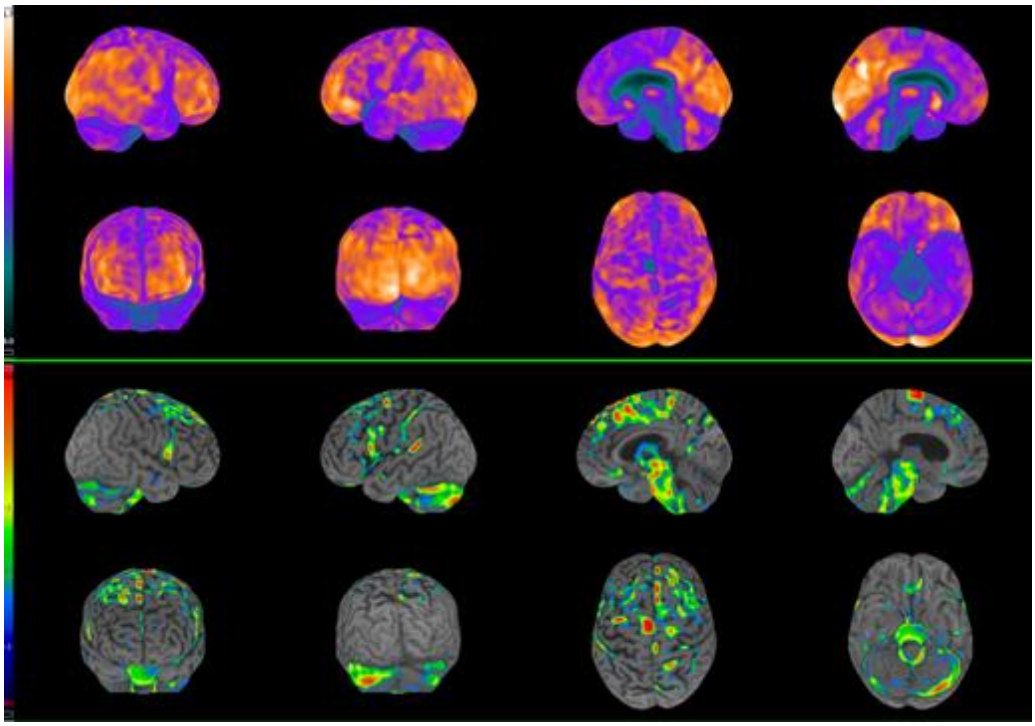


Figure 6 - FDG-PET disclosing PSP hypometabolic pattern
Upper row: FDG-PET 3D-stereotactic surface projection (3D-SSP, software Cortex ID Suite, GE Healthcare): hypometabolism predominantly at medial frontal gyrus, the anterior and middle cingulate gyri, and also with basal ganglia involvement. Lower row: 3D-SSP projections on the individual comparison z-score map metabolic pattern in relation to age-matched normal individuals.

Among all patients with PIB-PET, 17/30 (56.7%) had negative and 13/30 (43.3%) had positive results. In the CBS FDG-nonAD group, 17/20 (85%) were negative, and 3/20 (15%) were positive for cortical amyloid deposition. In the CBS FDG-AD group, all patients (100%) had positive PIB-PET results (p<0,001). (Figure 7 and 8)

The classification according to FDG-PET patterns in AD vs non-AD demonstrated 76.92% of sensitivity (CI 46.19 - 94.16%) and 100% of specificity (CI 80.49-100%) to detect amyloid deposition on PIB-PET. These values translate to a positive predictive value (PPV) of 100% (CI 69.2 – 100%), negative predictive value of 85% (CI 62.1 – 96.8%), negative likelihood ratio of 0.23 (CI 0.09 - 0.62), overall accuracy of 90% and balanced accuracy of 88.5%.

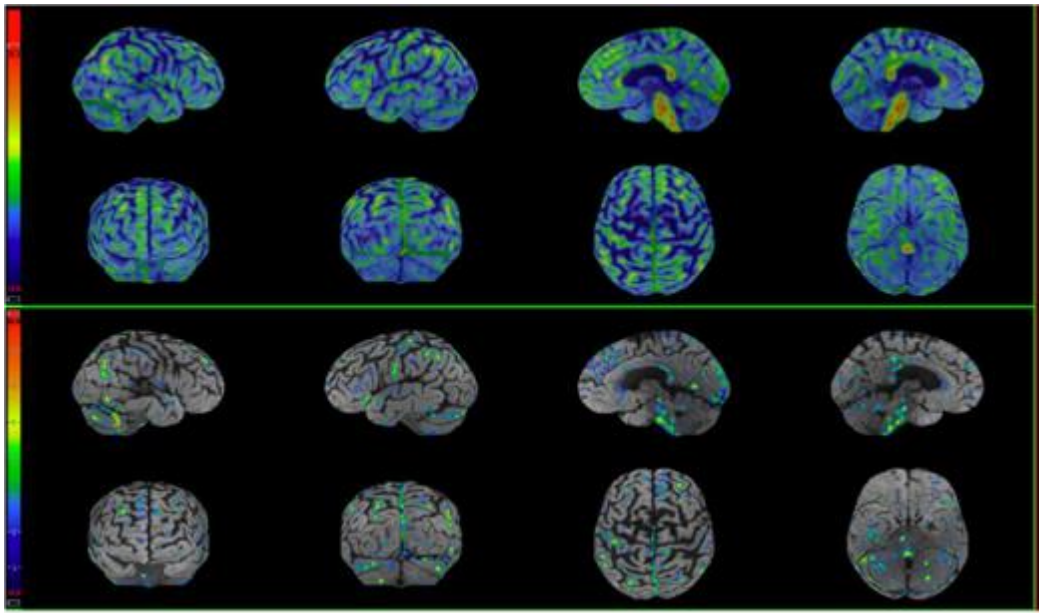


Figure 7- PIB-PET showing negative case for cortical amyloid deposition. 3D-SSP projections, software Cortex ID Suite, GE Healthcare) PET-MRI with acquisition of the biomarker PIB. Upper row: absence of significant uptake in the cortex. Lower row: comparison map with age-matched standard deviation with a group of healthy individuals, plotted on the individual's MRI.

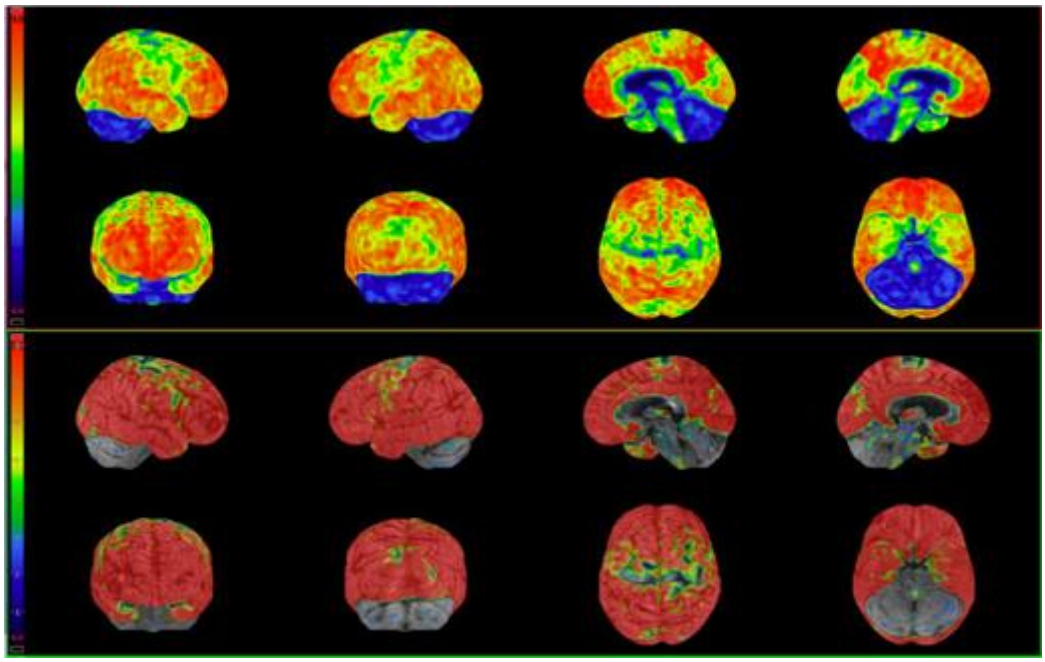


Figure 8 - PIB-PET showing positive case for cortical amyloid deposition
3D-SSP projections (software Cortex ID Suite, GE Healthcare) from PET-MRI with acquisition of the biomarker PIB. Upper row: presence of significant uptake in the cortex. Lower row: comparison map with age-matched standard deviation with a group of healthy individuals, plotted on the individual's MRI.

4.3 Clinical features according to FDG-PET groups

CBS FDG-AD and nonAD groups did not significantly differ regarding age, symptoms duration, and years of education. At the cognitive assessment, the CBS FDG-AD group had lower scores at MMSE, ACE-R total score and attention, memory, and visuospatial ACE-R subscores. CBS FDG-AD group also performed worse on the delayed recall subtest at BCSB (table 3).

Concerning cortical, motor and neuropsychiatric features, CBS FDG-AD patients had more myoclonus (100% vs. 50%, p=0.001) and visual hallucinations (40% vs. 10%, p = 0.042) compared to CBS FDG-nonAD patients. In addition, visual neglect also demonstrated a tendency of higher frequency in the CBS FDG-AD group (40% vs. 13.3%, p= 0.052).

Conversely, CBS FDG-nonAD patients presented more often limb dystonia (56.7% vs. 13.3%, p = 0.009), ocular motor dysfunction (26.7% vs. 0%, p= 0.038), dysarthria (39.1% vs. 0%, p =0.015) and motor perseveration (40% vs. 6.7%, p= 0.034). Motor and cortical signs are represented in figure 9.

When we applied the criteria for probable 4R-tauopathies[26], ten patients (33.3%) previously classified as CBS FDG-nonAD fulfilled the criteria compared to none in the CBS FDG-AD group (p = 0.019).

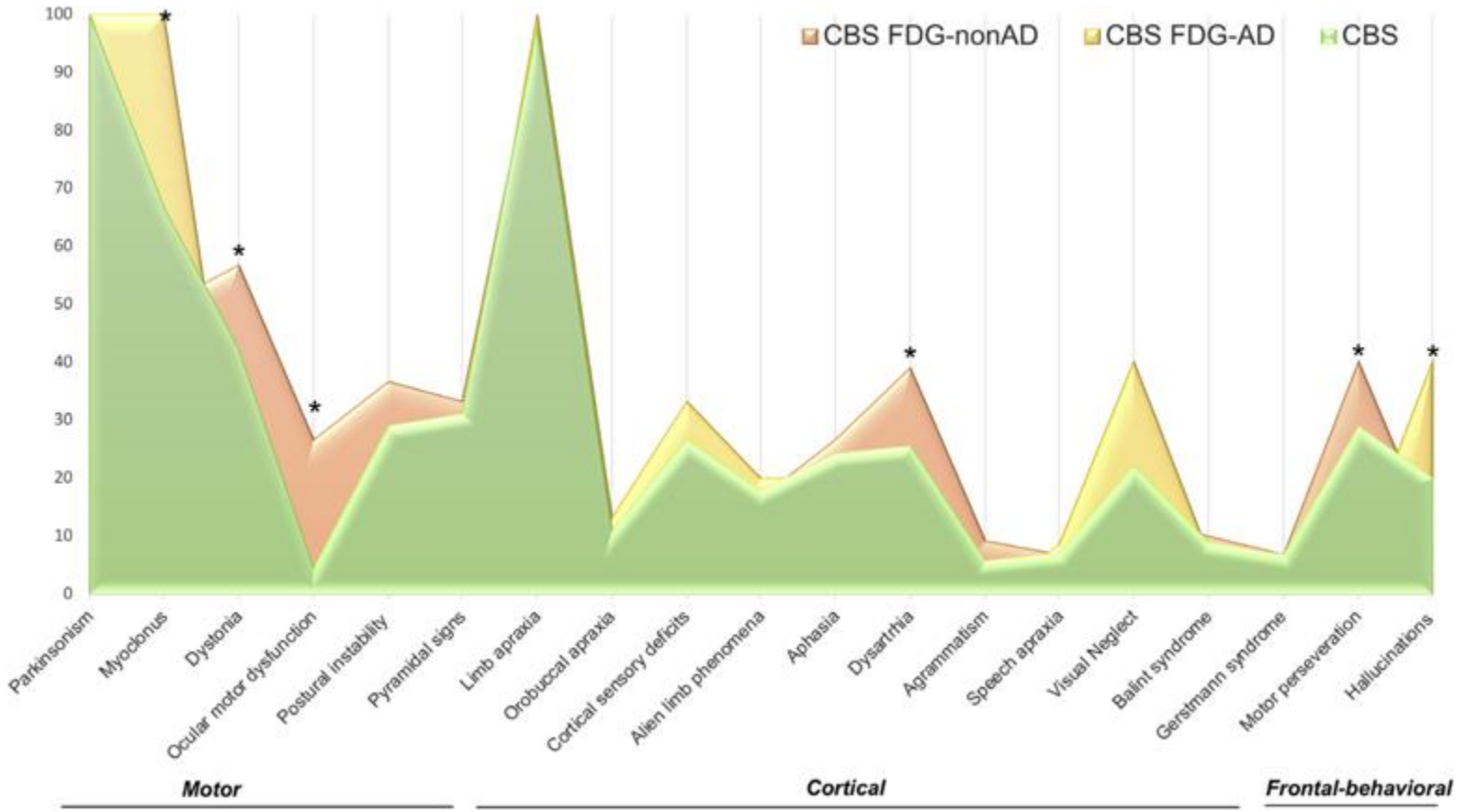


Figure 9 - Motor and cortical signs in the whole corticobasal syndrome cohort and according to the metabolic patterns

Data are presented as the frequency of the symptoms, in the total sample and according to the FDG-PET classification. The symbol (*) indicates statistically significant differences between the percentage of the feature in CBS FDG-AD vs CBS FDG-nonAD groups. Comparison analysis was performed with Pearson's χ2 and Fisher's exact test. (Myoclonus: P = 0.001; Dystonia: P = 0.009; Ocular motor dysfunction: P = 0.038; Dysarthria: P = 0.015; Perseveration: P = 0.034; Hallucinations: P = 0.042). Abbreviations: AD = Alzheimer's disease; CBS=Corticobasal Syndrome; FDG, [^{18}F] fluorodeoxyglucose; CBS FDG-AD, group with a metabolic pattern likely related to AD; CBS FDG-nonAD, group with a metabolic pattern likely not related to AD. *Adapted from Parmera, Jacy Bezerra et al. Movement disorders. vol. 36,3 (2021): 651-661.*

4.4 Clinical features according to PIB-PET status

Demographic variables did not differ regarding the presence of cortical amyloid deposition (CBS-A+ vs. CBS-A- patients). We were able to add one more patient after the main analysis, thus PIB-PET was classified negative (CBS-A-) in 18/31 (58%) and positive in 13/31 (42%) patients, after visual and semi-quantitative classification of cortical amyloid deposition.

The CBS-A+ group performed significantly worse on cognitive assessment through MMSE and ACE-R subscores (attention, memory, and visuospatial), but did not differ in total ACE-R score (table 4). Also, CBS-A+ patients had worse BCSB delayed recall performance, although it did not reach statistical significance (table 4).

There were no significant differences in higher cortical or motor symptoms or signs between groups (figure 10, table 4).

Concerning motor speech and language deficits, patients with negative amyloid deposition on PIB-PET displayed significantly more often dysarthria than the CBS-A+ group (10/18, 55.6% vs. 1/13, 7.7%, p= 0.008) (figure 10, table 5). The main characteristics were mixed hypokinetic and spastic dysarthria.

There were no statistically significant differences in the frequency of aphasia (p=0.452) (figure 10, table 5) and scores in the functional language assessment at ASHA-FACS between CBS-A- and CBS-A+ groups (p=0.961) (table 4). Only patients classified as CBS-A- showed agrammatism (two patients). Also, CBS-A- patients had more often AOS than CBS-A+ patients, although not statistically significant (p=0.35).

CBS-A- patients appeared to show more compromised phonemic verbal fluency (17/18, 94.4%) than semantic fluency (13/18, 72%), although this did not reach statistical significance (p=0.177).

Conversely, all patients (13/13, 100%) of the CBS-A+ group showed impaired semantic verbal fluency, and phonemic verbal fluency was impaired in 92.3% (12/13) of patients. (figure 10, table 4)

Table 4 - Demography, functional, cognitive, and language assessment of patients with corticobasal syndrome and comparison by amyloid-PET results

	CBS (n=31)	CBS-A- (n=18)	CBS-A+ (n=13)	*P* value
Demography				
Age at symptom onset, y	61 (58 -67)	60 (55-68)	63 (60- 66)	ns
Age at main assessment, y	65 (61 - 71)	63.5 (59 - 71)	66 (64 -71)	ns
Symptom duration at main assessment, y	4.0 (3.0- 4.5)	3.5 (2.2 - 4.7)	4.0 (3.0- 4.0)	ns
Gender (female)	14 (45.2%)	7 (38.9%)	7 (53.8%)	ns
Education, y	10 (6 - 15)	9.5 (6 -15)	10 (6-15)	ns
Side of more severely involved limbs (right)	13 (41.9)	8 (44.4%)	5 (38.5%)	ns
Handedness (right-handed)	26 (83.9%)	16 (88.9%)	10 (76.9%)	ns
Phenotype Cognitive Motor Language	 18 (58.1 %) 10 (32.3 %) 3 (9.7 %)	 8 (44.4 %) 7 (38.9 %) 3 (16.7 %)	 10 (76.9 %) 3 (23.1 %) 0 (0.0 %)	ns
Funcional assessment				
Clinical Dementia Rating	2.0 (1.5 – 2.0)	2.0 (0.6-2.0)	2.0 (1.0 – 2.0)	ns
Functional activities questionnaire	22 (14- 26)	18.5 (11- 25)	25 (16 -27)	ns
Hoehn &Yahr scale	2 (2 -3.5)	3.00 (2 - 3.75)	2.00 (2 -3)	ns
ASHA-FACS scale	3.2 (1.8 – 5.3)	3.2 (2.4 – 5.0)	3.0 (1.6-5.0)	ns
General cognitive assessment				
ACE-R total	41 (30- 62)	49 (31.5-74.5)	34 (27.5-46.5)	ns
ACE-R attention	11 (9- 13.75)	12.5 (11- 16.25)	9 (8-10.5)	**0.008**
ACE-R memory	8 (5.25 -15.75)	12.5 (7.75-18.25)	5 (2.25- 8)	**0.008**
ACE-R fluency	2.5 (1- 6)	3 (2 - 6.25)	1.5 (1- 4.5)	ns
ACE-R language	16.5 (14- 24.5)	19 (14.25-25)	14.5 (14-20.75)	ns
ACE-R visuospatial	7 (4 - 8.75)	8 (7 - 11.25)	4 (3.25- 5.75)	**0.001**
MMSE	18 (13- 21.50)	20.5 (16.5-25.75)	14 (11- 17)	**0.005**
Digits backward	2 (0 - 3.75)	3 (2 - 3)	0 (0 -4)	ns
Delayed recall (BCSB)	3 (0.5 -6)	5.50 (1.75- 6)	1 (0- 3)	ns
Language assessment				
Aphasia quotient (WAB-R)	68.8 (51.1-88.2)	70.35(38.7-83.3)	68.8 (63.7-90.2)	ns
Total spontaneous speech (WAB-R)	16.0 (9.5-17.5)	17.0 (10.0 - 18.0)	14.5 (10.0-16.75)	ns
Auditory word recognition (WAB-R)	54.0 (19.0 – 57.5)	57.0 (48.0 – 60.0)	50.0 (25.0 – 55.0)	ns
Sequential commands (WAB-R)	63.0 (25.0 – 80.0)	63.0 (28.0 – 80.0)	48.0 (15.2 – 73.2)	ns
Total repetition (WAB-R)	8.6 (3.3 -9.1)	8.6 (3.8- 9.2)	7.6 (3.0- 8.9)	ns
Naming and word Finding (WAB-R)	6.2 (3.25- 8.45)	7.1 (3.3- 8.5)	5.4 (2.5-7.1)	ns
Phonemic fluency (letter P)	3 (1.75- 6)	3 (2- 6.25)	2.5 (1- 5.25)	ns
Semantic fluency (animals)	5.5 (3.75 -10)	6.5 (3 - 11.75)	5 (4- 7)	ns

Clinical data comparison between CBS-A+ and CBS-A-. Data expressed as median (interquartile range) or number (frequency). Statistical significance was set as $p < 0.05$ (Mann–Whitney or Fischer's exact). Abbreviations: ns, non-significant; AD, Alzheimer's disease; CBS, Corticobasal syndrome; MMSE, Mini-mental State Examination; ACE-R, Addenbrooke Cognitive Examination-Revised; BCSB, Brief Cognitive Screening Battery; ASHA-FACS: Functional assessment of communication skills for adults.

Table 5 - Cortical and motor features of patients with corticobasal syndrome and comparison by amyloid-PET results

	CBS (n=31)	CBS-A- (n=18)	CBS-A+ (n=13)	*P* value
Cortical symptoms				
Limb apraxia	30 (96.8%)	17 (94.4 %)	13 (100.0 %)	ns
Orobuccal apraxia	5 (16.1%)	2 (11.1 %)	3 (23.1 %)	ns
Cortical sensory deficits	8 (25.8%)	3 (16.7 %)	5 (38.5 %)	ns
Alien limb phenomena	8 (25.8 %)	5 (27.8 %)	3 (23.1 %)	ns
Motor symptoms				
Parkinsonism	31 (100.0%)	18 (100.0 %)	13 (100.0 %)	ns
Myoclonus	21 (67.7%)	10 (55.6 %)	11 (84.6 %)	ns
Dystonia	10 (32.3%)	7 (38.9 %)	3 (23.1 %)	ns
Language symptoms				
Aphasia	21 (67.7 %)	11 (61.1 %)	10 (76.9 %)	ns
Dysarthria	11 (35.48 %)	10 (55.6 %)	1 (7.7 %)	**0.008**
Agrammatism	2 (6.45 %)	2 (11.1 %)	0 (0.0%)	ns
Apraxia of speech	7 (22.6 %)	5 (27.8 %)	2 (15.4 %)	ns
Abnormal semantic fluency	26 (83.9 %)	13 (72.2 %)	13 (100.0 %)	ns
Abnormal phonemic fluency	29 (93.5 %)	17 (94.4 %)	12 (92.3 %)	ns

Comparison between amyloid-PET positive (CBS-A+) and negative (CBS-A-). Data expressed as number (frequency). Statistical significance was set as $p < 0.05$ (Fischer's exact)

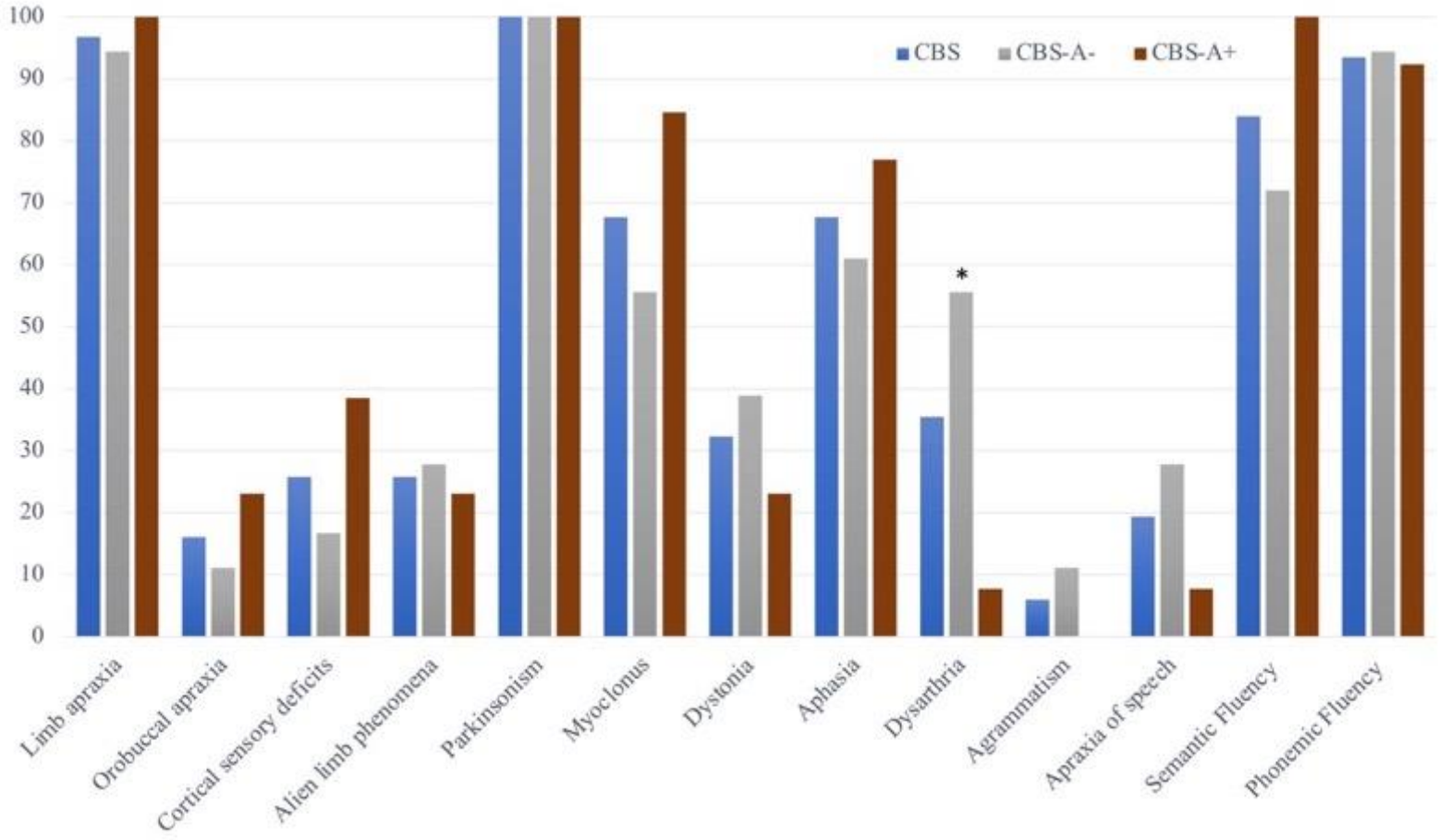


Figure 10 - Motor, cortical, and language deficits in the whole corticobasal syndrome cohort and according to amyloid-PET results. Data are presented as the frequency of the symptoms or the percentual of altered verbal fluency tasks among total sample and in the subgroups according to cortical amyloid deposition. The symbol (*) indicates statistically significant differences between CBS-A+ and CBS-A- groups. Dysarthria 10/18, 55.6% vs. 1/13, 7.7%, p= 0.008, Fisher's exact test. *Adapted from Parmera, Jacy Bezerra et al. "Metabolic and Structural Signatures of Speech and Language Impairment in Corticobasal Syndrome: A Multimodal PET/MRI Study." Frontiers in neurology vol. 12, 702052. 30 Aug. 2021*

4.5 A brief note about an interesting clinical feature

Interestingly, two patients from our sample presented with foot-hand synkinesis, which is a subset of motor overflow where voluntary movements of one part of the body are accompanied by involuntary activation of other, non-mirroring muscles[44]. One patient was a 52-year-old man referred to our service with a 2-year history of progressive language impairment and limb rigidity. Neurological examination disclosed hypomimia, asymmetrical right-sided parkinsonism, cervical dystonia, ideomotor apraxia worse on the right side, right arm levitation, and nonfluent aphasia. He showed an asymmetrical hypometabolism at the left frontoparietal region contralateral to the affected side at FDG-PET (figure 11, A) and negative PIB-PET (figure 11, B).

The other patient was a 65-year-old man with a 4-year history of progressive cognitive impairment and asymmetric rigidity. His neurological examination demonstrated right-sided parkinsonism, bilateral myoclonus, and ideomotor apraxia, both worse on the right side, and cortical sensory deficits. This patient showed an asymmetrical hypometabolism predominantly at posterior temporoparietal regions at FDG-PET (figure 11, D) and positive cortical amyloid deposition at PIB-PET (figure11, E).

Thus, the former patient was diagnosed as CBS probably with a 4R-tauopathy underlying pathology, while the later as CBS probably related to Alzheimer's disease. Both patients revealed hypometabolism at the supplementary motor area (SMA) and premotor cortex, contralateral to the affected side where synkinesis occurred.

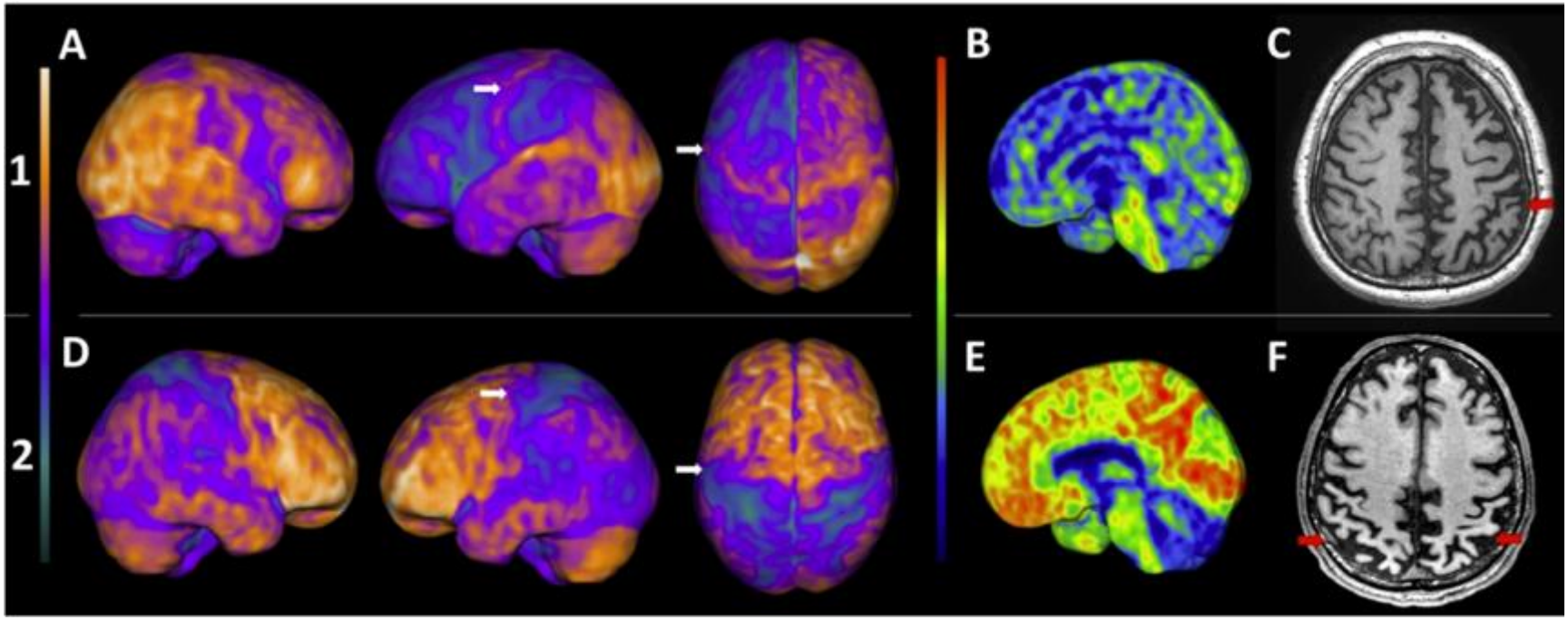


Figure 11 - FDG-PET, PIB-PET and MRI in two patients presenting foot-hand synkinesis
Upper row (1) – Patient 1: (A) FDG-PET 3D-stereotactic surface projection (3D-SSP, software Cortex ID Suite, GE Healthcare): asymmetric frontoparietal hypometabolism, including the sensory and motor cortex, worst on the left side. PIB-PET 3D-SSP (B) negative for amyloid deposition, and T1-weighted MRI (C) with asymmetric frontoparietal atrophy, also worst on the left (red arrows). Lower row (2) – Patient 2 – (C) FDG-PET 3D-SSP: asymmetric posterior temporoparietal hypometabolism, also including the sensory and motor cortex, worst on the left side. PIB-PET 3D-SSP (E) positive for diffuse cortical amyloid deposition, and T1-weighted MRI (F) showing bilateral parietal cortical atrophy (red arrows). The white arrows on A and D point to the supplementary motor cortex, probably related to the synkinesis. *Adapted from Parmera et al. Movement Disorders Clinical Practice 2021; 8(3): 491-492*

4.6 FDG-PET and PIB-PET quantitative group analysis

4.6.1 Comparison of metabolic patterns according to amyloid-PET results

Direct comparisons of FDG uptake in individuals with positive and negative PIB-PET showed three large clusters of reduced rBGM surviving correction for multiple comparisons at the cluster level in CBS-A+ patients. There were two major clusters contralateral to the most affected side, located in the posterior superior and middle temporal gyri, and in the angular gyrus and superior parietal lobule (figure 12). Other cluster, ipsilateral to the most affected side, was located at fusiform gyrus extending to inferior temporal gyrus (figure 12).

Individuals with negative PIB-PET presented two major clusters of reduced metabolism, contralateral to the most affected side, at the thalamus extending to diencephalon and mesencephalon, and at the SMA and paracentral lobule (figure 12). The SPM8 statistics and areas of reduced rBGM are disclosed at Table 6 and 7.

When exploring the individual variability of rBGM in these clusters, the three individuals with positive PIB-PET and a CBS FDG-nonAD pattern had levels of rBGM above the median of the group in temporoparietal areas (figure 12, colored dots in 1,2,3), and presented with similar levels of rBGM in thalamus and SMA to the CBS-A- individuals (figure 12, colored dots in 4 and 5).

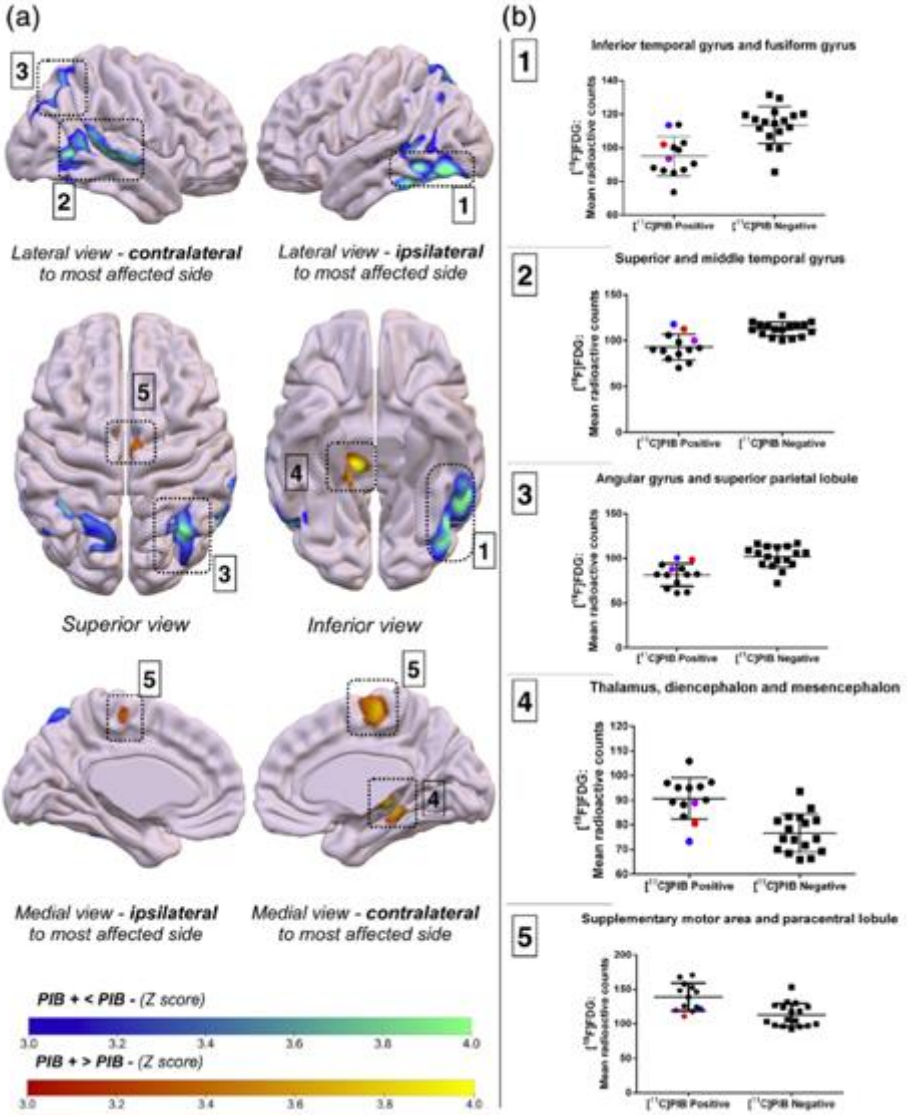


Figure 12 - Brain glucose metabolism in patients with corticobasal syndrome according to amyloid imaging status

Images on the left: clusters with differences in regional brain glucose metabolism (rBGM) in individuals with CBS according to brain amyloid status. Reduced FDG uptake in CBS with positive PIB-PET is consistently seen in posterior temporal and parietal areas, mainly contralateral to most affected side (areas in blue), suggesting an "AD metabolic signature" on FDG-PET. Clusters in red-yellow indicate areas of reduced rBGM in individuals with negative PIB-PET, contralateral to most affected side, at the thalamus, diencephalon and mesencephalon and at supplementary motor area and paracentral lobule. Parametric maps were generated with an unpaired t-test ($p<0.001$, uncorrected) in the SPM8 software and plotted on surface maps with the Surf Ice software – http://www.nitrc.org/projects/surfice/.). Cluster 1,2 and 3 survived correction for multiple comparisons (pFWE and pFDR<0.05). Bars in the lower-left indicate Z-scores, ranging from $p = 10^{-3}$ (Z-score=3.0) to $p= 10^{-4}$ (Z-score=4.0). Images on the right: Scatter Plot graphical representation showing the dispersion of the FDG uptake in the clusters of reduced rBGM for each participant (mean radioactive counts), obtained in the group analysis shown in the left. Dots highlighted in color represent the three individual exceptions classified as CBS FDG-nonAD with positive PIB-PET. *Adapted from Parmera, Jacy Bezerra et al. Movement disorders. vol. 36,3 (2021): 651-661.*

Table 6 - Areas of regional brain glucose metabolism reduction in corticobasal syndrome subjects with positive amyloid deposition in comparison with subjects with negative cortical amyloid deposition at PIB-PET

Area	cluster-level				peak-level				MNI coordinates		
	p_{FWE}	p_{FDR}	k	p_{uncorr}	p_{FWE}	p_{FDR}	$Z_{(E)}$	p_{uncorr}	mm	mm	mm
Superior temporal gyrus (contralateral to most affected side)	**0.003**	**0.014**	**1288**	**0.001**	**0.294**	**0.501**	**3.89**	**<0.001**	**58**	**-16**	**2**
Middle temporal gyrus (contralateral to most affected side)					0.338	0.501	3.83	<0.001	54	-32	2
Fusiform gyrus (contralateral to most affected side)					0.393	0.501	3.77	<0.001	52	-58	-2
Angular gyrus (contralateral to most affected side)	**0.042**	**0.071**	**620**	**0.013**	**0.403**	**0.501**	**3.76**	**<0.001**	**34**	**-62**	**38**
Superior parietal lobule (contralateral to most affected side)					0.800	0.762	3.37	<0.001	30	-64	58
Fusiform gyrus (ipsilateral to most affected side)	**0.012**	**0.030**	**911**	**0.004**	**0.202**	**0.501**	**4.02**	**<0.001**	**-54**	**-50**	**-16**
Inferior temporal gyrus (ipsilateral to most affected side)					0.628	0.614	3.54	<0.001	-58	-38	-24

Abbreviations: MNI: Montreal Neurological Institute; FDG: [^{18}F]fluorodeoxyglucose; FWE: Familywise Error; FDR: False Discovery Rate; p_{FWE}: *p* value corrected for multiple comparisons using FWE method; p_{FDR}: *p* value corrected for multiple comparisons using FDR method; p_{uncorr}: *p* value uncorrected for multiple comparisons; k_E: cluster size (in number of voxels), $Z_{(E)}$: Z-score, GM: gray matter.

Table 7 - Areas of regional brain glucose metabolism reduction in corticobasal syndrome subjects with negative amyloid deposition in comparison with subjects with positive cortical amyloid deposition at PIB-PET

Area	cluster-level				peak-level				MNI coordinates		
	p_{FWE}	p_{FDR}	k	p_{uncorr}	p_{FWE}	p_{FDR}	$Z_{(E)}$	p_{uncorr}	mm	mm	mm
Thalamus, diencephalon and mesencephalon (contralateral to most affected side)	**0.099**	**0.291**	**440**	**0.032**	**0.163**	**0.774**	**4.09**	**<0.001**	**10**	**-26**	**-2**
Supplementary motor area (contralateral to most affected side)	**0.202**	**0.315**	**300**	**0.070**	**0.764**	**0.809**	**3.41**	**<0.001**	**8**	**-14**	**70**
Paracentral lobule (contralateral to most affected side)					0.806	0.809	3.36	<0.001	8	-20	64

Abbreviations: MNI: Montreal Neurological Institute; FDG: [^{18}F]fluorodeoxyglucose; FWE: Familywise Error; FDR: False Discovery Rate; p_{FWE}: *p* value corrected for multiple comparisons using FWE method; p_{FDR}: *p* value corrected for multiple comparisons using FDR method; p_{uncorr}: *p* value uncorrected for multiple comparisons; k_E: cluster size (in number of voxels), $Z_{(E)}$: Z-score, GM: gray matter.

4.6.2 Comparison of cortical amyloid deposition according to the FDG-PET patterns

Areas of increased PIB uptake corresponding to cortical amyloid deposition were markedly more evident in the CBS FDG-AD group (figure 13). The three exceptions of patients classified as CBS FDG-nonAD with positive PIB-PET demonstrated the lowest individual PIB uptake ratio among CBS-A+ patients. However, they presented individual levels of amyloid deposition above the standard deviation of their metabolic group (figure 13, colored dots on (b)).

The SPM8 statistics and areas of PIB uptake are disclosed at Table 8.

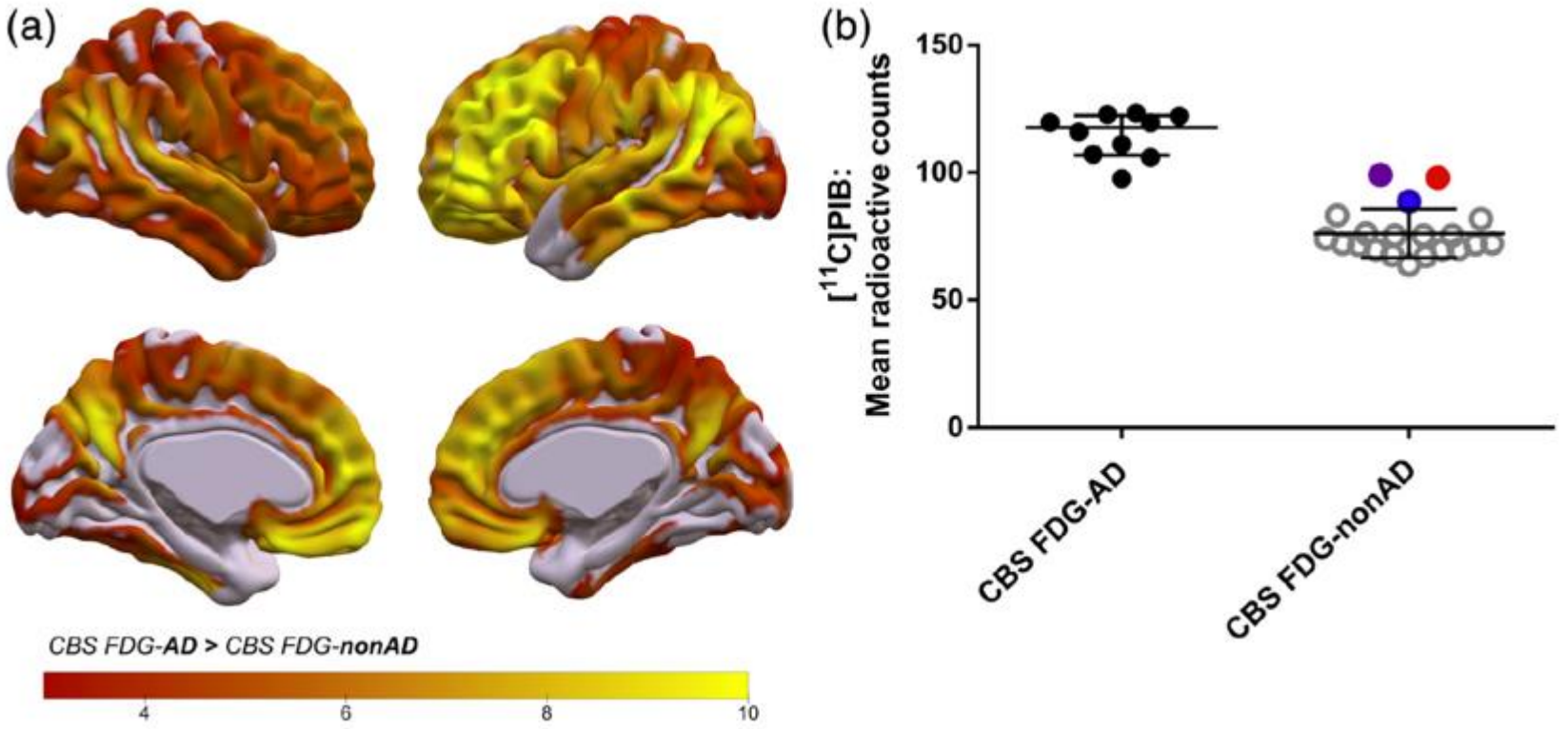


Figure 13 - Amyloid deposition in patients with corticobasal syndrome (CBS) according to the FDG-PET patterns. Images on the left: areas with differences in cortical amyloid deposition measured with PIB-PET according to their classification as CBS FDG-AD or CBS FDG-nonAD. Increased PIB uptake in CBS FDG-AD is seen diffusely throughout the cortex, as shown in red-yellow areas. Parametric maps were generated with an unpaired t-test ($p<0.001$, uncorrected) in the SPM8 software and plotted on surface maps with the Surf Ice software (http://www.nitrc.org/projects/surfice/). A large cluster comprising all areas shown in the graphic survived correction for multiple comparisons (pFWE and pFDR<0.05). Bars in the lower-left indicate Z-scores, ranging from p = 10-3 (Z-score=3.0) to p= 10-10 (Z-score=10.0). Images on the right: Scatter Plot graphical representation showing the dispersion of the PIB uptake in the large cluster obtained in the group analysis shown in the left (mean radioactive counts). Dots highlighted in color represent the three individual exceptions classified as CBS FDG-nonAD with positive PIB-PET in the visual classification. *Adapted from Parmera, Jacy Bezerra et al. Movement Disorders. vol. 36,3 (2021): 651-661.*

Table 8 - Localization of the increased PIB uptake in subjects with corticobasal syndrome with metabolic pattern likely related to AD (CBS FDG-AD group) in comparison with individuals with metabolism likely not related to AD (CBS FDG-nonAD group)

Area	cluster-level				peak-level				MNI coordinates		
	p_{FWE}	p_{FDR}	k	p_{uncorr}	p_{FWE}	p_{FDR}	$Z_{(E)}$	p_{uncorr}	mm	mm	mm
Left middle temporal gyrus	**<0.001**	**<0.001**	**25750**	**<0.001**	**<0.001**	**<0.001**	**7.18**	**<0.001**	**-54**	**-60**	**22**
Left inferior frontal gyrus					<0.001	<0.001	7.15	<0.001	-42	22	24
Left superior frontal gyrus					<0.001	<0.001	7.04	<0.001	-22	32	42
Right superior temporal gyrus	**<0.001**	**<0.001**	**3713**	**<0.001**	**<0.001**	**0.003**	**6.02**	**<0.001**	**48**	**-70**	**24**
Right middle temporal gyrus					<0.001	0.004	5.93	<0.001	62	-28	2
Right insula area					<0.001	0.005	5.87	<0.001	38	8	6
Left postcentral gyrus	**0.001**	**0.045**	**95**	**0.012**	**0.001**	**0.048**	**5.31**	**<0.001**	**-30**	**-42**	**60**

Abbreviations: MNI: Montreal Neurological Institute; FDG: [^{18}F]fluorodeoxyglucose; FWE: Familywise Error; FDR: False Discovery Rate; p_{FWE}: *p* value corrected for multiple comparisons using FWE method; p_{FDR}: *p* value corrected for multiple comparisons using FDR method; p_{uncorr}: *p* value uncorrected for multiple comparisons; k_E: cluster size (in number of voxels), $Z_{(E)}$: Z-score, GM: gray matter.

4.6.3 Metabolic patterns on FDG-PET in corticobasal syndrome patients compared to the healthy control group and regarding the presence of dysarthria

Compared to healthy controls, quantitative group analysis from the whole cohort showed an extended pattern of rBGM reduction at frontoparietal areas, striatum, and thalamus, mostly contralateral to the affected body side (figure 14 (a)).

Patients with dysarthria were characterized by a predominant left-side hypometabolic pattern (figure 14, (b)), and more prominent hypometabolic areas surviving correction for multiple comparisons at the cluster level at frontal regions, with a significant cluster at the left inferior frontal gyrus (opercular area) and left premotor cortex (figure 14 (b)), with additional features typical of CBS (inferior parietal cortex and striatum).

Conversely, patients without dysarthria showed bilateral rBGM reduction, with major clusters at the posterior cingulate, dorsolateral prefrontal cortex, posterior temporoparietal areas, striatum, and thalamus and without hemisphere predominance. Figure 14 illustrates the areas. Peak voxels of rBGM are shown in tables 9, 10, and 11.

4.6.4 Brain atrophy patterns on VBM in corticobasal syndrome patients compared to the healthy control group and regarding to the presence of dysarthria

Compared to healthy controls, the whole CBS cohort showed a widespread brain atrophy pattern with major clusters at the bilateral striatum, SMA, posterior cingulate cortex, and posterior temporoparietal areas mostly contralateral to the affected body side (figure 14, (d)).

In regard to patients with dysarthria, a major cluster of brain atrophy was found predominantly in the right inferior frontal gyrus and putamen, with other significant areas such as the left SMA, premotor cortex, and putamen (figure 14, (e)), whereas patients without dysarthria showed gray matter loss at posterior temporal and inferior parietal areas (figure 14, (f)). There was, however, no evident predominant left-side brain atrophy in patients with dysarthria. Peak voxels of VBM contrasts are shown in tables 12, 13 and 14 .

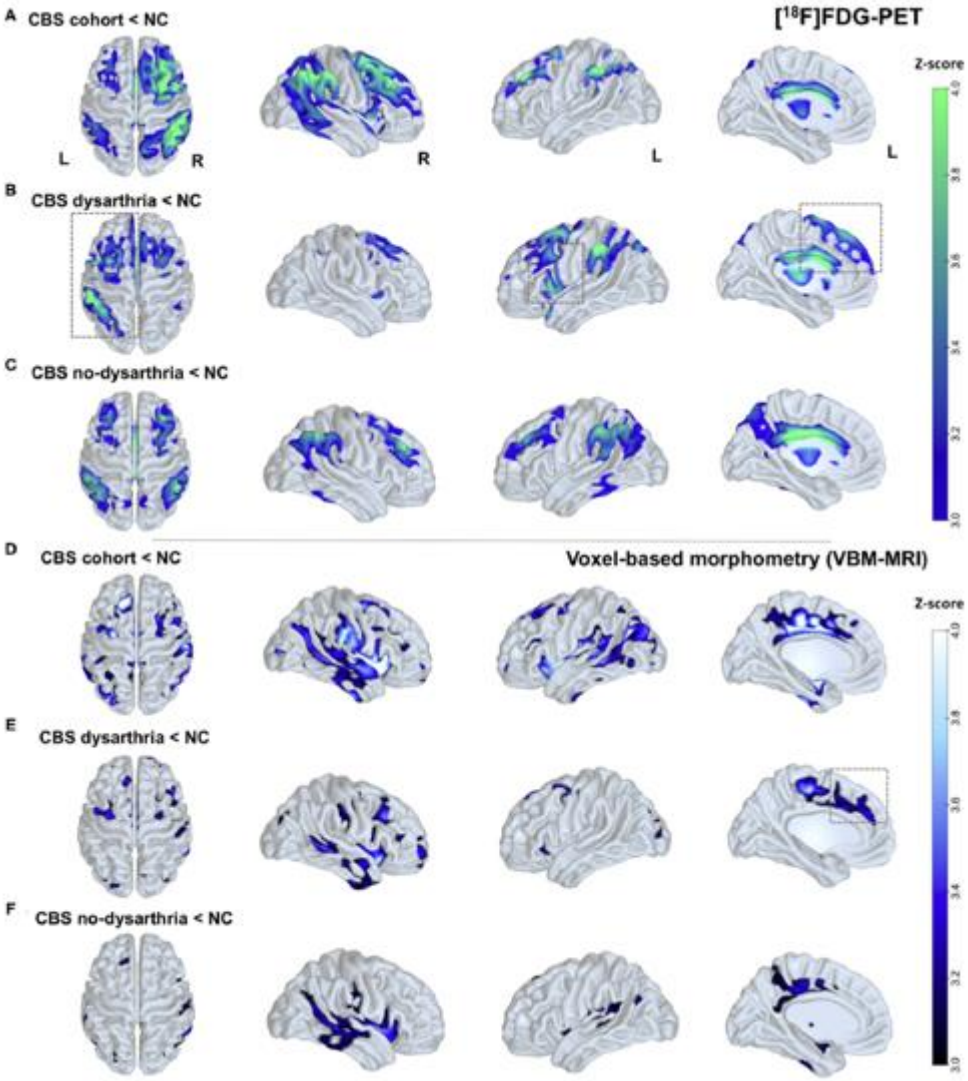


Figure 14 - Brain glucose metabolism and brain atrophy patterns in the whole corticobasal syndrome cohort and according to the presence or absence of dysarthria

(A) Clusters with differences in rBGM in individuals with CBS compared to healthy controls (NC). Reduced FDG uptake in the whole CBS cohort is consistently seen in the frontoparietal and temporal areas, striatum, and thalamus, mainly contralateral to the most affected side. (B) Clusters with differences in rBGM in CBS individuals presenting dysarthria. Reduced FDG uptake surviving correction for multiple comparisons at the cluster level is predominant at left frontal regions, with a major cluster at the left inferior frontal gyrus (opercular area) and left premotor cortex. (C) Hypometabolism in CBS patients without dysarthria showing bilateral rBGM reduction, mainly at the temporoparietal areas, striatum, and thalamus, and without hemisphere predominance. (D) VBM analysis showing brain atrophy patterns in CBS patients compared to NC: widespread brain atrophy pattern with major clusters at the bilateral striatum, SMA, and posterior temporoparietal areas, mostly contralateral to the affected body side. (E) VBM showing brain atrophy patterns in CBS patients with dysarthria compared to NC: predominantly in the frontal areas and striatum. (F) VBM showing brain atrophy patterns in CBS patients without dysarthria compared to NC: posterior temporal and inferior parietal areas. Parametric maps were generated with an unpaired t-test ($p < 0.001$, uncorrected) in the SPM8 software and plotted on surface maps with the Surf Ice software—http://www.nitrc.org/projects/surfice/). Bars in the right side indicate z scores, ranging from $p = 10{-}3$ (z-score = 3.0) to $p = 10{-}4$ (z-score = 4.0). *Adapted from Parmera, Jacy Bezerra et al. "Metabolic and Structural Signatures of Speech and Language Impairment in Corticobasal Syndrome: A Multimodal PET/MRI Study." Frontiers in neurology vol. 12 702052. 30 Aug. 2021*

Table 9 - Areas of regional brain glucose metabolism reduction in corticobasal syndrome subjects compared to healthy controls

Area	cluster-level				peak-level				MNI coordinates		
	p_{FWE}	p_{FDR}	k	p_{uncorr}	p_{FWE}	p_{FDR}	$Z_{(E)}$	p_{uncorr}	mm	mm	mm
Middle frontal gyrus (contralateral to most affected side)	**0.000**	**0.000**	**13273**	**0.000**	**0.000**	**0.000**	**inf**	**0.000**	**44**	**10**	**56**
Supplementary motor area (contralateral to most affected side)					0.000	0.000	inf	0.000	32	-5	56
Premotor cortex (contralateral to most affected side)					0.000	0.000	7.36	0.000	48	5	38
Posterior cingulate cortex (contralateral to most affected side)	**0.000**	**0.000**	**1329**	**0.000**	**0.000**	**0.000**	**7.33**	**0.000**	**4**	**-24**	**32**
Ventral cingulate area (contralateral to most affected side)					0.000	0.000	7.24	0.000	5	10	30
Thalamus (contralateral to most affected side)	**0.000**	**0.000**	**429**	**0.000**	**0.000**	**0.000**	**7.02**	**<0.001**	**12**	**-18**	**12**
Supramarginal gyrus (contralateral to most affected side)	**0.000**	**0.009**	**134**	**0.002**	**0.002**	**0.048**	**5.34**	**0.000**	**50**	**-40**	**-34**
Caudate (ipsilateral to most affected side)	**0.000**	**0.017**	**109**	**0.004**	**0.000**	**0.000**	**6.78**	**0.000**	**-12**	**8**	**10**

Abbreviations: MNI: Montreal Neurological Institute; FDG: [^{18}F]fluorodeoxyglucose; FWE: Familywise Error; FDR: False Discovery Rate; p_{FWE}: *p* value corrected for multiple comparisons using FWE method; p_{FDR}: *p* value corrected for multiple comparisons using FDR method; p_{uncorr}: *p* value uncorrected for multiple comparisons; k_E: cluster size (in number of voxels), $Z_{(E)}$: Z-score, GM: gray matter.

Table 10 - Areas of regional brain glucose metabolism reduction in corticobasal syndrome patients with dysarthria compared to healthy controls

Area	cluster-level				peak-level				MNI coordinates		
	p_{FWE}	p_{FDR}	k	p_{uncorr}	p_{FWE}	p_{FDR}	$Z_{(E)}$	p_{uncorr}	mm	mm	mm
Left Premotor cortex	**0.000**	**0.000**	**2189**	**0.000**	**0.018**	**0.018**	**4.95**	**0.000**	**-36**	**8**	**58**
Left inferior frontal/opercular gyrus					0.059	0.047	4.66	0.000	-50	6	24
Left temporal pole					0.059	0.047	4.66	0.000	-50	18	-20
Left supramarginal gyrus	**0.000**	**0.000**	**1208**	**0.000**	**0.008**	**0.014**	**5.12**	**0.000**	**-58**	**-30**	**46**
Left angular gyrus					0.173	0.068	4.37	0.000	-42	-50	44
Left caudate	**0.001**	**0.001**	**587**	**0.000**	**0.002**	**0.010**	**5.45**	**0.000**	**-14**	**2**	**16**
Left thalamus					0.096	0.052	4.53	0.000	-8	-16	12
Left supplementary motor area	**0.349**	**0.142**	**119**	**0.045**	**0.236**	**0.083**	**4.27**	**0.000**	**-6**	**6**	**72**
Right dorsomedial prefrontal cortex	**0.000**	**0.000**	**2350**	**0.000**	**0.079**	**0.052**	**4.58**	**0.000**	**44**	**10**	**56**
Right anterior cingulate					0.141	0.062	4.43	0.000	4	16	26
Right caudate	**0.339**	**0.142**	**121**	**0.043**	**0.009**	**0.014**	**5.11**	**0.000**	**16**	**8**	**10**

Abbreviations: MNI: Montreal Neurological Institute; FDG: [^{18}F]fluorodeoxyglucose; FWE: Familywise Error; FDR: False Discovery Rate; p_{FWE}: *p* value corrected for multiple comparisons using FWE method; p_{FDR}: *p* value corrected for multiple comparisons using FDR method; p_{uncorr}: *p* value uncorrected for multiple comparisons; k_E: cluster size (in number of voxels), $Z_{(E)}$: Z-score, GM: gray matter.

Table 11 - Areas of regional brain glucose metabolism reduction in corticobasal syndrome patients without dysarthria compared to healthy controls

Area	cluster-level				peak-level				MNI coordinates		
	p_{FWE}	p_{FDR}	k	p_{uncorr}	p_{FWE}	p_{FDR}	$Z_{(E)}$	p_{uncorr}	mm	mm	mm
Right ventral posterior cingulate cortex	**0.000**	**0.000**	**1246**	**0.000**	**0.000**	**0.000**	**7.43**	**0.000**	**0**	**-24**	**32**
Right dorsal posterior cingulate					0.000	0.000	6.76	0.000	14	-28	40
Right dorsolateral Prefrontal cortex	**0.000**	**0.000**	**2329**	**0.000**	**0.000**	**0.000**	**6.90**	**0.000**	**40**	**34**	**38**
Right superior frontal gyrus					0.000	0.003	6.13	0.000	40	20	52
Right supramarginal gyrus	**0.000**	**0.000**	**2026**	**0.000**	**0.000**	**0.001**	**6.59**	**0.000**	**58**	**-44**	**48**
Right angular gyrus					0.000	0.006	5.92	0.000	50	-58	48
Right superior temporal gyrus					0.001	0.026	5.56	0.000	56	-36	20
Left supramarginal gyrus	**0.000**	**0.000**	**2483**	**0.000**	**0.000**	**0.001**	**6.46**	**0.000**	**-58**	**-38**	**46**
Left angular gyrus					0.000	0.002	6.25	0.000	-46	-66	48
Left dorsolateral Prefrontal cortex	**0.000**	**0.000**	**616**	**0.000**	**0.000**	**0.003**	**6.21**	**0.000**	**-36**	**38**	**34**
Left superior frontal gyrus					0.004	0.114	5.19	0.000	-44	18	44
Left Caudate	**0.000**	**0.000**	**201**	**0.000**	**0.000**	**0.001**	**6.52**	**0.000**	**-14**	**8**	**10**
Left Thalamus					0.000	0.005	5.99	0.000	-8	-14	12

Abbreviations: MNI: Montreal Neurological Institute; FDG: [^{18}F]fluorodeoxyglucose; FWE: Familywise Error; FDR: False Discovery Rate; p_{FWE}: *p* value corrected for multiple comparisons using FWE method; p_{FDR}: *p* value corrected for multiple comparisons using FDR method; p_{uncorr}: *p* value uncorrected for multiple comparisons; k_E: cluster size (in number of voxels), $Z_{(E)}$: Z-score, GM: gray matter.

Table 12 - Areas of brain atrophy in corticobasal syndrome subjects compared to healthy controls

Area	cluster-level				peak-level				MNI coordinates		
	p_{FWE}	p_{FDR}	k	p_{uncorr}	p_{FWE}	p_{FDR}	$Z_{(E)}$	p_{uncorr}	mm	mm	mm
Putamen (contralateral to most affected side)	**0.000**	**0.000**	**1331**	**0.000**	**0.000**	**0.000**	**7.21**	**0.000**	**26**	**10**	**-10**
Insula (contralateral to most affected side)					0.004	0.112	5.20	0.000	42	10	2
Posterior cingulate cortex (contralateral to most affected side)	**0.000**	**0.000**	**294**	**0.000**	**0.000**	**0.003**	**5.98**	**0.000**	**6**	**-14**	**48**
Supplementary motor area (contralateral to most affected side)					0.000	0.016	5.65	0.000	4	-10	46
Putamen (ipsilateral to most affected side)	**0.000**	**0.000**	**1145**	**0.000**	**0.000**	**0.000**	**7.47**	**0.000**	**-24**	**10**	**-6**

Abbreviations: MNI: Montreal Neurological Institute; FDG: [^{18}F]fluorodeoxyglucose; FWE: Familywise Error; FDR: False Discovery Rate; p_{FWE}: *p* value corrected for multiple comparisons using FWE method; p_{FDR}: *p* value corrected for multiple comparisons using FDR method; p_{uncorr}: *p* value uncorrected for multiple comparisons; k_E: cluster size (in number of voxels), $Z_{(E)}$: Z-score, GM: gray matter.

Table 13 - Areas of brain atrophy in corticobasal syndrome patients with dysarthria compared to healthy controls

Area	cluster-level				peak-level				MNI coordinates		
	p_{FWE}	p_{FDR}	k	p_{uncorr}	p_{FWE}	p_{FDR}	$Z_{(E)}$	p_{uncorr}	mm	mm	mm
Right Putamen	**0.000**	**0.000**	**1794**	**0.000**	**0.000**	**0.000**	**6.05**	**0.000**	**26**	**12**	**-10**
Right inferior frontal/opercular gyrus					0.821	0.509	3.70	0.000	40	10	4
Left Putamen	**0.000**	**0.001**	**753**	**0.000**	**0.057**	**0.076**	**4.65**	**0.000**	**-16**	**10**	**-8**
Left supplementary motor area	**0.010**	**0.007**	**435**	**0.001**	**0.314**	**0.253**	**4.16**	**0.000**	**-4**	**-18**	**52**
Left Premotor cortex					0.997	0.791	3.27	0.001	-4	6	44
Right middle temporal gyrus	**0.017**	**0.010**	**379**	**0.002**	**0.194**	**0.209**	**4.32**	**0.000**	**58**	**-32**	**-2**
Right angular gyrus					0.993	0.744	3.34	0.000	60	-50	18
Right middle cingulate cortex	**0.024**	**0.011**	**351**	**0.003**	**0.707**	**0.509**	**3.81**	**0.000**	**6**	**24**	**32**
Right anterior cingulate cortex					0.97	0.678	3.46	0.000	8	2	40
Right Cerebellum	**0.053**	**0.020**	**281**	**0.006**	**0.402**	**0.253**	**4.07**	**0.000**	**8**	**-56**	**-52**
Left Cerebellum	**0.123**	**0.042**	**211**	**0.015**	**0.841**	**0.509**	**3.68**	**0.000**	**-18**	**-70**	**-56**
Left Precentral	**0.421**	**0.151**	**114**	**0.061**	**0.952**	**0.678**	**3.51**	**0.000**	**-36**	**-10**	**48**

Abbreviations: MNI: Montreal Neurological Institute; FDG: [^{18}F]fluorodeoxyglucose; FWE: Familywise Error; FDR: False Discovery Rate; p_{FWE}: *p* value corrected for multiple comparisons using FWE method; p_{FDR}: *p* value corrected for multiple comparisons using FDR method; p_{uncorr}: *p* value uncorrected for multiple comparisons; k_E: cluster size (in number of voxels), $Z_{(E)}$: Z-score, GM: gray matter.

Table 14 - Areas of brain atrophy in corticobasal syndrome patients without dysarthria compared to healthy controls

Area	cluster-level				peak-level				MNI coordinates		
	p_{FWE}	p_{FDR}	k	p_{uncorr}	p_{FWE}	p_{FDR}	$Z_{(E)}$	p_{uncorr}	mm	mm	mm
Right Putamen	**0.000**	**0.000**	**1327**	**0.000**	**0.000**	**0.000**	**7.18**	**0.000**	**28**	**8**	**0**
Right Insula					0.001	0.041	5.50	0.000	42	10	2
Left Striatum	**0.000**	**0.000**	**664**	**0.000**	**0.000**	**0.000**	**6.55**	**0.000**	**-22**	**10**	**-6**
Right Anterior Cingulate	**0.000**	**0.001**	**118**	**0.001**	**0.000**	**0.003**	**6.10**	**0.000**	**10**	**-18**	**44**
Right middle temporal gyrus	**0.000**	**0.001**	**125**	**0.001**	**0.003**	**0.079**	**5.29**	**0.000**	**62**	**-32**	**0**
Right superior temporal gyrus					0.009	0.190	5.07	0.000	62	-40	6

Abbreviations: MNI: Montreal Neurological Institute; FDG: [^{18}F]fluorodeoxyglucose; FWE: Familywise Error; FDR: False Discovery Rate; p_{FWE}: *p* value corrected for multiple comparisons using FWE method; p_{FDR}: *p* value corrected for multiple comparisons using FDR method; p_{uncorr}: *p* value uncorrected for multiple comparisons; k_E: cluster size (in number of voxels), $Z_{(E)}$: Z-score, GM: gray matter.

4.6.5 Metabolic correlations between brain regions and verbal fluency tasks

Additionally, due to the prominent deficit concerning verbal fluency in the CBS patients, we investigated which brain regions on FDG-PET correlated with semantic and phonemic verbal fluency task performance.

There was a positive correlation between rBGM and semantic verbal fluency at the left inferior (p=0.006, R^2 =0.2326), middle (0.0054, R^2 = 0.2376), and superior temporal gyri (p=0.0066, R^2 =0.2276) (figure 15).

Relative to the phonemic verbal fluency, we found a positive correlation between FDG uptake and letter P fluency at the left frontal opercular gyrus (p=0.0003, R^2 =0.3685) and the inferior (p= 0.0004, R^2 =0.3537) and middle temporal gyri (p=0.0001, R^2 =0.3993) (figure 15).

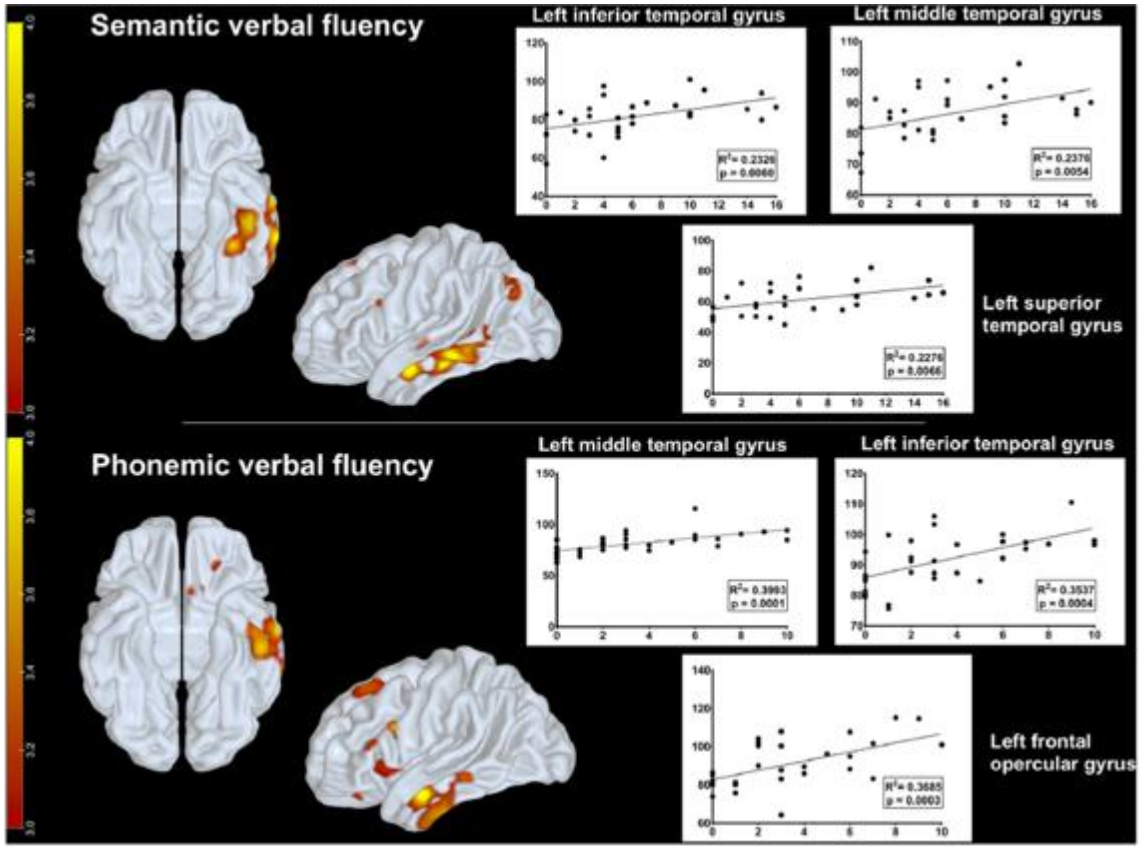


Figure 15 - Metabolic correlations between brain regions and verbal fluency task
Upper row: positive correlation between glucose uptake on FDG-PET and semantic verbal fluency at the left inferior, middle, and superior temporal gyri. Lower row: positive correlation between FDG-PET and phonemic fluency at the left frontal opercular gyrus and the inferior and middle temporal gyri. Parametric maps were generated with an unpaired t-test (threshold: $p < 0.001$, uncorrected) in the SPM8 software and plotted on surface maps with the Surf Ice software http://www.nitrc.org/projects/surfice/). Bars in the left side indicate z scores, ranging from $p = 10-3$ (z-score = 3.0) to $p = 10-4$ (z-score = 4.0). *Adapted from Parmera, Jacy Bezerra et al. "Metabolic and Structural Signatures of Speech and Language Impairment in Corticobasal Syndrome: A Multimodal PET/MRI Study." Frontiers in neurology vol. 12 702052. 30 Aug. 2021*

DISCUSSION

5 Discussion

In this prospective, cross-sectional and observational study, we evaluated a cohort of 45 patients with a clinical diagnosis of probable CBS, according to current clinical criteria[22]. All patients performed a comprehensive neurological, speech-language, and biomarkers assessment. All underwent FDG-PET, and 31 underwent PET-MRI with a specific ligand for brain amyloid deposition (PIB-PET).

To our knowledge, few studies have assessed specific-pathology ligands as biomarkers in CBS population[50,94,104], and the largest cohorts were mainly characterized by retrospective methodology[38] or using CSF biomarkers[47].

Moreover, little research has addressed the FDG-PET role in investigating CBS underlying pathologies, and most of them have focused on group quantitative analyses[94,97]. In this regard, the present study aimed to evaluate the role of FDG-PET at the individual level in the clinical setting to predict amyloid status and guide the identification of CBS pathologic variants.

We aimed to perform a detailed and blind clinical assessment to investigate if a metabolic FDG-PET individual classification would disclose two main clinical groups and if they resembled the clinical patterns described in previous clinicopathologic cohorts (AD versus non-AD underlying pathology). Worth mentioning, a classification based on metabolic patterns to investigate the clinical profiles generated has not been extensively approached before.

As our main findings, the strategy of splitting CBS patients in two groups based on FDG-PET patterns identified a group likely related to AD (CBS FDG-

AD) as having worst cognitive performances and amyloid deposition in all cases, versus a non-AD metabolic group (CBS FDG-nonAD) with prominent motor signs such as dystonia, ocular motor dysfunction, dysarthria, and motor perseveration, and a lower prevalence of brain amyloid deposition.

Additionally, a post-hoc quantitative group analysis showed hypometabolism comprising the posterior temporoparietal areas, mainly contralateral to the most affected side, as the areas with hypometabolism in amyloid-positive (CBS-A+) patients. This possible CBS-AD metabolic signature may guide physicians in the interpretation of FDG-PET scans. Amyloid-negative patients, conversely, showed more heterogeneous metabolic patterns and disclosed areas of rBGM reduction at the thalamus and SMA.

Previous studies using imaging biomarkers identified neural correlates from different aspects of language in CBS[52,127]. However, speech-language impairment's profile in CBS and its relation to specific pathologies are still poorly understood. Therefore, another purpose of our study was to distinguish language and motor speech deficits related to amyloid-positive and negative CBS patients and explore its brain metabolic and structural signatures through a multimodal imaging approach.

In this concern, CBS patients with negative amyloid-PET presented significantly more often dysarthria than patients with positive amyloid deposition. A quantitative FDG-PET and MRI group analysis disclosed differential hypometabolic and brain atrophy patterns in CBS patients regarding the presence or absence of dysarthria. Namely, CBS patients with dysarthria had a left-sided hypometabolism and bilateral brain atrophy pattern mainly at the opercular frontal region, premotor cortex, and SMA.

5.1 Metabolic degeneration patterns at FDG-PET predict amyloid deposition in CBS

Previous works have demonstrated that differences in rBGM potentially predict the presence of cortical amyloid deposition in focal-onset dementias such as PPA and CBS with better sensitivity and specificity than clinical evaluation and visual interpretation of MRI[94,95].

In line with this, our individual metabolic analysis has shown that all ten patients classified as CBS FDG-AD had positive PIB-PET scans compared to three out of 20 classified as CBS FDG-nonAD. Our classification had higher specificity (100% vs. 58% and 83%) and overall accuracy (90% vs. 73% and 84%) than these prior studies[94,95], pointing towards the critical role of FDG-PET in the diagnostic workup of CBS.

Moreover, a recent study with neuropathologic examination showed that CBS's underlying pathologies are associated with different metabolic degeneration patterns and described hypometabolism for CBS-CBD, CBS-AD, and CBS-PSP[97]. The CBS-AD metabolic pattern described was similar to what we observed, comparing patients with positive and negative PIB-PET. This potential CBS-AD metabolic signature matches previous works using amyloid imaging[94] and CSF biomarkers[128] in CBS, is classically seen in typical AD[122,123], and is closely associated with positive PIB-PET scans in the continuum of amnestic cognitive decline[125], supporting our FDG-PET classification.

The individual FDG-PET classification also demonstrated high inter-observer agreement, PPV, and accuracy to predict amyloid deposition. The interrater agreement for the subclassification into different nonAD patterns, otherwise, was more modest. Considering this finding, and given the clinical and

imaging ambiguity in PSP and CBD cases, it might be rational to use a combined PSP-CBD tauopathy category for PET readings, which reached a good sensitivity and specificity (87% and 100%) in previous cohorts[82].

5.2 Metabolic degeneration patterns at FDG-PET predict clinical profile in CBS

Following prior studies[5,37,56], CBS patients presented a distinct clinical phenotype primarily characterized by parkinsonism and limb apraxia. Despite the current knowledge that clinical aspects cannot reliably disclose pathologic substrate, some might have a role as disease-related clues[38,39].

The CBS FDG-AD patients performed significantly worse in the general cognitive assessment. Similarly, CBS-A+ individuals performed worse in the MMSE and ACE-R subscores. This pattern of ominous cognitive progression associated with underlying AD pathology is consistent with studies including histopathology[38,56] and *in vivo* biomarkers[50]. Also, in line with clinicopathologic studies, episodic memory was more impaired in the CBS FDG-AD group[38,39].

Furthermore, the same group showed more visuospatial dysfunction. Previous studies suggested a preferential affection of the parietal-dorsal stream in CBS-AD than in other underlying pathologies, identifying lower scores in visuoperceptual tests[50,55]. Besides, visual neglect, which also reflects parietal-dorsal disturbance, has been considered a potential clue for AD pathology [38,50,56,94]. The CBS FDG-AD group also presented myoclonus more often than CBS FDG-nonAD, mirroring previous neuropathology[38,39], CSF[47], and PIB-PET studies[50]. On the other hand, CBS FDG-nonAD patients displayed dystonia more often.

Interestingly, hallucinations were more frequent in the CBS FDG-AD group, a finding only previously described by one clinicopathologic study[38]. Hence, our observation sheds light on this unusually mentioned aspect. Further studies are necessary to investigate this topic and its pathophysiological basis.

Noteworthily, our combined findings of memory impairment, myoclonus, and hallucinations related to the CBS FDG-AD group and dystonia referring to the non-AD metabolic group are congruent with one of the most extensive clinicopathologic series of CBS[38], strengthening the concept of FDG-PET as a possible surrogate of CBS pathological substrate antemortem.

Ocular motor dysfunction was significantly more present in the CBS FDG-nonAD group. Prior video-oculographic observations showed reduced peak velocities of vertical pro-saccades in CBS patients without CSF biomarkers for AD[129]. Besides, vertical supranuclear palsy or slowness of vertical saccades, associated with CBS phenotype, are required to fulfill the MDS probable 4R-tauopathy criteria[26]. Notably, the criteria demonstrated to be significantly related to the CBS FDG-nonAD group, but only present in 33% of these patients, highlighting its low sensitivity, as recently reported in a validation study[130].

Nonetheless, the same MDS criteria could not separate CBS-A+ from CBS-A- individuals, as one patient with positive PIB-PET fulfilled them. Worth mentioning that this single patient was blindly classified as CBS FDG-nonAD, raising the question of whether the primary pathology could be a tauopathy with associated amyloid deposition. Further studies are needed to investigate these novel criteria' accuracy to identify 4R-tauopathies and their relation to AD biomarkers.

A recent study demonstrated that CBS-AD was a biomarker-defined group with distinct clinical features apart from CBS-4R tauopathy[131]. Our findings are consistent with these observations, and the 4R-tauopathies criteria might aid in diagnostic reasoning and clinical trial purposes.

Therefore, the approach of performing a blind clinical evaluation and splitting them based on metabolic patterns unfolded two well-differentiated variants with similar demographic features but distinct cognitive performances. Thus, favoring the hypothesis that they were not necessarily in different stages of the disease but rather had different diseases and the same syndrome, one (CBS-AD) with more severe cognitive impairment, and another (CBS non-AD) with prominent motor features, mostly equivalent to prior observations from clinicopathological cohorts.

5.3 Speech-language profile in light of a multimodal imaging approach

Aphasia was one of the most prominent cognitive impairments in this cohort, present in 67.7% of the cases, second only to limb apraxia (96.8%). We identified a broad spectrum of the linguistic profile, ranging from nfvPPA phenotype to lexical-semantic deficits. Our data are congruent with a previous systematic literature review[22] and a recent clinicopathologic study[38], which demonstrated that aphasia occurred in more than 50% of CBS cases during the disease course.

Likewise, a prior retrospective study with a large cohort suggested that CBS consisted of a primarily language-motor disease with a predominant phenotype of mixed aphasia, thereby being the main cognitive feature[47]. Our findings, along with these reports, strengthen the concept that language

impairment, initially underscored in CBS, should be considered a cognitive hallmark of the disease.

Motor speech production deficits such as dysarthria and AOS have been previously linked to CBS with underlying 4R-tauopathies pathologies, such as CBD or PSP[37,39,51,132]. Dysarthria is considered a CBD and PSP frequent symptom from its first descriptions[2,133] until their latest criteria[22,26]. Our results are in line with these previous studies. Furthermore, the regions with significant clusters of brain atrophy at MRI-based VBM in CBS patients with dysarthria were previously described as anatomically involved in the motor speech production network[134]. It is worth mentioning that AOS was also more commonly found in CBS-A- patients, although not achieving statistical significance.

In addition, patients with dysarthria showed clusters of rBGM reduction at frontal regions, mainly at the left opercular region, premotor cortex, and SMA, corroborating a previous finding that patients with nfvPPA who later evolved into CBS shared a left-sided pattern involving the inferior frontal gyrus and the SMA cortex[127]. We also provided further evidence that the topography of brain hypometabolism could reflect dysfunctional signatures of different language deficits. Although most patients with dysarthria in our cohort did not fulfill the criteria for nfvPPA, they might pertain to the same language dysfunctional spectrum commonly found in the CBS with underlying 4R-tauopathies pathology.

A logopenic-like aphasia phenotype has been associated with CBS-AD underlying pathology in a previous clinicopathological series[38] and a study using amyloid-PET[50]. However, we could not replicate these prior findings in the CBS-A+ group from our cohort. We hypothesize that the advanced functional stage and compromised cognition detected in the CBS-A+ group may have prevented

us from obtaining this observation. Otherwise, one additional possibility is that the language profiles are too heterogeneous in CBS, and it is often impossible to delineate a unique pattern.

The majority of our patients demonstrated phonemic and semantic verbal fluency impairment. It is recognized that verbal fluency performance relates to language dysfunction and other cognitive domains such as executive function and attention, reflecting initiation and processing speed. Notably, the CBS-A- group tended to show a more compromised phonemic verbal fluency, while the CBS-A+ group had a worse semantic verbal fluency performance, even though it did not reach statistical significance. Most studies have reported reduced word fluency in CBS patients[47,135], especially concerning phonemic fluency. In line with our findings, a previous research work revealed significant impairment in the CBS-A− group regarding the phonemic verbal fluency task compared to the CBS-A+ group[129]. As we consider that cases from the CBS-A- group probably encompass CBD and PSP pathologies, and adding that PSP studies have shown even more impairment related to phonemic verbal fluency, we might thus find a rationale to this pattern[106,136].

Furthermore, we also assessed neural correlates from verbal fluency performance in CBS patients, a matter that has not been extensively investigated [136]. Semantic verbal fluency correlated positively with glucose metabolism in the left temporal gyri, whereas phonemic verbal fluency correlated with metabolism in the left temporal but also at frontal areas. These findings are also consistent with data from functional imaging in healthy adults[137].

5.4 Foot-hand synkinesis as a single clinical feature with distinct molecular imaging biomarkers

Two patients with probable CBS from our cohort presented ipsilateral and contralateral foot-hand synkinesis and distinct amyloid imaging biomarkers results. Both patients also revealed hypometabolism at the SMA and premotor cortex, contralateral to the affected side, where synkinesis occurred.

Although the brain networks involved in synkinesis are poorly understood, they are likely related to dysfunction in the secondary motor areas, such as the premotor cortex, SMA, cingulate, and their connections to the primary motor cortex[44]. A previous study using fMRI data in patients with foot-hand synkinesis showed that the SMA was activated during hand movements besides the foot motor cortex region. Thus, the SMA might orchestrate the coordination of involuntary movements, probably being anatomically correlated with synkinesis[138]. Consonant with this, our cases revealed hypometabolism in this area.

Therefore, we demonstrated that synkinesis might be a motor CBS finding, and they are probably not related to its underlying pathology. Instead, they occur due to dysfunction of secondary motor areas, mainly the SMA, a specific anatomical affected region in CBS.

5.5 Limitations

The main limitation of our study was the lack of histopathological data. In its absence, three amyloid-positive patients classified in the CBS FDG-nonAD group could not be properly investigated. However, it should be noted that these individuals had a lower PIB uptake than amyloid-positive patients with an AD

pattern on FDG-PET. The possibilities of misclassification or comorbid pathologies should be considered, as almost 30% of the elderly with normal cognition can present positive amyloid imaging[98]. Meanwhile, the NIA-AA Research Framework[139] classifies any individual with cortical amyloid deposition pertaining to the “AD continuum”. Then, we should consider these cases as possible dual pathology, and the lower level of amyloid deposition could represent early-stage AD.

Furthermore, *in vivo* biomarkers for tau pathology could provide valuable information to these cases[102,104,140]. Thus, the absence of tau biomarkers represents another limitation of our study. Although tau-PET might become the ideal strategy to assess underlying pathology in CBS, its use in clinical practice is limited, mainly restricted to the research context.

One more limitation was that 14 patients from our sample could not perform PET-MRI and complete the whole imaging protocol. These patients had major issues as severe motor impairment or MRI contra-indications that prevented them from undergoing the exam. Other patients had withdrawn the trial before completing the total neuroimaging evaluation due to diverse reasons, mainly because of disease progression and institutionalization in a nursing home.

5.6 Future directions

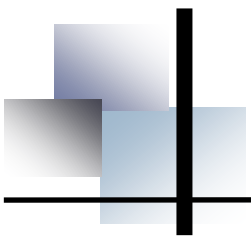
Although the present study delineates and addresses the CBS clinical conundrum, better and larger studies should tag along and explore different facets of this entity.

We demonstrated in our cohort a worse cognitive profile in patients with AD metabolic patterns and positive amyloid biomarkers. If these findings should be translated into a worse prognosis is yet to be defined, and longitudinal clinical analysis of the present sample is warranted. Therefore, clinical and biomarkers longitudinal analyses of the present sample, or maybe multicenter longitudinal analyses with larger cohorts, would potentially clarify this issue, which is a matter of greater importance concerning counseling patients and caregivers.

Moreover, structural MRI measures of regional atrophy using more advanced methods such as *FreeSurfer* might better evaluate the cortical thickness and subcortical deep gray volumes from the present sample. In addition, brain networks analyses with DTI from MRI and metabolic covariance patterns from FDG-PET would equally enrich the observations obtained from our cohort.

There is a pressing need for imaging biomarkers that can differentiate the underlying CBS pathologies in life, to aid in diagnosis and enable treatment trials. Therefore, what will be the ideal imaging biomarker to investigate patients with CBS remains an open question. Perhaps, molecular imaging with tau-tracers shortly will become the most powerful tool across CBS pathological spectrum. However, it is still unclear which will become the preferred choice, if it would be the first-generation tau-PET, already approved for clinical use, even though with appropriate affinity only for paired helical tau filaments, or the second generation tau-PET, with better affinity to straight tau filaments, but still restricted to the research context.

Although the ideal strategy remains to be defined, it is becoming clear that molecular imaging biomarkers should be incorporated in the following proposed clinical criteria for CBS and CBD.



CONCLUSIONS

6 Conclusions

a) FDG-PET individual metabolic patterns can distinguish AD from non-AD CBS variants *antemortem* based on amyloid-PET.

b) Metabolic patterns in CBS patients unfolded two main variants with distinct clinical features. Patients with an AD metabolic pattern display worst cognitive performances and myoclonus, while CBS patients with non-AD metabolic patterns might present more prominent motor features, including dystonia and ocular motor dysfunction. These clinical observations may be helpful in the clinical routine.

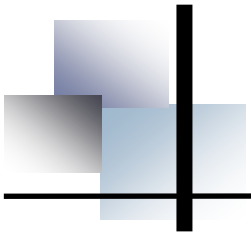
c) CBS patients with cortical amyloid deposition demonstrate worst cognitive performances compared to the group with negative amyloid-PET results.

d) CBS patients with positive PIB-PET show hypometabolism in posterior temporoparietal areas. Conversely, patients with negative PIB-PET show hypometabolism at the thalamus and brainstem. These patterns possibly represent metabolic signatures concerning CBS pathological variants.

e) Areas of increased PIB uptake are more evident in the group with an AD metabolic pattern.

f) CBS patients present a broad spectrum of language deficits. Patients with negative amyloid-PET results present more dysarthria than patients with positive results. Dysarthria might be helpful to distinguish CBS patients not related to AD.

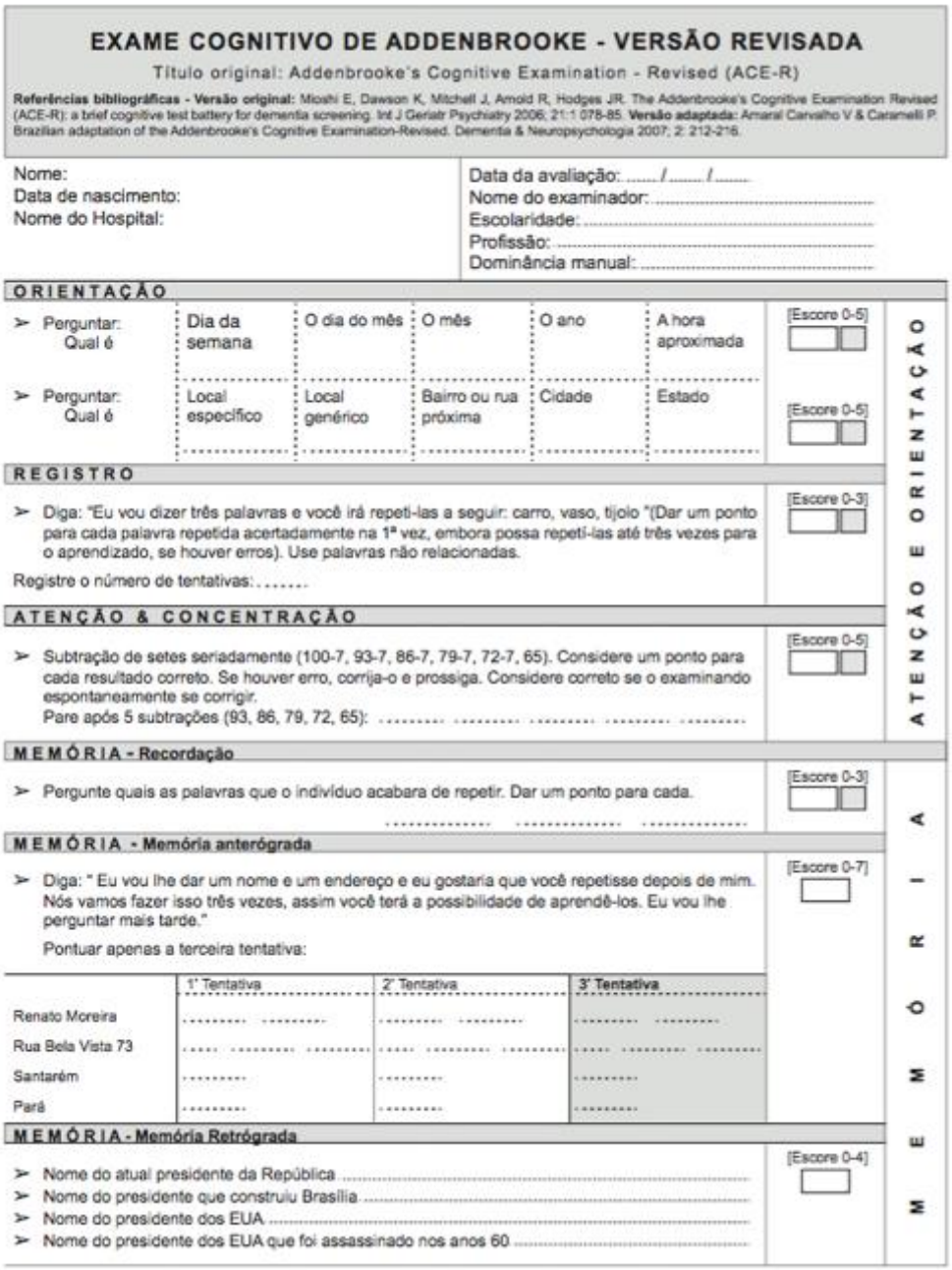
g) CBS patients with dysarthria show hypometabolism and brain atrophy predominantly at the inferior frontal gyrus and premotor cortex, regions previously associated with the motor speech production network.



SUPLEMENTARY MATERIALS

7. Suplementary Materials

7.1 Supplementary material A – Addenbrooke Cognitive examination-Revised



EXAME COGNITIVO DE ADDENBROOKE - VERSÃO REVISADA

Título original: Addenbrooke's Cognitive Examination - Revised (ACE-R)

Referências bibliográficas - Versão original: Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry 2006; 21:1 078-85. **Versão adaptada:** Amaral Carvalho V & Caramelli P. Brazilian adaptation of the Addenbrooke's Cognitive Examination-Revised. Dementia & Neuropsychologia 2007; 2: 212-216.

Nome:
Data de nascimento:
Nome do Hospital:

Data da avaliação: ..../..../.....
Nome do examinador: .....
Escolaridade: .....
Profissão: .....
Dominância manual: .....

ORIENTAÇÃO

➢ Perguntar: Qual é	Dia da semana	O dia do mês	O mês	O ano	A hora aproximada	[Escore 0-5]
➢ Perguntar: Qual é	Local específico	Local genérico	Bairro ou rua próxima	Cidade	Estado	[Escore 0-5]

REGISTRO

➢ Diga: "Eu vou dizer três palavras e você irá repeti-las a seguir: carro, vaso, tijolo "(Dar um ponto para cada palavra repetida acertadamente na 1ª vez, embora possa repetí-las até três vezes para o aprendizado, se houver erros). Use palavras não relacionadas. [Escore 0-3]

Registre o número de tentativas: .....

ATENÇÃO & CONCENTRAÇÃO

➢ Subtração de setes seriadamente (100-7, 93-7, 86-7, 79-7, 72-7, 65). Considere um ponto para cada resultado correto. Se houver erro, corrija-o e prossiga. Considere correto se o examinando espontaneamente se corrigir. [Escore 0-5]
Pare após 5 subtrações (93, 86, 79, 72, 65): ....

ATENÇÃO E ORIENTAÇÃO

MEMÓRIA - Recordação

➢ Pergunte quais as palavras que o indivíduo acabara de repetir. Dar um ponto para cada. [Escore 0-3]

....

MEMÓRIA - Memória anterógrada

➢ Diga: " Eu vou lhe dar um nome e um endereço e eu gostaria que você repetisse depois de mim. Nós vamos fazer isso três vezes, assim você terá a possibilidade de aprendê-los. Eu vou lhe perguntar mais tarde." [Escore 0-7]

Pontuar apenas a terceira tentativa:

	1' Tentativa	2' Tentativa	3' Tentativa
Renato Moreira	....	....	....
Rua Bela Vista 73	....	....	....
Santarém	.....	.....	.....
Pará	.....	.....	.....

MEMÓRIA - Memória Retrógrada

[Escore 0-4]

➢ Nome do atual presidente da República .....
➢ Nome do presidente que construiu Brasília .....
➢ Nome do presidente dos EUA .....
➢ Nome do presidente dos EUA que foi assassinado nos anos 60 .....

MEMÓRIA

EXAME COGNITIVO DE ADDENBROOKE - VERSÃO REVISADA

FLUÊNCIA VERBAL – Letra "P" e Animais

➢ **Letras**
Diga: " Eu vou lhe dizer uma letra do alfabeto e eu gostaria que você dissesse o maior número de palavras que puder começando com a letra, mas não diga nomes de pessoas ou lugares. Você está pronto(a) ? Você tem um minuto e a letra é "P".

[Escore 0-7] ☐

0-15 seg	16-30 seg	31-45 seg	46-60 seg		
				>17	7
				14-17	6
				11-13	5
				8-10	4
				6-7	3
				4-5	2
				2-3	1
				<2	0
				total	acertos

➢ **Animais**
Diga: "Agora você poderia dizer o maior número de animais que conseguir, começando com qualquer letra?"

[Escore 0-7] ☐

0-15 seg	16-30 seg	31-45 seg	46-60 seg		
				>21	7
				17-21	6
				14-16	5
				11-13	4
				9-10	3
				7-8	2
				5-6	1
				<5	0
				total	acertos

FLUÊNCIA

LINGUAGEM - Compreensão

➢ Mostrar a instrução escrita e pedir ao indivíduo para fazer o que está sendo mandado (não auxilie se ele pedir ajuda ou se só ler a frase sem realizar o comando):

[Escore 0-1] ☐☐

Feche os olhos

➢ Comando :
" Pegue este papel com a mão direita, dobre-o ao meio e coloque -o no chão."
Dar um ponto para cada acerto. Se o indivíduo pedir ajuda no meio da tarefa não dê dicas.

[Escore 0-3] ☐☐

LINGUAGEM - Escrita

➢ Peça ao indivíduo para escrever uma frase: Se não compreender o significado, ajude com: *alguma frase que tenha começo, meio e fim; alguma coisa que aconteceu hoje; alguma coisa que queira dizer.* Para a correção não são considerados erros gramaticais ou ortográficos. Dar um ponto.

[Escore 0-1] ☐☐

LINGUAGEM

EXAME COGNITIVO DE ADDENBROOKE - VERSÃO REVISADA

LINGUAGEM - Repetição

➢ Peça ao indivíduo para repetir:
" hipopótamo" ; "excentricidade"; "ininteligível" ; "estatístico".
Diga uma palavra por vez e peça ao indivíduo para repetir imediatamente depois de você.
Pontue 2, se todas forem corretas; 1, se 3 forem corretas; 0, se 2 ou menos forem corretas.

[Escore 0-2] ☐

➢ Peça ao indivíduo que repita: **"Acima, além e abaixo"**

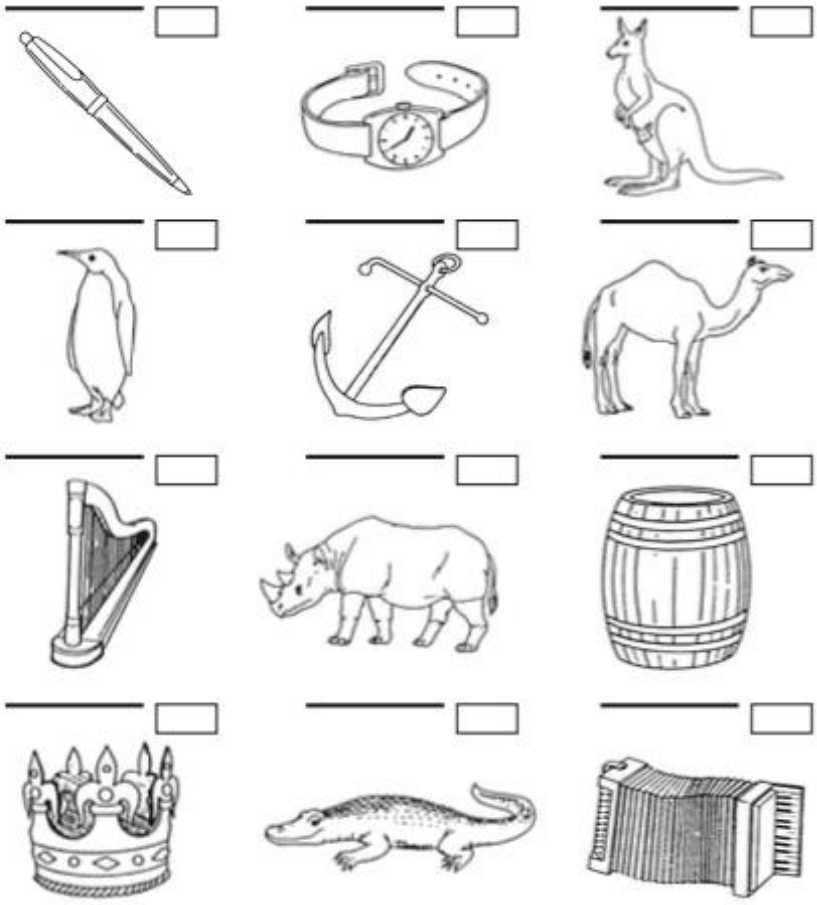
[Escore 0-1] ☐

➢ Peça ao indivíduo que repita: **" Nem aqui, nem ali, nem lá"**

[Escore 0-1] ☐☐

LINGUAGEM - Nomeação

➢ Peça ao indivíduo para nomear as figuras a seguir:



[Escore 0-2] caneta + relógio ☐☐

[Escore 0-10] ☐

LINGUAGEM

LINGUAGEM - Compreensão

➢ Utilizando as figuras acima, peça ao indivíduo para:

- Apontar para aquela que está associada com a monarquia _____
- Apontar para aquela que é encontrada no Pantanal _____
- Apontar para aquela que é encontrada na Antártica _____
- Apontar para aquela que tem uma relação náutica _____

[Escore 0-4] ☐

EXAME COGNITIVO DE ADDENBROOKE - VERSÃO REVISADA

LINGUAGEM - Leitura

➢ Peça ao indivíduo para ler as seguintes palavras: [Pontuar com 1, se todas estiverem corretas] [Escore 0-1] ☐

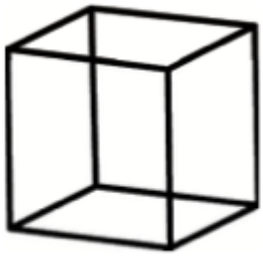
táxi
testa
saxofone
fixar
ballet

LINGUAGEM

HABILIDADES VISUAIS-ESPACIAIS

➢ **Pentágonos sobrepostos:** Peça ao indivíduo para copiar o desenho e para fazer o melhor possível. [Escore 0-1] ☐☐

➢ **Cubo**: Peça ao indivíduo para copiar este desenho (para pontuar, veja guia de instruções) [Escore 0-2] ☐



➢ **Relógio:** Peça ao indivíduo para desenhar o mostrador de um relógio com os números dentro e os ponteiros marcando 5:10 h.(para pontuar veja o manual de instruções: círculo = 1; números = 2; ponteiros = 2, se todos corretos) [Escore 0-5] ☐

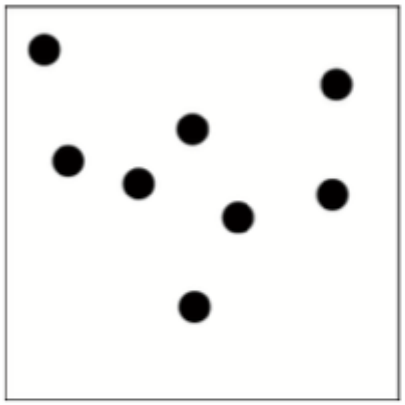
VISUAL-ESPACIAL

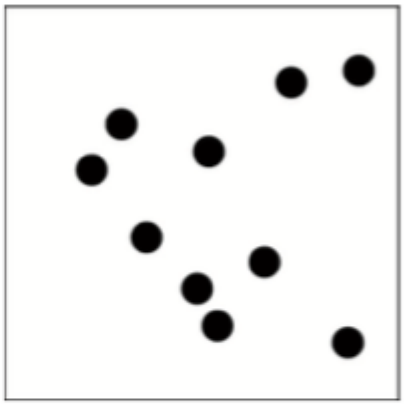
EXAME COGNITIVO DE ADDENBROOKE - VERSÃO REVISADA

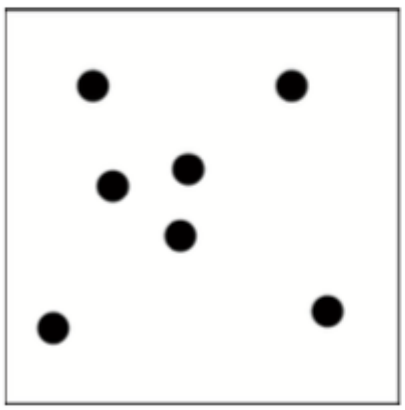
HABILIDADES PERCEPTIVAS

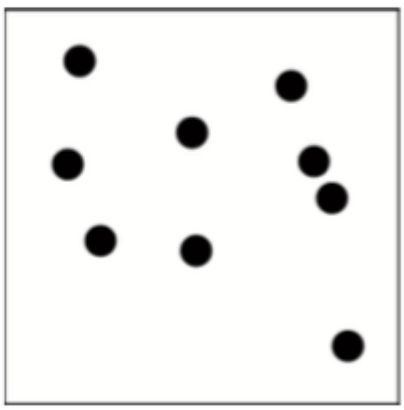
➢ Peça ao indivíduo para contar os pontos sem apontá-los.

[Escore 0-4]









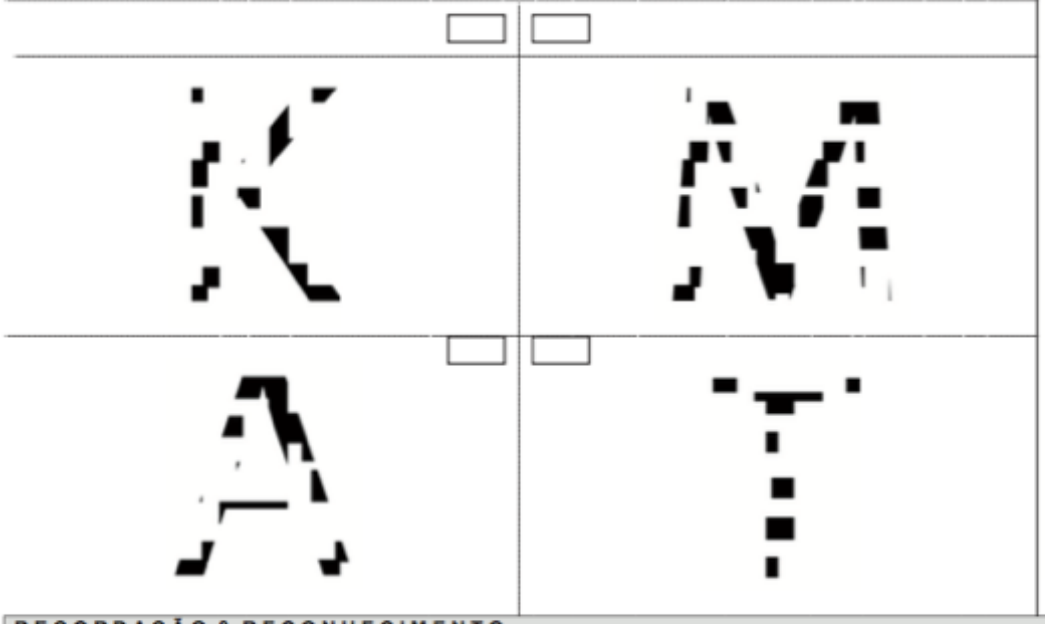
VISUAL - ESPACIAL

EXAME COGNITIVO DE ADDENBROOKE - VERSÃO REVISADA

HABILIDADES PERCEPTIVAS

➢ Peça ao indivíduo para identificar as letras:

[Escore 0-4] ☐



VISUAL-ESPACIAL

RECORDAÇÃO & RECONHECIMENTO

➢ Peça " Agora você vai me dizer o que você se lembra daquele nome e endereço que nós repetimos no começo".

Renato Moreira	....
Rua Bela Vista 73	....
Santarém	.....
Pará	.....

[Escore 0-7] ☐

➢ Este teste deve ser realizado caso o indivíduo não consiga se recordar de um ou mais itens. Se todos os itens forem recordados, salte este teste e pontue 5. Se apenas parte for recordada , assinale os itens lembrados na coluna sombreada do lado direito. A seguir, teste os itens que não foram recordados dizendo "**Bom, eu vou lhe dar algumas dicas: O nome / endereço era X, Y ou Z?**" e assim por diante. Cada item reconhecido vale um ponto que é adicionado aos pontos obtidos pela recordação.

[Escore 0-5] ☐

Ricardo Moreira		Renato Moreira		Renato Nogueira		Recordação	
Bela Vida		Boa Vista		Bela Vista		Recordação	
37		73		76		Recordação	
Santana		Santarém		Belém		Recordação	
Pará		Ceará		Paraíba		Recordação	

MEMÓRIA

Escores Gerais

MEEM	/30
ACE-R	/100

Subtotais

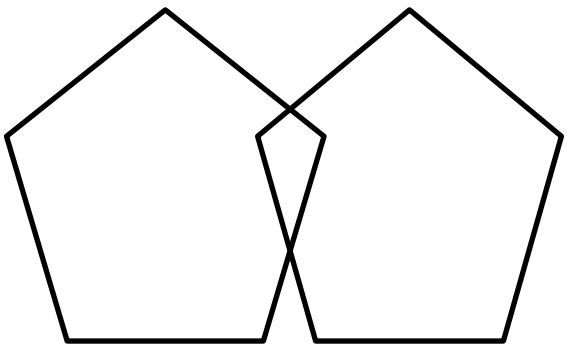
Atenção e Orientação	**/18**
Memória	**/26**
Fluência	**/14**
Linguagem	**/26**
Visual-espacial	**/16**

ESCORES

7.2 Supplementary material B – Mini-mental state examination

Orientação temporal - dia ( ) mês ( ) ano ( ) dia da semana ( ) hora aproximada ( )	
Orientação espacial - local específico ( ) local ou andar ( ) bairro ( ) cidade ( ) estado ( )	
Memória imediata - vaso ( ) carro ( ) tijolo ( )	
Atenção e cálculo - 93 ( ) 86 ( ) 79 ( ) 72 ( ) 65 ( )	
Evocação - vaso ( ) carro ( ) tijolo ( )	
Nomeação - relógio ( ) caneta ( )	
Repetição ("nem aqui, nem ali, nem lá") - repetição correta na 1ª tentativa ( )	
Comando verbal - pegar o papel com a mão direita ( ) dobrar ao meio ( ) colocar no chão ( )	
Comando escrito ("Feche os olhos") - fechou os olhos ( )	
Escrita (escrever uma frase) - Sentença com sujeito + verbo e que faça sentido ( )	
Desenho - copiar o desenho da interseção de 2 pentágonos ( )	
TOTAL (máximo 30)	
Atenção/memória operacional - O ( ) D ( ) N ( ) U ( ) M ( )	
TOTAL (máximo 35)	

Feche os olhos



7.3 Supplementary material C – Brief Cognitive Screening Battery

Identificação e Nomeação de 10 figuras

Apresente a folha de papel com as figuras desenhadas e pergunte: Que figuras são estas? Se não for capaz de perceber adequadamente um ou dois itens ou de nomeá-los não corrija. Aceite o nome que o paciente deu e considere-os corretos na avaliação da memória.

Memória incidental

Terminada a nomeação, esconda a folha e pergunte: Que figuras eu acabei de lhe mostrar?
O número de itens evocados fornece o escore de Memória Incidental

Memória imediata

Ao terminar, entregue novamente a folha ao examinando e diga: Olhe bem e procure memorizar estas figuras.
O tempo máximo permitido é de 30 segundos.
Novamente, esconda a folha e pergunte: Que figuras eu acabei de lhe mostrar?
O número de itens evocados fornece o escore de Memória Imediata.

Aprendizado

Ao terminar, entregue novamente a folha ao examinando e diga: Olhe bem e procure memorizar estas figuras.
O tempo máximo permitido é de 30 segundos.
Novamente, esconda a folha e pergunte: Que figuras eu acabei de lhe mostrar?
O número de itens evocados fornece o escore do Aprendizado.

Testes de Iniciativa e Planejamento (Interferência)

Dois testes são utilizados para avaliar funções executivas, linguagem e habilidades visuais-contrutivas.

Teste de Fluência Verbal

No teste de fluência verbal solicita-se ao examinando: Você deve falar todos os nomes de animais (qualquer bicho) que se lembrar, no menor tempo possível. Pode começar. Anote o número de animais lembrados em 1 minuto

Desenho do relógio (Sunderland et al., 1989)

Dê uma folha de papel em branco e diga: Desenhe um relógio com todos os números. Coloque ponteiros marcando 2h45.

10 - hora certa

9 - leve distúrbio nos ponteiros (p. ex.: ponteiro das horas sobre o 2)

8 - distúrbios mais intensos nos ponteiros (p. ex.: anotando 2:20)

7 - ponteiros completamente errados

6 - uso inapropriado (p. ex.: uso de código digital ou de círculos envolvendo números)

5 - números em ordem inversa ou concentrados em alguma parte do relógio

4 - números faltando ou situados fora dos limites do relógio

3 - números e relógio não mais conectados. Ausência de ponteiros

2 - alguma evidência de ter entendido as instruções, mas vaga semelhança com relógio

1 - não tentou ou não conseguiu representar um relógio

Memória tardia (5 minutos)

Ao terminar o desenho, pergunte: Que figuras eu lhe mostrei há alguns minutos? Se necessário, reforce, dizendo figuras desenhadas numa folha de papel plastificada.

O examinando tem até 60 segundos para responder.

O número de itens evocados fornece o escore de Memória Tardia.

Reconhecimento

Mostre a folha contendo 20 figuras e diga: Aqui estão as figuras que eu lhe mostrei hoje e outras figuras novas. Quero que você me diga quais você já tinha visto há alguns minutos.

Para o Reconhecimento, o escore final é obtido pela subtração: corretas - intrusões.

7.4 Supplementary material D – Functional Activities Questionnaire

1. Ele (ela) manuseia seu próprio dinheiro?

0 - Normal
1 - Faz com dificuldade
2 - Necessita de ajuda
3 - Não é capaz

0 - Nunca o fez, mas poderia fazê-lo agora
1 - Nunca o fez e agora teria dificuldade

2. Ele (ela) é capaz de comprar roupas, comida, coisas para casa sozinho (a)?

0 - Normal
1 - Faz com dificuldade
2 - Necessita de ajuda
3 - Não é capaz

0 - Nunca o fez, mas poderia fazê-lo agora
1 - Nunca o fez e agora teria dificuldade

3. Ele (ela) é capaz de esquentar a água para o café e apagar o fogo?

0 - Normal
1 - Faz com dificuldade
2 - Necessita de ajuda
3 - Não é capaz

0 - Nunca o fez, mas poderia fazê-lo agora
1 - Nunca o fez e agora teria dificuldade

4. Ele (ela) é capaz de preparar uma comida?

0 - Normal
1 - Faz com dificuldade
2 - Necessita de ajuda
3 - Não é capaz

0 - Nunca o fez, mas poderia fazê-lo agora
1 - Nunca o fez e agora teria dificuldade

5. Ele (ela) é capaz de manter-se em dia com as atualidades, com os acontecimentos da comunidade ou da vizinhança?

0 - Normal
1 - Faz com dificuldade
2 - Necessita de ajuda
3 - Não é capaz

0 - Nunca o fez, mas poderia fazê-lo agora
1 - Nunca o fez e agora teria dificuldade

6. Ele (ela) é capaz de prestar atenção, entender e discutir um programa de rádio ou televisão, um jornal ou uma revista?

0 - Normal
1 - Faz com dificuldade
2 - Necessita de ajuda
3 - Não é capaz

0 - Nunca o fez, mas poderia fazê-lo agora
1 - Nunca o fez e agora teria dificuldade

7. Ele (ela) é capaz de lembrar-se de compromissos, acontecimentos familiares, feriados?

0 - Normal
1 - Faz com dificuldade
2 - Necessita de ajuda
3 - Não é capaz

0 - Nunca o fez, mas poderia fazê-lo agora
1 - Nunca o fez e agora teria dificuldade

8. Ele (ela) é capaz de manusear seus próprios remédios?

0 - Normal
1 - Faz com dificuldade
2 - Necessita de ajuda
3 - Não é capaz

0 - Nunca o fez, mas poderia fazê-lo agora
1 - Nunca o fez e agora teria dificuldade

9. Ele (ela) é capaz de passear pela vizinhança e encontrar o caminho de volta para casa?

0 - Normal
1 - Faz com dificuldade
2 - Necessita de ajuda
3 - Não é capaz

0 - Nunca o fez, mas poderia fazê-lo agora
1 - Nunca o fez e agora teria dificuldade

10. Ele (ela) pode ser deixado(a) em casa sozinho(a) de forma segura?

0 - Normal
1 - Sim, com precauções
2 - Sim, por curtos períodos
3 - Não poderia

0 - Nunca ficou, mas poderia ficar agora
1 - Nunca ficou e teria dificuldade

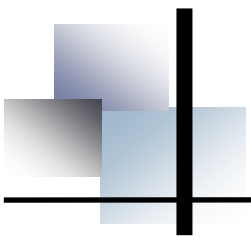
7.5 Supplementary material E – Clinical Dementia Rating (CDR)

Escore Clínico de Demência (CDR)	0	0,5	1	2	3

	Comprometimento				
	Normal - 0	**Questionável - 0,5**	**Leve - 1**	**Moderado - 2**	**Severo - 3**
Memória	Sem perda de memória ou esquecimento leve e inconstante.	Esquecimento leve e constante (em oposição a eventual); recordação parcial de eventos; esquecimento "benigno".	Moderada perda de memória; mais marcada para eventos recentes; déficit interfere nas atividades cotidianas.	Perda de memória grave; somente retém material intensamente aprendido; material novo rapidamente perdido.	Perda de memória grave; restam apenas fragmentos.
Orientação	Plenamente orientado.	Plenamente orientado, exceto por leve dificuldade nas relações temporais.	Dificuldade moderada com relações temporais; orientado para o lugar do exame; pode ter desorientação geográfica em outros lugares.	Dificuldade grave com relações temporais; usualmente desorientado para o tempo, frequentemente para o espaço.	Orientado apenas para pessoa.
Julgamento e resolução de problemas	Resolve bem problemas diários e administra bem negócios e finanças; bom julgamento em relação ao desempenho prévio.	Leve dificuldade em resolver problemas, similaridades e diferenças.	Dificuldade moderada para administrar problemas, similaridades e diferenças; julgamento social usualmente mantido.	Grave dificuldade em administrar problemas, similaridades e diferenças; julgamento social usualmente comprometido.	Incapaz de fazer julgamentos ou de resolver problemas.
Assuntos Comunitários	Função independente no nível usual no trabalho, em compras, grupos sociais ou de voluntários.	Leve dificuldade nessas atividades	Incapaz de funcionar independentemente nessas atividades, embora ainda possa engajar-se em algumas; parece normal à inspeção casual.	Nenhuma referência a funcionamento independente fora de casa. Parece estar bem para ser levado a atividades fora de ambiente familiar.	Nenhuma referência a funcionamento independente fora de casa. Parece estar muito doente para ser levado a atividades fora de ambiente familiar
Tarefas do Lar e Atividades de Lazer	Vida no lar, passatempos e interesses intelectuais bem mantidos.	Vida no lar, passatempos e atividades intelectuais levemente comprometidos.	Dificuldade leve mas evidente nas funções do lar; tarefas mais difíceis abandonadas; passatempos e interesses mais complexos abandonados.	Somente tarefas simples preservadas, interesses muito restritos e mal sustentados.	Sem função significativa em casa.
Autocuidado	Plenamente capaz de autocuidado.		Necessita estímulo.	Requer ajuda para vestir-se, higiene e cuidado com objetos pessoais.	Requer muita ajuda para o cuidado pessoal, incontinência frequente.

7.6 Supplementary material F – Neuropsychiatric Inventory (NPI)

ITEM	NA	Aus	Freq	Int	F x I
Delírios	X	0	1 2 3 4	1 2 3	
Alucinações	X	0	1 2 3 4	1 2 3	
Agitação	X	0	1 2 3 4	1 2 3	
Depressão/disforia	X	0	1 2 3 4	1 2 3	
Ansiedade	X	0	1 2 3 4	1 2 3	
Euforia/elação	X	0	1 2 3 4	1 2 3	
Apatia/indiferença	X	0	1 2 3 4	1 2 3	
Desinibição	X	0	1 2 3 4	1 2 3	
Irritabilidade/labilidade	X	0	1 2 3 4	1 2 3	
Comportamento motor aberrante	X	0	1 2 3 4	1 2 3	
Comportamentos noturnos	X	0	1 2 3 4	1 2 3	
Apetite/alterações alimentares	X	0	1 2 3 4	1 2 3	
TOTAL					



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Appendicies

Appendix A – Informed consent

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO
HCFMUSP
TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

DADOS DA PESQUISA

Título da pesquisa – **SÍNDROME CORTICOBASAL: ESTUDO LONGITUDINAL DOS PERFIS CLÍNICOS E FISIOPATOLÓGICOS.**

Pesquisador principal - Profa. Dra. Sonia Maria Dozzi Brucki
Pesquisador executante – Dra. Jacy Bezerra Parmera
Departamento/Instituto – Neurologia / Instituto Central

De acordo com a resolução 466/2012 os seguintes conteúdos devem fazer parte das explicações sobre a pesquisa

Convidamos o(a) Sr(a). para participar da pesquisa **SÍNDROME CORTICOBASAL: ESTUDO LONGITUDINAL DOS PERFIS CLÍNICOS E FISIOPATOLÓGICOS.**

O objetivo do estudo é analisar o perfil neuropsicológico de pacientes com a síndrome Corticobasal e comparar a presença de biomarcadores da doença de Alzheimer (PET-CT com marcador amiloide, PET com marcador fluordeoxiglicose e ressonância magnética estrutural) e da patologia TAU (ressonância magnética estrutural e PET com marcador fluordeoxiglicose) neste grupo, a fim de encontrar aspectos sugestivos destas patologias. Portanto, este presente projeto propõe-se a colaborar com esse crescente conhecimento, fundamental para compreendermos tal enfermidade, sua evolução e seu substrato patológico, e assim direcioná-los como alvos de futuras intervenções terapêuticas. A primeira avaliação ocorrerá de acordo com sua disponibilidade,

englobando questionários e testes que envolvem raciocínio, atenção e memória. Não deverá ocorrer desconforto durante a execução das tarefas. O tempo previsto para a realização dos testes é de 2 horas, podendo durar um pouco mais em cada caso. Essa avaliação será feita por um neurologista e por uma fonoauddiológa.

De acordo com o seu resultado nesses testes, você será convocado a realizar três exames de imagem (ressonância magnética, PET com marcador para glicose e PET com marcador para amilóide, que é a proteína que estar presente na doença de Alzheimer). O exame de ressonância magnética não causa nenhum mal conhecido à saúde, sendo contra-indicado na presença de alguns metais, e para isto, é necessário o preenchimento de um questionário de verificação antes do exame. Há um ruído desconfortável, mas haverá um protetor de ouvido. O médico estará o tempo todo observando o exame e pode se comunicar com a pessoa dentro do aparelho. A qualquer momento você poderá apertar um botão para conclusão deste exame. Se este for o caso, basta pedir e você será retirado (a) prontamente. O aparelho possui diversos microfones e você irá se comunicar com o pesquisador em alguns intervalos durante o exame. O túnel é iluminado e tem um ventilador. Você não poderá ter problemas de ficar em ambiente fechado (claustrofobia). Apesar das imagens deste experimento não terem a finalidade de fazer diagnóstico, algumas vezes podem mostrar alterações. Caso isto aconteça, você será comunicado e, se desejar, encaminhado para acompanhamento no Hospital das Clínicas. Os exames de PET são exames tomográficos que utiliza material radioativo para formar as imagens. Todos esses exames já são utilizados na prática médica há vários anos e não causam nenhum mal às pessoas. A exposição à radiação é baixa e por isso são exames considerados seguros, com risco mínimo. Antes do início do exame você precisará receber uma picada na veia para a coleta do exame e para injeção dos materiais (glicose marcada e marcador para amilóide). Você precisará vir em jejum para realização do exame de PET. Os exames de PET e ressonância duram cerca de 30 a 45 minutos cada. Trata-se de uma pesquisa de risco mínimo. Você será reconvocado a repetir os testes neuropsicológicos (os mesmos da primeira avaliação) após um, dois e três anos dos primeiros testes.

Não há benefício direto para o participante e não há ganho financeiro para participação na pesquisa. A sua participação na pesquisa contribuirá ao conhecimento sobre a Síndrome Corticobasal doença de Alzheimer e, portanto, no futuro ajudar no desenvolvimento de novos tratamentos. Você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas durante todo o período da pesquisa. Após o término da pesquisa, os participantes permanecerão em

acompanhamento neurológico no ambulatório de Neurologia Cognitiva do Hospital das Clínicas. Não há despesas decorrentes da pesquisa, incluindo exames e consultas. Em eventuais danos à saúde decorrentes da pesquisa, o participante terá toda assistência médica da instituição. Todos os dados pessoais serão mantidos em sigilos e os dados da pesquisa serão divulgados de forma impessoal, sem identificação do participante. Também serão garantidas as condições de plena liberdade a(o) senhor(a) de recusar-se a participar ou retirar o seu consentimento em qualquer fase da pesquisa sem penalização alguma, de sigilo e privacidade. Em qualquer momento do estudo você poderá solicitar sua retirada do protocolo de pesquisa sem que isso apresente qualquer consequência no seu acompanhamento no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. A (o) senhor(a) será entregue uma via original do termo de consentimento.

O principal investigador é o **Professora Dra.** Sonia Maria Dozzi Brucki e a pesquisadora executante é a **Dra. Jacy Bezerra Parmera**, que podem ser encontrados no endereço Av. Dr. Enéas de Carvalho Aguiar, 255, CEP 05403-900, Cerqueira César, 5º andar. Telefone(s): 2661 6401 ou 26617877. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Ovídio Pires de Campos, 225, 5º andar, telefones: (11) 2661-7585, (11) 2661-1548, (11) 2661-1549; e-mail: cappesq.adm@hc.fm.usp.br.

Fui suficientemente informado a respeito do estudo "**SÍNDROME CORTICOBASAL: ESTUDO LONGITUDINAL DOS PERFIS CLÍNICOS E FISIOPATOLÓGICOS.**". Eu discuti as informações acima com a Pesquisadora Responsável (Profa. Dra. Sonia Maria Dozzi Brucki) ou pessoa (s) por ele delegada (s) (Dra. Jacy Bezerra Parmera) sobre a minha decisão em participar nesse estudo. Ficaram claros para mim os objetivos, os procedimentos, os potenciais desconfortos e riscos e as garantias. Concordo voluntariamente em participar deste estudo, assino este termo de consentimento e recebo uma via rubricada pelo pesquisador.

Assinatura do paciente/representante legal: _____

Data: _____/_____/_____

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.
Profa. Dra. Sonia Maria Dozzi Brucki:

_____

Data: _____/_____/_____

Dra Jacy Bezerra Parmera: _____

Data: _____/_____/_____

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU RESPONSÁVEL LEGAL

1. NOME:_____
DOCUMENTO DE IDENTIDADE Nº: _____
SEXO: M □ F □ DATA NASCIMENTO: _____/_____/_____
ENDEREÇO: _____
BAIRRO:_____ CIDADE:_____
CEP:_____ TELEFONE: (_____) _____
2. RESPONSÁVEL LEGAL: _____
NATUREZA (grau de parentesco, tutor, curador etc.):_____.
DOCUMENTO DE IDENTIDADE Nº: _____
SEXO: M □ F □ DATA NASCIMENTO: _____/_____/_____
ENDEREÇO: _____
BAIRRO:_____ CIDADE:_____
CEP:_____ TELEFONE: (_____) _____

Appendix B – Ethics committee approval

USP - HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: SÍNDROME CORTICOBASAL: ESTUDO LONGITUDINAL DOS PERFIS CLÍNICOS E FISIOPATOLÓGICOS.

Pesquisador: SONIA MARIA DOZZI BRUCKI

Área Temática:

Versão: 1

CAAE: 67195517.4.0000.0068

Instituição Proponente: HOSPITAL DAS CLINICAS DA FACULDADE DE MEDICINA DA U S P

Patrocinador Principal: FUNDACAO DE AMPARO A PESQUISA DO ESTADO DE SAO PAULO

DADOS DO PARECER

Número do Parecer: 2.046.113

Apresentação do Projeto:

A apresentação do projeto está adequada a seus métodos e fundamentos.

Objetivo da Pesquisa:

O estudo tem por objetivo comparar a presença de biomarcadores da doença de Alzheimer e da patologia TAU em uma coorte acometida pela Síndrome Corticobasal.

Avaliação dos Riscos e Benefícios:

Há uma inconsistência quanto ao perfil de riscos do projeto. No TCLE o projeto é (corretamente) avaliado como de risco mínimo, enquanto que nas informações básicas há a afirmação (sempre incorreta) de que não há riscos na execução do projeto. Quanto aos benefícios, são indiretos e estão bem descritos no TCLE.

Comentários e Considerações sobre a Pesquisa:

A pesquisa tem boas chances de obter conhecimentos relevantes.

Considerações sobre os Termos de apresentação obrigatória:

O Termo de Consentimento Livre e Esclarecido informa adequadamente os eventuais participantes sobre os procedimentos e sobre seus direitos e prerrogativas.

Conclusões ou Pendências e Lista de Inadequações:

O projeto pode ser aprovado pela comissão.

Endereço: Rua Ovidio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

Considerações Finais a critério do CEP:

Em conformidade com a Resolução CNS nº 466/12 – cabe ao pesquisador: a) desenvolver o projeto conforme delineado; b) elaborar e apresentar relatórios parciais e final; c)apresentar dados solicitados pelo CEP, a qualquer momento; d) manter em arquivo sob sua guarda, por 5 anos da pesquisa, contendo fichas individuais e todos os demais documentos recomendados pelo CEP; e) encaminhar os resultados para publicação, com os devidos créditos aos pesquisadores associados e ao pessoal técnico participante do projeto; f) justificar perante ao CEP interrupção do projeto ou a não publicação dos resultados.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_848326.pdf	18/04/2017 09:19:45		Aceito
Outros	soniajacycadastro160240001.pdf	18/04/2017 09:17:34	SONIA MARIA DOZZI BRUCKI	Aceito
Folha de Rosto	folhaderosto.pdf	08/03/2017 22:31:11	SONIA MARIA DOZZI BRUCKI	Aceito
Projeto Detalhado / Brochura Investigador	projetodeestudo_Parmera_Brucki.docx	02/03/2017 20:00:07	SONIA MARIA DOZZI BRUCKI	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_atualizado.docx	02/03/2017 19:48:48	SONIA MARIA DOZZI BRUCKI	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO PAULO, 04 de Maio de 2017

Assinado por:
ALFREDO JOSE MANSUR
(Coordenador)

Appendix C – Funding – São Paulo Research Foundation

FAPESP SAGe

Processo

Identificação do Processo

Número do Processo	2017/10033-4 - Projeto de Pesquisa - Regular
Situação	Em Execução
Grupo de Financiamento	Auxílio à Pesquisa
Linha de Fomento	Programas Regulares / Auxílios a Pesquisa / Projeto de Pesquisa / Projeto de Pesquisa - Regular - Fluxo Contínuo
Beneficiário	Sonia Maria Dozzi Brucki
Responsável	Sonia Maria Dozzi Brucki
Data Início	01/08/2018
Duração	24 mês(es)

Instituição de Pesquisa/Empresa	Hospital das Clínicas de São Paulo/HC/SSSP
Departamento	Neurologia
Data de Abertura	17/05/2017

Projeto - Identificação

Título em Português

SÍNDROME CORTICOBASAL: ESTUDO LONGITUDINAL DOS PERFIS CLÍNICOS E FISIOPATOLÓGICOS.

Título em Inglês

CORTICOBASAL SYNDROME: CLINICAL AND PHYSIOPATHOLOGICAL CORRELATES.

Classificação

Grande Área	Ciências da Saúde
Área	Medicina
Sub-área	Outra Subárea Medicina
Especialidade	NEUROLOGIA

Palavras-chave	degeneração corticobasal, Demências, Doença de Alzheimer, Parkinsonismo, síndrome corticosabal

Projeto - Instituições

Instituição de Pesquisa/Empresa Principal

Nome	Hospital das Clínicas de São Paulo/HC/SSSP

Projeto - Pessoas Envolvidas

Equipe

Nome	Função	Horas Semanais Dedicadas ao Projeto	Vigência	Vínculo Principal
Sonia Maria Dozzi Brucki	Pesquisador Responsável	10	01/08/2018 a 30/09/2018	Hospital das Clínicas de São Paulo/HC/SSSP
Sonia Maria Dozzi Brucki	Pesquisador Responsável *	10	01/10/2018 a 31/07/2020	Hospital das Clínicas de São Paulo/HC/SSSP
Artur Martins Novaes Coutinho	Pesquisador Associado	10	01/08/2018 a 31/07/2020	Faculdade de Medicina/FM/USP
Carlos Alberto Buchpiguel	Pesquisador Associado	8	01/08/2018 a 31/07/2020	Faculdade de Medicina/FM/USP
Claudia da Costa Leite	Pesquisador Associado	8	01/08/2018 a 31/07/2020	Universidade de São Paulo/USP
JACY BEZERRA PARMERA	Pesquisador Associado	20	01/08/2018 a 31/07/2020	Hospital das Clínicas de São Paulo/HC/SSSP

* Com Benefício Complementar

Appendix D – Research article published in Movement Disorders.

RESEARCH ARTICLE

FDG-PET Patterns Predict Amyloid Deposition and Clinical Profile in Corticobasal Syndrome

Jacy Bezerra Parmera, MD,[1*] Artur Martins Coutinho, MD, PhD,[2] Mateus Rozalem Aranha, MD,[2,3] Adalberto Studart-Neto, MD,[1] Camila de Godoi Carneiro, Msc,[2] Isabel Junqueira de Almeida, Msc,[4] Davi J. Fontoura Solla, MD,[5] Carla Rachel Ono, MD, PhD,[2] Egberto Reis Barbosa, MD, PhD,[1] Ricardo Nitrini, MD, PhD,[1] Carlos Alberto Buchpiguel, MD, PhD,[2] and Sonia Maria Dozzi Brucki, MD, PhD[1]

[1]*Department of Neurology, Hospital das Clinicas, Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo, Brazil*
[2]*Laboratory of Nuclear Medicine (LIM 43), Center of Nuclear Medicine, Institute of Radiology, Hospital das Clinicas, Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo, Brazil*
[3]*Laboratory of Magnetic Resonance in Neuroradiology (LIM 44), Institute of Radiology, Hospital das Clinicas, Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo, Brazil*
[4]*Department of Physical Therapy, Speech, and Occupational Therapy, Hospital das Clinicas, Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo, Brazil*
[5]*Department of Neurology, Division of Neurosurgery, Hospital das Clinicas, Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo, Brazil*

ABSTRACT: Background: Corticobasal syndrome (CBS) is an atypical parkinsonian syndrome related to multiple underlying pathologies.
Objective: To investigate if individual brain [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET) patterns could distinguish CBS due to Alzheimer's disease (AD) from other pathologies based on [^{11}C]Pittsburgh Compound-B (PIB)-PET.
Methods: Forty-five patients with probable CBS were prospectively evaluated regarding cognitive and movement disorders profile. They underwent FDG-PET and were distributed into groups: likely related to AD (CBS FDG-AD) or likely non-AD (CBS FDG-nonAD) pathology. Thirty patients underwent PIB-PET on a hybrid PET-magnetic resonance imaging equipment to assess their amyloid status. FDG and PIB-PET images were classified individually based on visual and semi-quantitative analysis, blinded to each other. Quantitative group analyses were also performed.
Results: CBS FDG-AD group demonstrated worse cognitive performances, mostly concerning attention, memory, visuospatial domains, and displayed more myoclonus and hallucinations. The non-AD metabolic group presented more often limb dystonia, ocular motor dysfunction, motor perseveration, and dysarthria. All patients classified as CBS FDG-AD tested positive at PIB-PET compared to 3 of 20 in the non-AD group. The individual FDG-PET classification demonstrated 76.92% of sensitivity, 100% of specificity and positive predictive value and 88.5% of balanced accuracy to detect positive PIB-PET scans. Individuals with positive and negative PIB-PET showed hypometabolism in posterior temporoparietal areas and in thalamus and brainstem, respectively, mainly contralateral to most affected side, disclosing possible metabolic signatures of CBS variants.
Conclusion: FDG-PET was useful to predict AD and non-AD CBS variants depicting their specific degeneration patterns, different clinical features, and brain amyloid deposition. © 2020 International Parkinson and Movement Disorder Society

Key Words: corticobasal syndrome; corticobasal degeneration; positron emission tomography; [^{18}F] fluorodeoxyglucose; amyloid PET

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Relevant conflicts of interest/financial disclosures: The author's declare no conflicts of interest.

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Corticobasal syndrome (CBS) is an atypical parkinsonian syndrome characterized by asymmetric motor and cortical deficits with cognitive impairment.[1] First considered a clinicopathological entity linked to corticobasal degeneration (CBD),[2] now this term denotes a phenotype also related to progressive supranuclear palsy (PSP) and Alzheimer's disease (AD), among others.[3-10] Anatomoclinical cohorts demonstrate AD pathology in 15%–50% of cases,[3-7] including CBS in its atypical spectrum.[11,12] Considering that no clinical features distinguish neuropathology and the advances in disease-modifying therapies for primary tauopathies and AD,[13,14] the need for biomarkers addressing CBS pathologies grows.

Amyloid-positron emission tomography (PET) and tau tracers have shown their role in suggesting pathology and were applied to investigate clinical characteristics and brain metabolism in CBS.[15-17] Nevertheless, their availability is still limited. PET with [^{18}F] fluorodeoxyglucose (FDG)-PET, otherwise, assists in the early diagnosis of neurodegenerative diseases[18] and helps differentiate Parkinson's disease from atypical parkinsonism.[19-21] Although CBD characteristically presents a frontoparietal asymmetric hypometabolism,[22] CBS shows a more complex set of patterns likely because of diverse neuropathologies.[23-25] A postmortem study recently demonstrated that neuropathology modulates metabolism and established CBS patterns related to CBD, PSP, and AD.[26] There is, however, a lack of evidence supporting FDG-PET in the diagnostic workup depicting pathologies antemortem.[24,25]

The present study aimed to use pre-established FDG-PET patterns to distinguish CBS due to AD from other possible pathologies, comparing the dichotomized groups regarding neurological assessment and amyloid PET status. Our main goal was to verify the potential of FDG-PET to identify CBS related or not to AD in the clinical routine.

Methods

Participants

Forty-five patients diagnosed with probable CBS[1] at the movement disorders and cognitive neurology clinics at our Hospital (Hospital das Clínicas, University of São Paulo School of Medicine, São Paulo, Brazil) were prospectively enrolled to prevent selection bias. All individuals were further evaluated regarding their clinical profile between February 2017 and December 2019 by two neurologists (JBP. and SMDB.) with board certification in movement disorders and cognitive neurology. Exclusion criteria included relevant non-degenerative brain lesions such as stroke sequelae, tumors, hydrocephalus, and remarkable premorbid psychiatric disease.

Clinical Assessment

The global cognitive assessment included the Addenbrooke's Cognitive Examination – Revised (ACE-R)[27,28] and the Mini-Mental State Examination (MMSE).[29] The Brief Cognitive Screening Battery (BCSB),[30] a test suitable for individuals with different educational backgrounds, was used to assess episodic memory. Attention and working memory were measured with forward and backward digit span tests, respectively. Limb and orobuccal apraxia were determined by imitation of meaningful and meaningless gestures and imaginary tool use.[31] Functional decline was investigated with the Functional Activities Questionnaire[32] and the Clinical Dementia Rating scale.[33] Cortical signs were evaluated by the presence of cortical sensory loss, alien limb phenomena, visual neglect, and Balint and Gerstmann syndromes. Motor impairment was categorized by the Hoehn and Yahr scale.[34] We evaluated motor signs such as parkinsonism, dystonia, myoclonus, pyramidal signs, postural instability, tremor, ocular motor dysfunction, and elementary motor perseveration. Behavioral aspects were evaluated with the Neuropsychiatric Inventory scale.[35] A speech-language therapist performed a comprehensive language assessment regarding aphasia, dysarthria, agrammatism, apraxia of speech, and verbal fluency tasks. According to the initial complaint, we classified the patient's first symptom as predominantly motor, cognitive, or behavioral. We also applied the Movement Disorders Society (MDS) criteria for probable 4-repeat (4R)-tauopathies.[36] All patients or caregivers provided written informed consent for the study. The ethical committee of our institution approved the investigation procedure and informed consent under protocol number 2.046.113.

[^{11}C]Pittsburgh Compound-B and [^{18}F] Fluorodeoxyglucose Production and Imaging Data Acquisition

Both [^{11}C]Pittsburgh Compound-B (PIB) and [^{18}F] FDG were produced in an on-site cyclotron (PET trace 880, GE Healthcare, São Paulo, SP, Brazil) at the Nuclear Medicine Center of the Institute of Radiology (CMN-InRad, São Paulo, SP, Brazil) of our Hospital. FDG-PET was performed in a Discovery 710 PET/CT scanner (GE Healthcare, Milwaukee, WI), whereas PIB-PET and MRI images were simultaneously acquired with a hybrid 3.0-Tesla SIGNA PET/MRI scanner (GE Healthcare, Milwaukee, WI) at CMN-InRad. The FDG-PET was performed within one month after clinical examination, and the time between FDG and PIB-PET varied from 2 days to 6 months.

MRI Visual Analysis

The MRI protocol included volumetric T_1, T_2, FLAIR sequences, and diffusion-weighted imaging. Images were visually inspected by a board-certified neuroradiologist (MRA) for the detection of structural brain

lesions, artifacts that could impair imaging processing, and the assessment of white matter hyperintensities (WMH), according to the Fazekas scale.[37]

FDG-PET and PIB-PET Visual Analysis and Classification

FDG-PET

Visual analysis of FDG-PET images, assisted by the 3D-SSP semi-quantitative software (Cortex ID Suite, GE healthcare) and normalized by at least two different methods (global cortex and pons), was performed by two board-certified nuclear physicians (AMC and CRO), blinded to each other's interpretation, clinical profile, and PIB-PET status.

Based on the FDG-PET findings, the patients were split into two groups, namely "CBS likely related to AD" (CBS FDG-AD), or "CBS likely not related to AD" (CBS FDG-nonAD), according to patterns of hypometabolism previously described for neurodegenerative diseases.[18,19,21,23-26] Hypometabolic pattern suggestive of AD included decreased regional brain glucose metabolism (rBGM) in the posterior temporoparietal, inferior temporal regions, precuneus, and posterior cingulate gyrus.[38,39] We considered the remaining patterns as non-AD group and performed a subclassification regarding these different patterns into CBD, PSP, frontotemporal dementia (FTD), Lewy Body dementia (LBD), and indeterminate (closely related to tauopathies), also according to patterns previously described.[18,19,21] We evaluated the inter-rater agreement in the FDG-PET classification and subclassification. If there was no consensus, a third independent reader rated the exam to reach consensus (MRA). There was no consensus reading for the non-AD subclassification.

PIB-PET

The same nuclear medicine physicians blindly evaluated the PIB-PET images. Participants were rated as "amyloid positive" (CBS-A+) or "amyloid negative" (CBS-A−), according to previously established criteria.[40,41] Our approach reached a high inter-rater agreement and similar amyloid positivity rates in the literature in a previous study.[41]

FDG and PIB-PET Quantitative Group Analysis

Quantitative group analyses were performed to investigate: (1) which brain areas were more consistently hypometabolic in CBS-A+ and CBS-A− patients, (2) the intensity of cortical amyloid deposition in CBS FDG-AD and CBS FDG-nonAD groups, and (3) the individual variability of rBGM and amyloid deposition of both groups.

FDG-PET and PIB-PET images were co-registered to their own T_1-weighted MRI using the Statistical Parametric Mapping 8 (SPM8) software (Wellcome Department of Cognitive Neurology, Functional Imaging Laboratory, London, UK). PIB-PET images were spatially normalized into an anatomic template generated with diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) algorithm. Regarding the FDG-PET quantitative analysis, we flipped the images to represent the hemisphere contralateral to the most affected limbs on the right side of the image, because of the asymmetric nature of CBS. The spatial normalization of FDG-PET scans was performed using a dementia-optimized brain FDG-PET template.[42] Scans were smoothed with an 8 mm full width at half-maximum Gaussian kernel to reduce misregistration into the template space and improve the signal-to-noise ratio. To ensure the analysis only included voxels mapping cerebral tissue, a default threshold of 0.8 of the mean uptake inside the brain was selected. Global uptake differences were adjusted using the "proportional scaling" SPM8 option.

For the group analyses, statistical parametric maps were generated with SPM8 threshold at the voxel level at P uncorrected (p unc) =0.001, with a minimum extension of 100 voxels in the cluster. Statistical results were considered valid when survived correction for multiple comparisons with the familywise error (FWE) or false discovery rate (FDR) methods, (pFWE/FDR ≤0.05), or without correction for multiple comparisons with p unc <0.001, when a priori regions were observed, according to established patterns of neurodegeneration.[18,19,21,23-26] Relevant peak voxels from the statistical parametric maps were identified in the Montreal Neurologic Institute (MNI) coordinates system. Numeric values representing the mean FDG uptake in the clusters of rGBM and PIB uptake for each individual were obtained with the toolbox MarsBar for SPM (http://marsbar.sourceforge.net/).

The study design is summarized in Fig 1.

Statistical Analysis

Groups were compared using the appropriate statistical tests at the Statistical Package for Social Sciences software, version 21.0 (SPSS, IBM Statistics, Chicago, IL) and SPM8. Categorical variables were expressed as absolute and relative frequencies and compared with Pearson's χ^2 on univariate analysis. Continuous variables were compared using independent samples Student's t-test or Mann–Whitney test according to data distribution, assessed with Kolmogorov–Smirnov's test. Data with normal distribution were expressed as mean ± standard deviation and data with non-normal distribution as median (interquartile range). All tests were two-tailed. Statistical significance was accepted for $P < 0.05$. The sensitivity and specificity of FDG-PET to

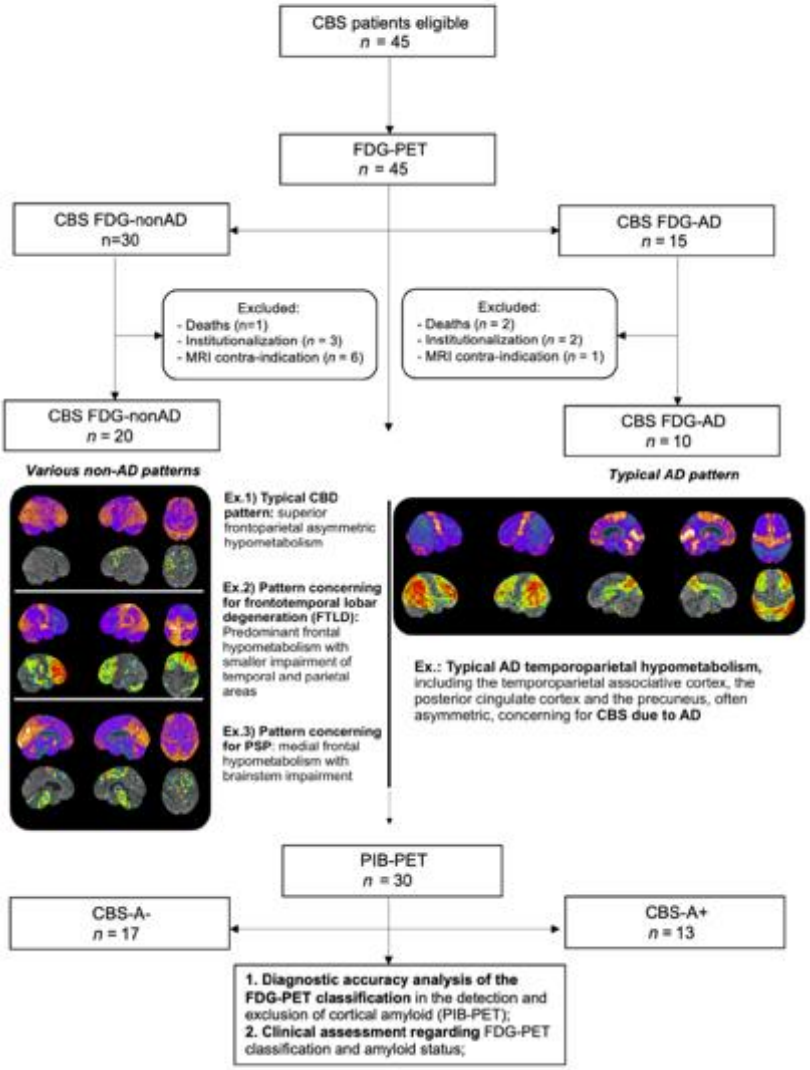

FIG. 1. Study design and flow of participants. **Legends:** 45 patients with probable corticobasal syndrome (CBS)[1] were eligible for clinical assessment and underwent FDG-PET. They were individually classified concerning their metabolic patterns as "CBS FDG-AD" or "CBS FDG-nonAD". Images on the left side depict 3D stereotactic surface projections (3D-SSP) for the CBS FDG-nonAD group, and, on the right side, 3D-SSP projections for the CBS FDG-AD group. After this, both groups were compared concerning the clinical evaluation, aiming to delineate the clinical variants based on the metabolic patterns. Thirty patients underwent PIB-PET. Diagnostic accuracy for FDG-PET to detect amyloid deposition was evaluated, as well as the clinical profile in patients with positive or negative PIB-PET status. A quantitative group analysis on SPM8 was also performed. **Abbreviations:** AD, Alzheimer's disease; CBS, Corticobasal Syndrome; FDG-PET, [18F]fluorodexyglucose-PET; PIB-PET, [11C]Pittsburgh Compound-B-PET; CBS FDG-AD, group with a metabolic pattern likely related to AD; CBS FDG-noAD, group with a metabolic pattern likely not related to AD; CBS-A+, CBS subjects with positive PIB-PET; CBS-A−, CBS subjects with negative PIB-PET. [Color figure can be viewed at wileyonlinelibrary.com]

detect amyloid deposition on PIB-PET were assessed. Positive and negative predictive values, likelihood ratios, overall and balanced accuracy were also calculated. Agreement in visual FDG-PET classification was measured using Cohen's kappa statistic (κ).

Results

Demography and Clinical Assessment

In total, 45 patients were included and clinically evaluated. Demographic data are summarized in Table 1.

The main initial complaints referred to cognitive (55.6%), followed by motor (40%) and psychiatric issues (4.4%). All patients (100%) presented with asymmetric parkinsonism, 30 (66.7%) with myoclonus, mostly stimulus-sensitive or poliminimyoclonus in upper limbs, and 19 (42.2%) demonstrated upper limb asymmetric dystonia. Seven (15.6%) had cervical dystonia. Regarding other motor signs, 14 patients (31.1%) had pyramidal signs, 13 (28.9%) had postural instability, and two (4.4%) had upper limb tremor. Eight patients (17.8%) presented ocular motor dysfunction, including vertical supranuclear gaze palsy (two patients) and slowness of vertical saccades (six patients). Ideomotor apraxia was the most frequent cortical feature, present in 44 (97.8%) patients. Five (11.1%) demonstrated orobuccal apraxia. Twelve patients (26.7%) had cortical sensory loss, and eight (17.8%) had alien limb phenomena (Fig. 2).

FDG-PET Individual Classification and Comparison to PIB-PET Status

All patients underwent FDG-PET and showed hypometabolism predominantly asymmetrical, contralateral to most affected side. Thirty (66.7%) patients had a non-AD FDG-PET pattern (CBS FDG-nonAD group), and 15 (33.3%) showed an AD pattern (CBS FDG-AD group). A subset of 30 patients underwent PIB-PET examinations. Fifteen patients, however, did not undergo because of distinct reasons (Fig. 1).

Regarding the 30 patients who underwent PIB-PET, 10 of 30 (33%) pertained to CBS FDG-AD group, and 20 of 30 (67%) to CBS FDG-nonAD group. Among all patients with PIB-PET, 17 of 30 (56.7%) had negative and 13 of 30 (43.3%) had positive results. In the CBS FDG-nonAD group, 17 of 20 (85%) were negative, and 3 of 20 (15%) were positive for cortical amyloid deposition. In the CBS FDG-AD group, all patients (100%) had positive PIB-PET results ($P < 0.001$).

The classification according to FDG-PET patterns in AD versus non-AD demonstrated 76.92% of sensitivity (confidence interval [CI] 46.19%–94.16%) and 100% of specificity (CI 80.49%–100%) to detect amyloid deposition on PIB-PET. These values translate to a positive predictive value (PPV) of 100% (CI 69.2%–100%), negative predictive value of 85% (CI 62.1%–96.8%), negative likelihood ratio of 0.23 (CI 0.09–0.62), overall accuracy of 90% and balanced accuracy of 88.5%. Inter-rater agreement regarding the AD and non-AD FDG-PET classification was high, reaching a 98% interobserver agreement ($\kappa = 0.95$). There was only one divergent classification, which the third independent reader blindly rated the scan as FDG-AD.

The subclassification concerning non-AD patterns disclosed CBD pattern in 50% by reader 1 and 58.1% by reader 2; PSP in 20% by reader 1 and 12.9% by reader 2; FTD in 3.3% by both readers; LBD in 3.3% by reader 1 and 6.6% by reader 2 and indeterminate in 20% by reader 1 and 16.1% by reader 2. The inter-rater agreement regarding this subclassification was more modest, reaching 73.3% agreement ($\kappa = 0.58$).

MRI Visual Analysis

The 30 patients who underwent PIB-PET on PET/MRI scanner were rated according to the Fazekas scale, and no differences of WMH were seen between the metabolic groups or PIB-PET results ($P = 0.44$).

Clinical Features According to FDG-PET Groups

CBS FDG-AD and nonAD groups did not significantly differ regarding age, symptoms duration, and years of education. At the cognitive assessment, the CBS FDG-AD group had lower scores at MMSE, ACE-R total score and attention, memory, and visuospatial subscores. CBS FDG-AD group also performed worse on the delayed recall subtest at BCSB (Table 1).

Concerning cortical, motor and neuropsychiatric features, CBS FDG-AD patients had more myoclonus (100% vs 50%, $P = 0.001$) and visual hallucinations (40% vs 10%, $P = 0.042$) compared to CBS FDG-nonAD patients. In addition, visual neglect also demonstrated a tendency of higher frequency in the CBS FDG-AD group (40% vs 13.3%, $P = 0.052$). Conversely, CBS FDG-nonAD patients presented more often limb dystonia (56.7% vs 13.3%, $P = 0.009$), ocular motor dysfunction (26.7% vs 0%, $P = 0.038$), dysarthria (39.1% vs 0%, $P = 0.015$), and motor perseveration (40% vs 6.7%, $P = 0.034$) (Fig. 2). When we applied the criteria for probable 4R-tauopathies, 10 patients (33.3%) previously classified as CBS FDG-nonAD fulfilled the criteria compared to none in the CBS FDG-AD group ($P = 0.019$).

Clinical Features According to PIB-PET Status

There were no demographic differences between CBS-A+ and CBS-A− patients. CBS-A+ individuals performed worse on MMSE ($P = 0.007$) and ACE-R subscores of attention (0.012), memory (0.009), and visuospatial (0.001) compared to CBS-A− patients. We found no significant differences regarding cortical, motor, and neuropsychiatric features regarding PIB-PET status. Six CBS-A− patients (35.3%) fulfilled the criteria for 4R-tauopathies compared to one CBS-A+ patient ($P = 0.104$) (comparisons disclosed as Appendix S1).

FDG and PIB-PET Quantitative Group Analysis on SPM8

Direct comparisons of FDG uptake in individuals with positive and negative PIB-PET showed three large

TABLE 1. Demography, functional decline, and cognitive assessment of patients with corticobasal syndrome and comparison according to the FDG-PET metabolic patterns

	CBS (n = 45)	CBS FDG-AD (n = 15)	CBS FDG-nonAD (n = 30)	*P* value
Demography				
Sex, M/F	18/27	6/9	12/18	0.62
Age at symptom onset, y	63.2 (± 8.5)	62.4 (± 7.1)	63.6 (± 9.2)	0.66
Age at main assess, y	67.3 (± 8.5)	66.8 (± 7.7)	67.5 (± 8.9)	0.79
Symptom duration at main assess, y	4.1 (± 2.2)	4.4 (± 1.7)	4.0 (± 2.4)	0.51
Education, y	8.7 (± 5.8)	10.8 (± 6.3)	7.7 (± 5.3)	0.91
Side of more severely involved limbs, R/L	28/17	10/5	18/12	0.46
First initial symptom	Cognitive: 25 (55.6%) Motor: 18 (40%) Psychiatric: 2 (4.4%)	Cognitive: 12 (80%) Motor: 2 (13.3%) Psychiatric: 1 (6.7%)	Cognitive: 13 (43.3%) Motor: 16 (53.3%) Psychiatric: 1 (3.3%)	0.073
Functional assessment				
CDR	0.5 13.3% 1.0 4.4% 2.0 51.1% 3.0 31.1%	0.5 0 1.0 6.7% 2.0 40% 3.0 53.3%	0.5 20% 1.0 3.3% 2.0 56.7% 3.0 20%	0.061
Functional activities questionnaire	20.4 (± 8.2)	23.6 (± 7.5)	18.7 (± 8.2)	0.062
Hoehn &Yahr	2.9 (± 1.2)	2.6 (± 1.1)	3.1 (± 1.2)	0.14
Cognitive assessment				
ACE-R total	39.8 (± 22.8)	26.6 (± 18.5)	45.6 (± 22.4)	**0.019**[a]
ACE-R attention	10.2 (± 4.1)	7.1 (± 3.3)	11.6 (± 3.7)	**0.003**[a]
ACE-R memory	8.7 (± 6.7)	3.9 (± 3.8)	10.9 (± 6.6)	**0.002**[b]
ACE-R fluency	2.8 (± 2.9)	1.9 (± 2.1)	3.2 (± 3.1)	0.22
ACE-R language	15.4 (± 6.7)	13.0 (± 7.8)	16.5 (± 6.0)	0.16
ACE-R visuospatial	5.8 (± 3.7)	2.9 (± 2.2)	7.0 (± 3.6)	**0.001**[b]
MMSE	15.4 (± 7.4)	9.4 (± 6.5)	18.7 (± 5.7)	**< 0.001**[b]
Delayed recall (BCSB)	3.4 (± 2.8)	1.7 (± 2.0)	4.1 (± 2.9)	**0.030**[a]
Verbal fluency (letter)	3.3 (± 2.9)	3.1 (± 2.6)	3.5 (± 3.1)	0.71
Verbal fluency (animals)	6.2 (± 4.2)	5.0 (± 3.3)	6.8 (± 4.6)	0.23
Digit span forward	5.7 (± 2.1)	4.7 (± 2.1)	6.3 (± 1.8)	0.30
Digit span backward	1.7 (± 1.7)	1.2 (± 1.8)	2.1 (± 1.7)	0.14
NPI	17.1 (± 13.6)	20.0 (± 16.3)	15.4 (± 11.8)	0.32

Comparison analysis was performed between CBS FDG-AD and CBS FDG-nonAD with [a] Student's t-test and [b] Mann–Whitney test. Data reported as mean ± SD; *P* is significant at the 0.05 level. Abbreviations: AD, Alzheimer's disease; CBS, Corticobasal syndrome; FDG, [^{18}F]fluorodeoxyglucose; CBS FDG-AD, group with a metabolic pattern likely related to AD; CBS FDG-nonAD, group with a metabolic pattern likely not related to AD; CDR, Clinical Dementia Rating; MMSE, Mini-mental State Examination; ACE-R, Addenbrooke Cognitive Examination-Revised; BCSB, Brief Cognitive Screening Battery; NPI, Neuropsychiatric Inventory scale. Bold faced values are statistically significant according to P values.

clusters of reduced rBGM surviving correction for multiple comparisons at the cluster level in CBS-A+ patients. There were two major clusters contralateral to most affected side, located in the posterior superior and middle temporal gyri and in the angular gyrus and superior parietal lobule. Other cluster, ipsilateral to most affected side, was located at fusiform gyrus extending to inferior temporal gyrus. Individuals with negative PIB-PET presented two major clusters of reduced metabolism, contralateral to most affected side, at the thalamus extending to diencephalon and mesencephalon and at the supplementary motor area (SMA) and paracentral lobule (Fig. 3). The SPM8 statistics and areas of reduced rBGM are disclosed as Appendix S1.

When exploring the individual variability of rBGM in these clusters, the three individuals with positive PIB-PET and a CBS FDG-nonAD pattern had levels of rBGM above the median of the group in temporoparietal areas (Fig. 3, colored dots in 1,2, and 3), and presented with similar levels of rBGM in thalamus and SMA to the CBS-A– individuals (Fig. 3, colored dots in 4 and 5).

Areas of increased PIB uptake corresponding to cortical amyloid deposition were markedly more evident in the CBS FDG-AD group (Fig. 4). The three exceptions of patients classified as CBS FDG-nonAD with positive PIB-PET demonstrated the lowest individual PIB uptake ratio among CBS-A+ patients; however, they presented individual levels of amyloid deposition above the standard deviation of their metabolic group (Fig. 4, colored dots on (b)).

Discussion

Our study represents a prospective observational cohort of 45 patients with probable CBS, aiming to evaluate the role of FDG-PET at the individual level in the clinical setting to predict amyloid status and guide the identification of CBS pathologic variants. As our main findings, the strategy of splitting CBS patients into two groups based at FDG-PET patterns identified a group likely related to AD (CBS FDG-AD) as having

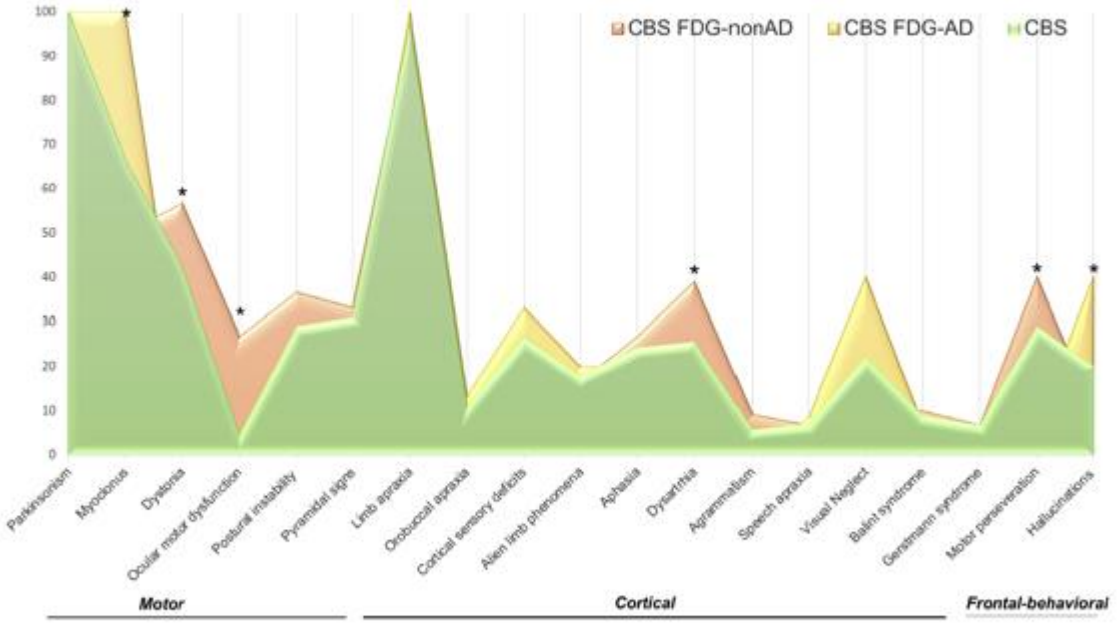

FIG. 2. Motor and cortical signs in the whole corticobasal syndrome (CBS) cohort and according to the metabolic patterns. **Legends**: data are presented as the frequency of the symptoms, both in the total sample and in the groups according to the FDG-PET classification. The symbol (*) indicates statistically significant differences between the percentage of the feature in CBS FDG-AD vs CBS FDG-nonAD groups. Comparison analysis was performed with Pearson's χ^2 and Fisher's exact test. (Myoclonus: $P = 0.001$; Dystonia: $P = 0.009$; Ocular motor dysfunction: $P = 0.038$; Dysarthria: $P = 0.015$; Perseveration: $P = 0.034$; Hallucinations: $P = 0.042$). **Abbreviations:** AD = Alzheimer's disease; CBS=Corticobasal Syndrome; FDG, [^{18}F] fluorodeoxyglucose; CBS FDG-AD, group with a metabolic pattern likely related to AD; CBS FDG-nonAD, group with a metabolic pattern likely not related to AD. [Color figure can be viewed at wileyonlinelibrary.com]

worst cognitive performances and amyloid deposition in all cases, versus a non-AD metabolic group (CBS FDG-nonAD) with prominent motor signs such as dystonia, ocular motor dysfunction, dysarthria, motor perseveration, and a lower prevalence of brain amyloid deposition. Additionally, a post-hoc quantitative group analysis showed hypometabolism comprising the posterior temporoparietal areas, mainly contralateral to most affected side, as the areas with the most consistent hypometabolism in amyloid-positive (CBS-A+) patients, a possible CBS-AD metabolic signature that may guide physicians in the interpretation of FDG-PET scans. Amyloid-negative patients, conversely, showed more heterogeneous metabolic patterns and disclosed areas of rBGM reduction at thalamus and SMA.

Previous works have demonstrated that differences in rBGM potentially predict the presence of cortical amyloid deposition in focal-onset dementias such as primary progressive aphasia and CBS with better sensitivity and specificity than clinical evaluation[17,43] and visual interpretation of MRI.[17] In line with this, our individual metabolic analysis has shown that all 10 patients classified as CBS FDG-AD had positive PIB-PET scans in contrast to three out of 20 classified as CBS FDG-nonAD. Our classification had higher specificity (100% vs 58% and 83%) and overall accuracy (90% vs 73% and 84%) than these studies,[17,43] pointing toward the critical role of FDG-PET in the diagnostic workup of CBS.

Moreover, a recent study with neuropathologic examination showed that CBS underlying pathologies are associated with different metabolic degeneration patterns and described hypometabolism for CBS-CBD, CBS-AD, and CBS-PSP[26]. The CBS-AD metabolic pattern described was similar to what we observed comparing patients with positive and negative PIB-PET. This potential CBS-AD metabolic signature also matches previous works using amyloid imaging[17] and CSF biomarkers[25] in CBS, is classically seen in typical AD,[38,39] and is closely associated with positive PIB-PET scans in the continuum of amnestic cognitive decline,[42] supporting our FDG-PET classification.

Following prior studies,[6-8,12] CBS patients presented a distinct clinical phenotype primarily characterized by parkinsonism and limb apraxia. Despite the current knowledge that clinical aspects cannot reliably disclose pathologic substrate, some might have a role as disease-related clues.[7,11,12]

The CBS FDG-AD patients performed significantly worse in the general cognitive assessment. Similarly,

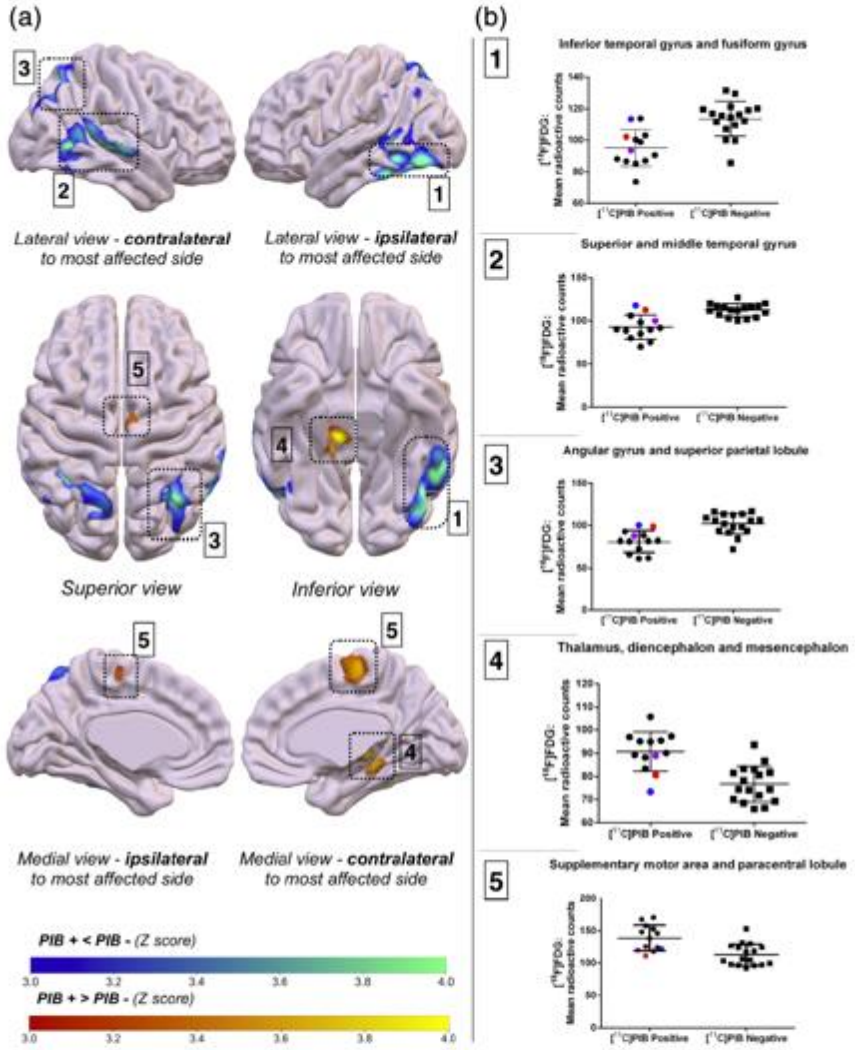

FIG. 3. Brain glucose metabolism in patients with corticobasal syndrome (CBS) according to amyloid imaging status. **Legends:** Images on the left: clusters with differences in regional brain glucose metabolism (rBGM) in individuals with CBS according to brain amyloid status. Reduced FDG uptake in CBS with positive PIB-PET is consistently seen in posterior temporal and parietal areas, mainly contralateral to most affected side (areas in blue), suggesting an "AD metabolic signature" on FDG-PET. Clusters in red-yellow indicate areas of reduced rBGM in individuals with negative PIB-PET, contralateral to most affected side, at the thalamus, diencephalon and mesencephalon, at supplementary motor area, and paracentral lobule. Parametric maps were generated with an unpaired *t*-test ($P < 0.001$, uncorrected) in the SPM8 software and plotted on surface maps with the Surf Ice software—http://www.nitrc.org/projects/surfice/.). Cluster 1, 2, and 3 survived correction for multiple comparisons (pFWE and pFDR < 0.05). Bars in the lower-left indicate z scores, ranging from $P = 10^{-3}$ (z score = 3.0) to $P = 10^{-4}$ (z score = 4.0). Images on the right: Scatter Plot graphical representation showing the dispersion of the FDG uptake in the clusters of reduced rBGM for each participant (mean radioactive counts), obtained in the group analysis shown in the left. Dots highlighted in color represent the three individual exceptions classified as CBS FDG-nonAD with positive PIB-PET. [Color figure can be viewed at wileyonlinelibrary.com]

CBS-A+ individuals performed worse in the MMSE and ACE-R subscores. This pattern of ominous cognitive progression associated with underlying AD pathology is consistent with studies including histopathology[8,12] and in vivo biomarkers.[15]

In line with clinicopathologic studies,[6,7] episodic memory was more impaired in the CBS FDG-AD group.

Furthermore, the same group showed more visuospatial dysfunction. Previous studies suggested a preferential

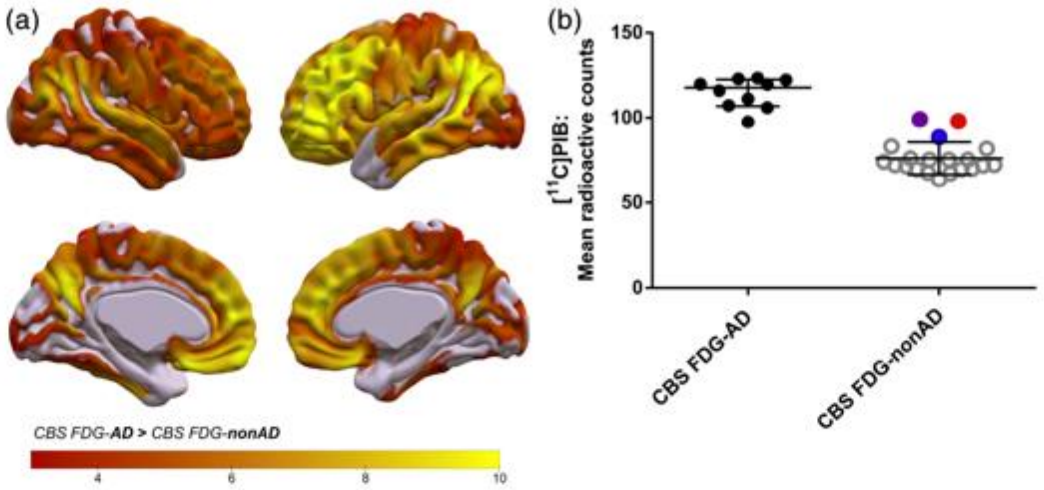

FIG. 4. Amyloid deposition in patients with corticobasal syndrome (CBS) according to the FDG-PET pattern. **Legends:** Images on the left: areas with differences in cortical amyloid deposition measured with [11C]Pittsburgh Compound-B (PIB)-PET according to their classification as CBS FDG-AD or CBS FDG-nonAD. Increased PIB uptake in CBS FDG-AD is seen diffusely throughout the cortex, as shown in red-yellow areas. Parametric maps were generated with an unpaired *t*-test ($P < 0.001$, uncorrected) in the SPM8 software and plotted on surface maps with the Surf Ice software (http://www.nitrc.org/projects/surfice/). A large cluster comprising all areas shown in the graphic survived correction for multiple comparisons (pFWE and pFDR < 0.05). Bars in the lower-left indicate *z* scores, ranging from $P = 10^{-3}$ (Z-score = 3.0) to $P = 10^{-10}$ (*z* score = 10.0). Images on the right: Scatter Plot graphical representation showing the dispersion of the PIB uptake in the large cluster obtained in the group analysis shown in the left (mean radioactive counts). Dots highlighted in color represent the three individual exceptions classified as CBS FDG-nonAD with positive PIB-PET in the visual classification. [Color figure can be viewed at wileyonlinelibrary.com]

affection of the parietal-dorsal stream in CBS-AD than in other underlying pathologies, identifying lower scores in visuoperceptual tests.[15,44] Besides, visual neglect, which also reflects parietal-dorsal disturbance, has been considered a potential clue for AD pathology.[8,12,15,17] CBS FDG-AD group also presented myoclonus more often than CBS FDG-nonAD, mirroring previous neuropathology,[11,12] CSF,[45] and PIB-PET studies.[15]

Interestingly, hallucinations were more frequent in the CBS FDG-AD group, a finding only described by one clinicopathologic study.[12] Hence, our observation sheds light on this unusually mentioned aspect. Further studies are necessary to investigate this topic and its pathophysiological basis.

Noteworthy, our combined findings of memory impairment, myoclonus, and hallucinations related to CBS FDG-AD group and dystonia referring to the non-AD metabolic group is congruent with one of the most extensive clinicopathologic series of CBS,[12] strengthening the concept of FDG-PET as a possible surrogate of CBS pathological substrate antemortem.

In our cohort, we found no specific language impairment based on metabolic patterns or amyloid deposition. Previous works, however, have associated logopenic-like aphasia to CBS-AD[45] and nonfluent language disturbance to CBS-CBD.[6] Conversely, dysarthria was significantly more common in the CBS FDG-nonAD group, and we hypothesize that it may correspond to a frontal motor articulatory deficit related to tauopathies. Indeed, motor perseveration, another frontal sign suggestive of PSP, was also more frequent in the CBS FDG-nonAD group.

Ocular motor dysfunction was significantly more present in the CBS FDG-nonAD group. Prior video-oculographic observations showed reduced peak velocities of vertical pro-saccades in CBS patients without CSF biomarkers for AD.[46] Besides, vertical supranuclear palsy or slowness of vertical saccades, associated with CBS phenotype, are required to fulfill the MDS probable 4R-tauopathy criteria.[36] Notably, the criteria demonstrated to be significantly related to the CBS FDG-nonAD group, but present in 33% of these patients, highlighting its low sensitivity, as recently reported in a validation study.[47]

Nonetheless, the same MDS criteria were unable to separate CBS-A+ and CBS-A− individuals, as one patient with positive PIB-PET fulfilled them. Worth mentioning that this single patient was blindly classified as CBS FDG-nonAD, raising the question if the primary pathology could be indeed a tauopathy with associated amyloid deposition. Further studies are needed to investigate these novel criteria accuracy to identify 4R-tauopathies and its relation to AD biomarkers.

A recent study demonstrated that CBS-AD was a biomarker-defined group with distinct clinical features apart from CBS-4R tauopathy.[48] Our findings are consistent with these observations, and the 4R-tauopathies criteria might aid in diagnostic reasoning and clinical trial purposes.

The main limitation of our study was the lack of histopathological data. In its absence, three amyloid-positive patients classified in the CBS FDG-nonAD group could not be properly investigated. It should be noted that these individuals had a lower PIB uptake than amyloid-positive patients with an AD pattern on FDG-PET. The possibilities of misclassification or comorbid pathologies (which we find more plausible) should be considered. Almost 30% of the elderly with normal cognition can present positive amyloid imaging.[41] Meanwhile, the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework[49] classifies any individual with cortical amyloid deposition as pertaining to the "AD continuum." We should consider these cases as possible dual pathology, and the lower level of amyloid deposition could represent early-stage AD.

In vivo biomarkers for tau pathology could provide valuable information in these cases.[16,50] Therefore, the absence of tau biomarkers represents another limitation of our study. Although tau-PET might become the ideal strategy to assess underlying pathology in CBS, its use in clinical practice is still limited, being mostly restricted to the research context.

Finally, we presented a prospective study with comprehensive neurological assessment and molecular imaging biomarkers in a large cohort of CBS patients. The approach of performing a blind clinical evaluation and splitting them based on metabolic patterns unfolded two well-differentiated variants, with similar demographic features but different cognitive performance, favoring the hypothesis that they were not necessarily in different stages of disease, but rather had different diseases and the same syndrome, one (CBS-AD) with more severe cognitive impairment, and another (CBS non-AD) with prominent motor features, mostly equivalent to prior observations from clinicopathological cohorts. The individual FDG-PET classification also demonstrated high inter-observer agreement, PPV, and accuracy to predict amyloid deposition. If the findings of the CBS FDG-AD group should be translated into a worse prognosis is yet to be defined, and longitudinal clinical analysis of the present sample is warranted.

Hence, our results strongly suggest that FDG-PET patterns can distinguish AD from non-AD CBS variants antemortem. Our data, therefore, may yield the concept that FDG-PET might be routinely used in the clinical workup of CBS. Future consensus criteria regarding diagnosis across the CBS spectrum would benefit from incorporating this biomarker as an ancillary tool in association with clinical features. ●

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Appendix E – Research article published in Frontiers in Neurology.

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ORIGINAL RESEARCH
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Metabolic and Structural Signatures of Speech and Language Impairment in Corticobasal Syndrome: A Multimodal PET/MRI Study

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Introduction: Corticobasal syndrome (CBS) is a progressive neurological disorder related to multiple underlying pathologies, including four-repeat tauopathies, such as corticobasal degeneration and progressive supranuclear palsy, and Alzheimer's disease (AD). Speech and language are commonly impaired, encompassing a broad spectrum of deficits. We aimed to investigate CBS speech and language impairment patterns in light of a multimodal imaging approach.

Materials and Methods: Thirty-one patients with probable CBS were prospectively evaluated concerning their speech–language, cognitive, and motor profiles. They underwent positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG-PET) and [^{11}C]Pittsburgh Compound-B (PiB-PET) on a hybrid PET-MRI machine to assess their amyloid status. PiB-PET images were classified based on visual and semi-quantitative analyses. Quantitative group analyses were performed on FDG-PET data, and atrophy patterns on MRI were investigated using voxel-based morphometry (VBM). Thirty healthy participants were recruited as imaging controls.

Results: Aphasia was the second most prominent cognitive impairment, presented in 67.7% of the cases, following apraxia (96.8%). We identified a wide linguistic profile, ranging from nonfluent variant-primary progressive aphasia to lexical–semantic deficits, mostly with impaired verbal fluency. PiB-PET was classified as negative (CBS-A– group) in 18/31 (58%) and positive (CBS-A+ group) in 13/31 (42%) patients. The frequency of dysarthria was significantly higher in the CBS-A– group than in the CBS-A+ group (55.6 vs. 7.7%, $p = 0.008$). CBS patients with dysarthria had a left-sided hypometabolism at frontal regions, with a major cluster at the left inferior frontal gyrus and premotor cortex. They showed brain atrophy mainly at the opercular frontal gyrus and putamen. There was a positive correlation between [^{18}F]FDG uptake and semantic verbal fluency

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at the left inferior ($p = 0.006$, $R^2 = 0.2326$), middle (0.0054, $R^2 = 0.2376$), and superior temporal gyri ($p = 0.0066$, $R^2 = 0.2276$). Relative to the phonemic verbal fluency, we found a positive correlation at the left frontal opercular gyrus ($p = 0.0003$, $R^2 = 0.3685$), the inferior ($p = 0.0004$, $R^2 = 0.3537$), and the middle temporal gyri ($p = 0.0001$, $R^2 = 0.3993$).

Discussion: In the spectrum of language impairment profile, dysarthria might be helpful to distinguish CBS patients not related to AD. Metabolic and structural signatures depicted from this feature provide further insights into the motor speech production network and are also helpful to differentiate CBS variants.

Keywords: corticobasal syndrome, frontotemporal lobar degeneration, nonfluent primary progressive aphasia, positron emission tomography, amyloid-PET, fluorodeoxyglucose F18, corticobasal degeneration

INTRODUCTION

Corticobasal syndrome (CBS) is a rare progressive neurological disorder distinguished by asymmetric motor features and higher cortical dysfunction associated with general cognitive impairment (1). Initially described as a clinicopathological entity (2), it is now considered a clinical phenotype related to multiple underlying pathologies (3). The majority of cases are due to four-repeat (4R) tauopathies (4), mainly corticobasal degeneration (CBD) (5), followed by progressive supranuclear palsy (PSP) (6, 7). Also, possible underlying pathologies include Alzheimer's disease (AD) (8, 9) and frontotemporal lobar degeneration with transactivation response (TAR) DNA binding protein 43 kDa (TDP-43) inclusions (7), among others (10–12).

Besides motor symptoms, cognitive and behavioral disturbances are common and often recognized as the first presentation in CBS (13, 14). Additionally, prominent language dysfunction is usually present from the early stages or during the disease course (1, 15, 16) and incorporated into previous diagnostic criteria (17).

Previous studies assessing the broad spectrum of speech and language in CBS patients have reported a phenotype similar to the nonfluent variant of primary progressive aphasia (nfv-PPA) and the primary progressive apraxia of speech (PPAOS) (18). Individuals may fulfill the criteria for nfv-PPA (19) or PPAOS (20) and only, later on, fit into probable CBS criteria (21, 22). Moreover, other studies described a wide variety of language deficits: Broca's aphasia, anomic aphasia, and fluent aphasia (23).

Recently, studies using imaging biomarkers such as structural magnetic resonance (MRI) (24), [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (FDG-PET) (25), and amyloid-PET (26) identified neural correlates from different aspects of language in CBS. Nevertheless, language impairment's profile in CBS and its relation to specific pathologies are still poorly understood.

This study aimed to investigate language and motor speech impairment in CBS patients in light of a multimodal imaging approach. Our main purpose was to compare speech–language deficits in CBS patients related to the presence or absence of brain amyloid deposition on amyloid-PET, a surrogate for underlying AD pathology. We also intended to explore metabolic and structural signatures related to these speech–language profiles.

MATERIALS AND METHODS

Participants

Thirty-one patients meeting the probable CBS (1) criteria were prospectively recruited at the movement disorders and cognitive neurology clinics at Hospital das Clínicas, University of São Paulo School of Medicine (São Paulo, Brazil), between February 2017 and December 2019. First, they were classified by assistant doctors (all board-certified neurologists) at both clinics as having probable CBS. Later, all individuals were further evaluated regarding their clinical profile to perform the study protocol by two neurologists (JBP and SMDB) with board certification in both movement disorders and cognitive neurology. All patients showed a progressive disease course with a duration of at least 1.5 years. They also presented an asymmetric combination of at least two out of three motor features, including akinetic-rigid parkinsonism, dystonia, and myoclonic movements, as well as two out of three higher cortical features, including limb or orobuccal apraxia, alien limb phenomena, and cortical sensory deficit (1). Then, alternative diagnoses among neurodegenerative diseases could be excluded, such as Creutzfeldt-Jakob disease, other atypical parkinsonian syndromes, Parkinson's disease, typical AD, and others.

Exclusion criteria included relevant non-degenerative brain lesions such as stroke sequelae, tumors, hydrocephalus, and remarkable premorbid psychiatric disease. All participants or their caregivers provided written informed consent for the study. The ethical committee of our institution approved the investigation procedure and informed consent under protocol number 2.046.113.

We also included 30 cognitively healthy participants (NC group) from the community as imaging controls after neuropsychological and neurological evaluations. They were all participants of another prospective research of our group (under protocol number 62047616.0.0000.0068). They matched the CBS patients by age (median age 67.0, interquartile range [IQR] 62.25–70.0) and scanner type. Data concerning demography

and neuropsychological evaluation obtained from the healthy controls are available in **Supplementary Table 1.1**.

Clinical Assessment

All patients received a standardized predefined clinical evaluation. Global cognitive impairment was assessed with Addenbrooke's Cognitive Examination-Revised (ACER) (27–29) and the Mini-Mental State Examination (MMSE) (30), both previously validated in Brazilian cohorts. Episodic memory was investigated with the Brief Cognitive Screening Battery (BCSB) (31), a test used to assess individuals with different educational backgrounds and attention or working memory with the backward digit span. Functional decline was assessed with the Clinical Dementia Rating scale (32) and Functional Activities Questionnaire (33).

Higher cortical functions were clinically evaluated by the presence of limb or orobuccal apraxia, cortical sensory deficits, alien limb phenomena, and Balint and Gerstmann syndromes. We characterized the presence of limb apraxia by imitation of meaningful and meaningless gestures and with imaginary tool use and orobuccal apraxia by meaningless orobuccal gestures (34).

A detailed examination of the motor signs was performed through a neurological examination that characterized the presence of parkinsonism, dystonia, and myoclonus. The motor impairment was also categorized by the Hoehn and Yahr scale (35).

The neurologists also questioned the participants and caregivers about their first symptoms and, together with major signs at first examination, designated the predominant clinical initial phenotype as mainly cognitive, motor, or language impairment. The extended motor and cognitive clinical assessment were described in a previous publication (36).

Speech and Language Assessment

A comprehensive speech and language evaluation was performed by two speech–language pathologists (IJA and MLS), including the Western Aphasia Battery-revised (WAB-R) (37), the American Speech–Language–Hearing Association Functional Assessment of Communication Skills (ASHA-FACS) (38), and verbal fluency tests. From the WAB-R, the following subtests were utilized: spontaneous speech, verbal comprehension, repetition, naming, and word finding. The aphasia quotient (AQ), a measure of aphasia severity, was derived from those tests. ASHA-FACS is a scale that measures functional communication. It evaluates the level of assistance that the patient needs to communicate effectively.

We also evaluated the presence of apraxia of speech (AOS), agrammatism, and dysarthria. AOS was evaluated based on all the speech productions and complemented by the following tasks: oral diadochokinesis, repetition of polysyllables, multiple repetitions of the same polysyllable, repetition of words that increase in length by suffix and prefix derivation, repetition of dissyllables, and dissociation between voluntary and automatic production. The presence of agrammatism was judged based on all oral productions and, when available, written productions.

Dysarthria was characterized as present or absent considering the different manifestations in the motor speech bases (i.e., breathing, phonation, articulation, resonance, and prosody), through the evaluation of reflexes (coughing and swallowing), saliva control, breathing, tonus, and mobility of phonoarticulatory structures (tongue, lips, jaw, palatine veil, and larynx), and speech intelligibility.

To characterize the presence of aphasia, we compared the AQ score of each CBS patient to the median value of the AQ of other 24 healthy control subjects with the same age and education level. If these data were not available, we categorized aphasia based on the language score at ACE-R with a cutoff obtained from a previous Brazilian study, based on age and formal education (29).

For the semantic fluency task, participants were asked to name as many animals as possible in 1 min. Participants named words beginning specifically with the letter P for the phonemic fluency task, which was assessed using the ACE-R. Based on a previous survey of a Brazilian sample, we determined cutoff scores of 9 for semantic fluency for illiterates or individuals with <8 years of formal education and 13 for persons with more than 8 years of formal education (39). We determined cutoff scores of 13 for phonemic fluency for illiterates or individuals with <8 years of education and 15 for persons with more than 8 years of education (40).

Neuroimaging Data Acquisition

Both [^{11}C]Pittsburgh Compound-B (PIB) and [^{18}F]FDG were produced in an on-site cyclotron (PET trace 880, GE Healthcare) at the Nuclear Medicine Center of the Institute of Radiology (CMN InRad, São Paulo, SP, Brazil) of our hospital. PIB-PET and MRI images were simultaneously acquired on a hybrid 3.0-T SIGNA PET/MRI scanner (GE Healthcare, Milwaukee, WI). The MRI protocol included volumetric sequences weighted on T1, T2, and T2/FLAIR (fluid attenuation inversion recovery) sequences, as well as diffusion-weighted imaging (DWI) in 6 and 33 directions, and susceptibility-weighted imaging (SWI). All images were visually inspected for the detection of structural lesions of the brain, skull, and head and neck lesions, as well as for the assessment of imaging artifacts that could impair imaging processing. Complete parameters of the MRI sequences are detailed as follows: T1-weighted (spoiled gradient recalled, SPGR), TR = 8 ms, TE = 3 ms, FOV (cm) = 25.6, slice thickness = isometric voxels of 1.0 × 1.0 × 1.0 mm, frequency = 256, phase = 256, NEX = 1, scan time = 5 min 16 s, [TI] = 600 ms, flip angle [FA] = 8, r, 196 sagittal slices; T2-weighted (CUBE technique), TR = 2,500 ms, TE = 88 ms, FOV (cm) = 25,6, slice thickness = isometric voxels of 1.0 × 1.0 × 1.0 mm, frequency = 256, phase = 256, NEX = 1, scan time (min) = 3 min 43 s, [TI] = 600 ms, flip angle [FA] = 90, r, 196 sagittal slices; FLAIR, TR = 6,500 ms, TE = 141 ms, FOV (cm) = 25.6, slice thickness (mm) = isometric voxels of 1.3 × 1.3 × 1.3 mm, frequency = 192, phase = 192, NEX = 1, scan time (min) = 4 min 4 s, [TI] = 1,905 ms, flip angle [FA] = 90, r, 152 sagittal slices; DTI 33 dir and DTI 6 dir, TR (ms) = 1,300 ms, TE (ms) = 73.9, FOV (cm) = 25.6, slice thickness (mm) = 2.2 × 2.2 × 2.2 mm, frequency = 116, phase = 116, NEX = 1, scan time (min) = 9 min 32 s and 2 min 36 s, [TI] = 1,905 ms, flip angle

[FA] = 90, r, 152 sagittal slices *b*-value 1,000, 33 directions; T2 images, 10 and 6 directions, no of T2 images = 5; Ax SWAN QSM, TR (ms) = minimum, TE = 29 ms, FOV (cm) = 24, slice thickness (mm) = 2, frequency = 480, phase = 480, NEX = 1, scan time (min) = 13 min 37 s, [TI] = 1,905 ms, flip angle [FA] = 90, r, 152 sagittal slices.

FDG-PET was acquired in a Discovery 710 PET/CT scanner (GE Healthcare, Milwaukee, WI). The radiotracer [^{18}F]FDG was injected intravenously in bolus with a mean activity of 5–6 mCi. Before the radiopharmaceutical injection of FDG, the subjects fasted for at least 6 h, and their blood glucose level was <180 mg/dl. The time interval between injection and scan start was at least 30 min, and scan duration was 15 min. Each PET scan was corrected for attenuation with CT data. Images were reconstructed using an ordered subset expectation maximization (OSEM) algorithm.

The production of the radiopharmaceutical compound PIB was entirely carried out in the cyclotron of our center and previously validated in our environment (41). The images of cortical amyloid deposition were analyzed in the acquisition time of 30 min, obtained in rest conditions, between 40 and 70 min after intravenous administration of 10–15 mCi of the radiopharmaceutical.

The FDG-PET was performed within 1 month after clinical examination, and the time between FDG and PIB-PET/MRI varied from 2 days to 6 months.

[^{11}C]PIB-PET Visual Classification

Two nuclear medicine physicians performed a visual evaluation of the PIB-PET images assisted by a 3D-SSP semi-quantitative software (Cortex ID Suite, GE healthcare). Participants were rated as "CBS-A+" or "CBS-A–" if they were positive or negative, respectively, for the presence of cortical amyloid deposition, according to previously established criteria (42). A previous study from our group observed a high interrater agreement and similar amyloid positivity rates from the literature (43).

Quantitative [^{18}F]FDG-PET Analysis

Quantitative FDG-PET group analyses were performed to investigate (1) which brain areas were more consistently hypometabolic in CBS patients compared to healthy controls; (2) which were the most consistently hypometabolic areas in CBS patients concerning the difference in language performance; and (3) which brain areas were correlated to the scores on phonemic and semantic verbal fluency tests.

PET images were co-registered with their respective MRI images (volumetric T1 sequence) and spatially normalized using the Statistical Parametric Mapping 8 (SPM8) software (Wellcome Department of Cognitive Neurology, Functional Imaging Laboratory, London, UK) into an anatomic template (44). To perform the first investigation mentioned above, we flipped the images to represent the hemisphere contralateral to the most affected limbs on the right side of the image because of CBS's asymmetric nature. The second and third analyses were performed within the images in their original lateralization to evaluate aspects of language hemisphere dominance.

The spatial normalization of FDG-PET scans was performed using a dementia-optimized brain FDG-PET template (44). Scans were smoothed with an 8-mm full width at half maximum Gaussian kernel to reduce misregistration into the template space and improve the signal-to-noise ratio. A default threshold of 0.8 of the mean uptake inside the brain was selected to ensure that the analysis included only voxels mapping cerebral tissue. Global uptake differences were adjusted using the "proportional scaling" SPM8 option.

For the group analyses, statistical parametric maps were generated with SPM8 threshold at the voxel level at p uncorrected (punc) = 0.001, with a minimum extension of 100 voxels in the cluster. Statistical results were considered valid when they survived correction for multiple comparisons with the familywise error (FWE) or false discovery rate (FDR) methods (pFWE/FDR $\leq$ 0.05). Relevant peak voxels from the statistical parametric maps were identified in the Montreal Neurologic Institute (MNI) coordinate system.

The numeric values representing the mean [^{18}F]FDG uptake for each individual (a proxy for regional brain glucose metabolism, rBGM) in the clusters with statistically significant results in the SPM group analyses) were obtained with the toolbox MarsBar for SPM (http://marsbar.sourceforge.net/) and later investigated using GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA, USA).

Voxel-Based Morphometry Analysis

We performed quantitative voxel-based MRI group analyses to investigate (1) brain atrophy patterns in CBS patients compared to healthy controls and (2) brain atrophy patterns in CBS patients in relation to the difference in language performance compared to healthy controls.

Like in the FDG-PET quantitative analysis, we flipped the images to represent the hemisphere contralateral to the most affected limbs on the right side in the first step of the investigation. The second analysis was performed within the images in their original lateralization to evaluate language hemisphere dominance aspects.

MRI T1-weighted volumetric images were processed using VBM on SPM8 using the SPM toolbox *Diffeomorphic Anatomical Registration using Exponentiated Lie algebra* (DARTEL) algorithm. This algorithm segmented MRI images into liquor, gray matter, and white matter.

Study Design

First, the patients were prospectively selected and clinically assessed (sections Participants, Clinical Assessment, and Speech and Language Assessment). They underwent FDG-PET, MRI, and PIB-PET and were classified as CBS-A– and CBS-A+, according to the PIB-PET status (described in section [^{11}1C]PIB-PET visual classification). After this initial distribution, both groups were compared concerning the clinical evaluation and speech and language assessment, aiming to possibly delineate the different clinical variants based on the presence of cortical amyloid deposition. Later, we performed quantitative group analyses to compare brain metabolic patterns and brain atrophy patterns between the whole CBS group and healthy controls

and between CBS patients concerning differences in language performances and healthy controls.

Statistical Analysis of Clinical Data

Demographic, clinical, and language data analysis was conducted in R (https://www.r-project.org/). Categorical variables were expressed as absolute and relative frequencies and compared with Pearson's chi-square (or Fisher's exact test, as appropriate). Continuous variables were compared using the Mann–Whitney test after failing to satisfy normality through visual inspection of their distribution. Data were expressed as median [IQR] or as number [frequency]. All tests were two-sided. Statistical significance was set as $p < 0.05$.

RESULTS

Demography and Clinical Features

Thirty-one CBS patients were included and underwent a comprehensive clinical evaluation. Demographic data are shown in **Table 1**. Eighteen patients presented initially with a cognitive clinical phenotype (58.1%), followed by 10 patients with motor (32.3%) and 3 (9.7%) with a predominant language profile (**Table 1**). These three patients possibly could have shown an nfv-PPA phenotype, based on chart review or patient report, and then evolved into probable CBS before enrollment in the study.

The motor features included asymmetric akinetic-rigid parkinsonism in all cases (100%). Dystonia was present in 10 (32.3%) and myoclonus in 21 (67.7%) patients. Limb apraxia was the most frequent cognitive sign, demonstrated in 30 (96.8%) patients. Buccolingual apraxia was less common, found in only five (16.1%). Cortical sensory deficits and alien limb phenomena were both present in eight (25.8%) cases. Two patients (6.45%) had Balint and Gerstmann syndromes (**Figure 1** and **Table 2**).

Concerning speech and language features, 21 patients (67.7%) had aphasia according to standard deviations of the AQ at WAB-R test or normative values on language subtest at ACE-R (**Figure 1** and **Table 2**). Most measures obtained from WAB-R showed impairment in naming, sentence comprehension, and spontaneous speech (**Table 1**). Phonemic and semantic verbal fluency tests were below the normative values in 29 (93.5%) and 26 (84%) patients of the whole sample, respectively. Dysarthria was detected in 11 (35.5%) and AOS in 7 (19.4%). Two patients (6.45%) presented agrammatism (**Figure 1** and **Table 2**).

Language, Cognitive, and Motor Features According to Amyloid-PET Status

PIB-PET was classified as negative (CBS-A–) in 18/31 (58%) and positive in 13/31 (42%) patients after visual and semi-quantitative classification of amyloid deposition. Demographic variables did not differ between CBS-A– and CBS-A+ groups (**Table 1**).

The CBS-A+ group performed significantly worse on cognitive assessment through MMSE and some ACE-R subscores (attention, memory, and visuospatial) but did not differ in total ACE-R score (**Table 1**). CBS-A+ patients had worse BCSB delayed recall performance, although it did not reach statistical significance (**Table 1**). There were no significant differences in higher cortical or motor symptoms or signs between groups (**Figure 1** and **Table 2**).

Concerning motor speech and language deficits, patients with negative amyloid deposition on PIB-PET displayed dysarthria significantly more often than did the CBS-A+ group (10/18, 55.6% vs. 1/13, 7.7%, $p = 0.008$, Fisher's exact) (**Figure 1** and **Table 2**). The main characteristics were mixed hypokinetic and spastic dysarthria. There were no statistically significant differences in the frequency of aphasia ($p = 0.452$, Fisher's exact) (**Table 2**) and scores in the functional language assessment at ASHA-FACS between CBS-A- and CBS-A+ groups ($p = 0.961$, Mann–Whitney) (**Table 1**). Only patients classified as CBS-A– showed agrammatism (two patients). Also, CBS-A– patients had AOS more often than did CBS-A+ patients, although not statistically significant ($p = 0.35$). All patients with a predominant language phenotype had negative amyloid-PET status (**Table 1**).

Interestingly, CBS-A– patients appeared to show more compromised phonemic verbal fluency (17/18, 94.4%) than semantic fluency (13/18, 72%), although this did not reach statistical significance ($p = 0.177$, Fisher's exact). Conversely, all patients (13/13, 100%) of the CBS-A+ group showed impaired semantic verbal fluency, and phonemic verbal fluency was impaired in 92.3% (12/13) of patients.

Metabolic Patterns on FDG-PET

Compared to healthy controls, group analysis on SPM from the whole cohort showed an extended pattern of rBGM reduction at frontoparietal areas, striatum, and thalamus, mostly contralateral to the affected body side (**Figure 2A**).

Patients with dysarthria were characterized by a predominant left-side hypometabolic pattern (**Figure 2B**), and more prominent rBGM reduction surviving correction for multiple comparisons at the cluster level at frontal regions, with a significant cluster at the left inferior frontal gyrus (opercular area) and left premotor cortex (**Figure 2B**), with additional features typical of CBS (inferior parietal cortex and striatum).

Conversely, patients without dysarthria showed bilateral rBGM reduction, with major clusters at the posterior cingulate, dorsolateral prefrontal cortex, posterior temporoparietal areas, striatum, and thalamus and no hemisphere predominance. See **Figure 2** for details. Peak voxels of rBGM are shown in **Supplementary Tables 1.1–1.3**.

Additionally, we investigated which brain regions on FDG-PET correlated with semantic and phonemic verbal fluency task performance. There was a positive correlation between rBGM and semantic verbal fluency at the left inferior ($p = 0.006$, $R^2 = 0.2326$), middle ($p = 0.0054$, $R^2 = 0.2376$), and superior temporal gyri ($p = 0.0066$, $R^2 = 0.2276$) (**Figure 3**). Relative to the phonemic verbal fluency, we found a positive correlation between [^{18}F]FDG uptake and letter P fluency at the left frontal opercular gyrus ($p = 0.0003$, $R^2 = 0.3685$) and the inferior ($p = 0.0004$, $R^2 = 0.3537$) and middle temporal gyri ($p = 0.0001$, $R^2 = 0.3993$) (**Figure 3**).

TABLE 1 | Demography, functional, cognitive, and language assessment of patients with CBS and comparison by amyloid-PET results.

	CBS ($n = 31$)	CBS-A– ($n = 18$)	CBS-A+ ($n = 13$)	p-value
Demography				
Age at symptom onset, years	61 (58–67)	60 (55–68)	63 (60–66)	ns
Age at main assessment, years	65 (61–71)	63.5 (59–71)	66 (64–71)	ns
Symptom duration at main assessment, years	4.0 (3.0–4.5)	3.5 (2.2–4.7)	4.0 (3.0–4.0)	ns
Gender (female)	14 (45.2%)	7 (38.9%)	7 (53.8%)	ns
Education, years	10 (6–15)	9.5 (6–15)	10 (6–15)	ns
Side of more severely involved limbs (right)	13 (41.9)	8 (44.4%)	5 (38.5%)	ns
Handedness (right-handed)	26 (83.9%)	16 (88.9%)	10 (76.9%)	ns
Phenotype				
Cognitive	18 (58.1%)	8 (44.4%)	10 (76.9%)	
Motor	10 (32.3%)	7 (38.9%)	3 (23.1%)	
Language	3 (9.7%)	3 (16.7%)	0 (0.0%)	ns
Functional assessment				
Clinical Dementia Rating	2.0 (1.5–2.0)	2.0 (0.6–2.0)	2.0 (1.0–2.0)	ns
Functional activities questionnaire	22 (14–26)	18.5 (11–25)	25 (16–27)	ns
Hoehn and Yahr scale	2 (2–3.5)	3.00 (2–3.75)	2.00 (2–3)	ns
ASHA-FACS scale	3.2 (1.8–5.3)	3.2 (2.4–5.0)	3.0 (1.6–5.0)	ns
General cognitive assessment				
ACE-R total	41 (30–62)	49 (31.5–74.5)	34 (27.5–46.5)	ns
ACE-R attention	11 (9–13.75)	12.5 (11–16.25)	9 (8–10.5)	0.008
ACE-R memory	8 (5.25–15.75)	12.5 (7.75–18.25)	5 (2.25–8)	0.008
ACE-R fluency	2.5 (1–6)	3 (2–6.25)	1.5 (1–4.5)	ns
ACE-R language	16.5 (14–24.5)	19 (14.25–25)	14.5 (14–20.75)	ns
ACE-R visuospatial	7 (4–8.75)	8 (7–11.25)	4 (3.25–5.75)	0.001
MMSE	18 (13–21.50)	20.5 (16.5–25.75)	14 (11–17)	0.005
Digits backward	2 (0–3.75)	3 (2–3)	0 (0–4)	ns
Delayed recall (BCSB)	3 (0.5–6)	5.50 (1.75–6)	1 (0–3)	ns
Language assessment				
Aphasia quotient (WAB-R)	68.8 (51.1–88.2)	70.35 (38.7–83.3)	68.8 (63.7–90.2)	ns
Total spontaneous speech (WAB-R)	16.0 (9.5–17.5)	17.0 (10.0–18.0)	14.5 (10.0–16.75)	ns
Auditory word recognition (WAB-R)	54.0 (19.0–57.5)	57.0 (48.0–60.0)	50.0 (25.0–55.0)	ns
Sequential commands (WAB-R)	63.0 (25.0–80.0)	63.0 (28.0–80.0)	48.0 (15.2–73.2)	ns
Total repetition (WAB-R)	8.6 (3.3–9.1)	8.6 (3.8–9.2)	7.6 (3.0–8.9)	ns
Naming and word finding (WAB-R)	6.2 (3.25–8.45)	7.1 (3.3–8.5)	5.4 (2.5–7.1)	ns
Phonemic fluency (letter P)	3 (1.75–6)	3 (2–6.25)	2.5 (1–5.25)	ns
Semantic fluency (animals)	5.5 (3.75–10)	6.5 (3–11.75)	5 (4–7)	ns

Clinical data comparison between CBS-A+ and CBS-A–. Data expressed as median (IQR) or number (frequency). Statistical significance was set as $p < 0.05$ (Mann–Whitney or Fischer's exact test). ns, nonsignificant; AD, Alzheimer's disease; CBS, corticobasal syndrome; MMSE, Mini-mental State Examination; ACE-R, Addenbrooke Cognitive Examination-Revised; BCSB, Brief Cognitive Screening Battery; ASHA-FACS, Functional assessment of Communication Skills for Adults.

Brain Atrophy Patterns on VBM

Compared to healthy controls, the whole CBS cohort showed a widespread brain atrophy pattern with major clusters at the bilateral striatum, supplementary motor area (SMA), posterior cingulate cortex, and posterior temporoparietal areas mostly contralateral to the affected body side (**Figure 2D**).

In CBS patients with dysarthria, a major cluster of brain atrophy was found predominantly in the right inferior frontal gyrus and putamen, with other significant areas such as the left SMA, premotor cortex, and putamen (**Figure 2E**), whereas patients without dysarthria showed gray matter loss at posterior temporal and inferior parietal areas (**Figure 2F**). There was, however, no evident predominant left-side brain atrophy in patients with dysarthria. Peak voxels of VBM contrasts are shown in **Supplementary Tables 1.5, 1.6**.

DISCUSSION

This prospective cross-sectional study described speech and language profiles in a cohort of 31 CBS patients assessed with a specific ligand for brain amyloid deposition. Our goal was to distinguish language and motor speech deficits related to amyloid-positive and amyloid-negative CBS patients and explore its brain metabolic and structural signatures through a multimodal imaging approach.

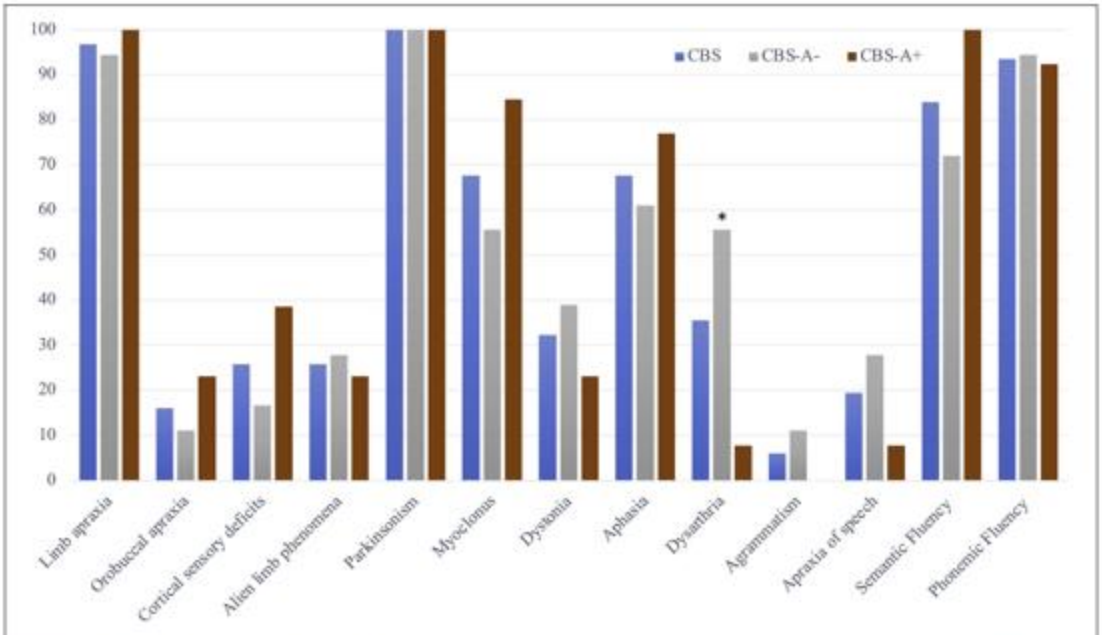

FIGURE 1 | Motor, cortical, and language deficits in the whole CBS cohort and according to subgroups with positive (CBS-A+) and negative (CBS-A–) amyloid-PET. Data are presented as the frequency of the symptoms or the percentage of altered verbal fluency tasks among the CBS sample and in the subgroups according to cortical amyloid deposition. The symbol * indicates statistically significant differences between CBS-A+ and CBS-A– groups. Dysarthria 10/18, 55.6% vs. 1/13, 7.7%, $p = 0.008$, Fisher's exact test.

TABLE 2 | Clinical symptoms and signs of patients with CBS and comparison by amyloid-PET results.

	CBS ($n = 31$)	CBS-A– ($n = 18$)	CBS-A+ ($n = 13$)	*p*-value
Cortical symptoms				
Limb apraxia	30 (96.8%)	17 (94.4%)	13 (100.0%)	ns
Orobuccal apraxia	5 (16.1%)	2 (11.1%)	3 (23.1%)	ns
Cortical sensory deficits	8 (25.8%)	3 (16.7%)	5 (38.5%)	ns
Alien limb phenomena	8 (25.8%)	5 (27.8%)	3 (23.1%)	ns
Motor symptoms				
Parkinsonism	31 (100.0%)	18 (100.0%)	13 (100.0%)	ns
Myoclonus	21 (67.7%)	10 (55.6%)	11 (84.6%)	ns
Dystonia	10 (32.3%)	7 (38.9%)	3 (23.1%)	ns
Language symptoms				
Aphasia	21 (67.7%)	11 (61.1%)	10 (76.9%)	ns
Dysarthria	11 (35.48%)	10 (55.6%)	1 (7.7%)	0.008
Agrammatism	2 (6.45%)	2 (11.1%)	0 (0.0%)	ns
Apraxia of speech	7 (22.6%)	5 (27.8%)	2 (15.4%)	ns
Abnormal semantic fluency	26 (83.9%)	13 (72.2%)	13 (100.0%)	ns
Abnormal phonemic fluency	29 (93.5%)	17 (94.4%)	12 (92.3%)	ns

Comparison between amyloid-PET positive (CBS-A+) and negative (CBS-A–). Data expressed as number (frequency). Statistical significance was set as $p < 0.05$ (Fischer's exact test).

As our main findings, CBS patients with negative amyloid-PET presented dysarthria significantly more often than did patients with positive amyloid deposition. Additionally, quantitative FDG-PET and MRI group analyses showed differential hypometabolic and brain atrophy patterns in patients with and without dysarthria compared to healthy

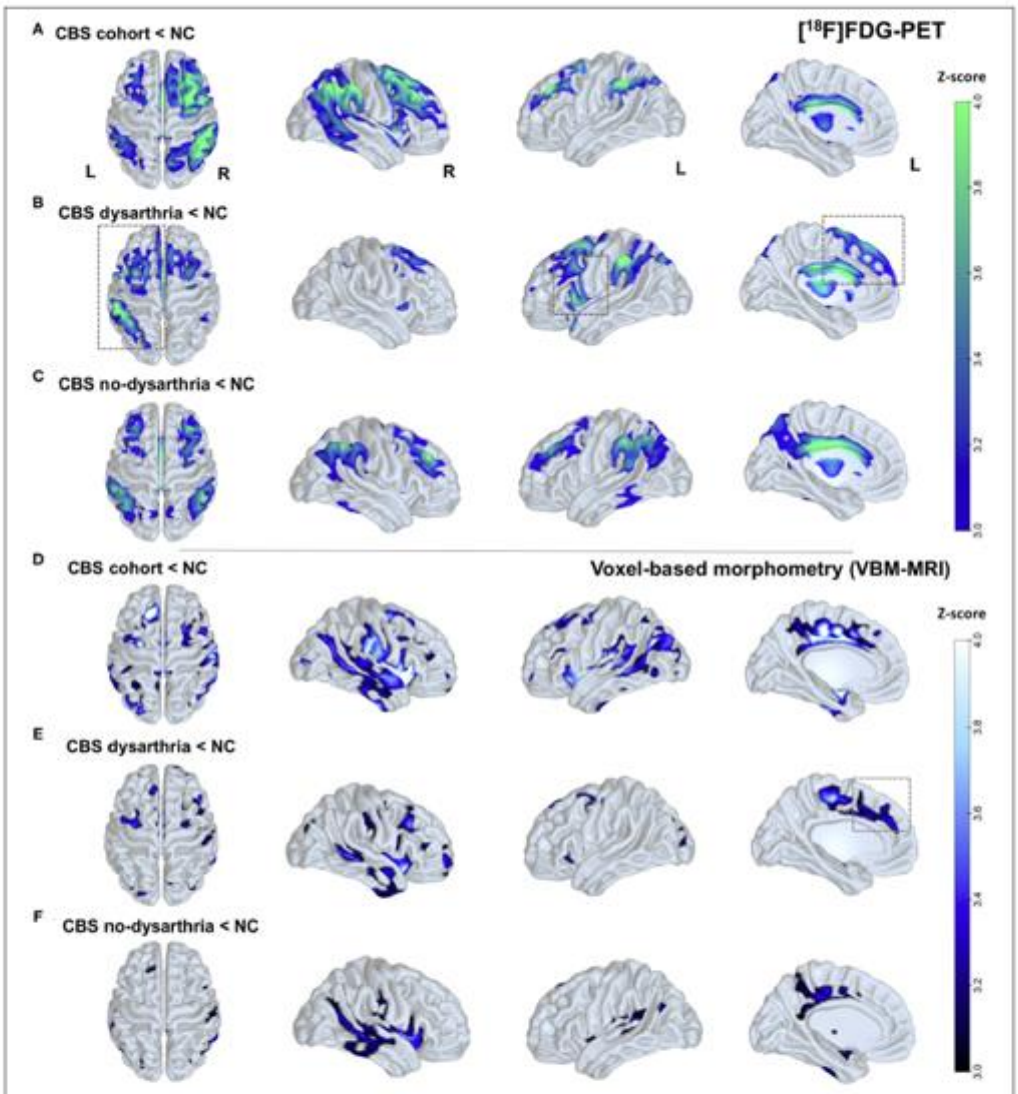

FIGURE 2 | Brain glucose metabolism and brain atrophy patterns in patients with CBS and according to the presence or absence of dysarthria. **(A)** Clusters with differences in rBGM in individuals with CBS compared to healthy controls (NC). Reduced [^{18}F]FDG uptake in the whole CBS cohort is consistently seen in the frontoparietal and temporal areas, striatum, and thalamus, mainly contralateral to the most affected side. **(B)** Clusters with differences in rBGM in CBS individuals presenting dysarthria. Reduced [^{18}F]FDG uptake surviving correction for multiple comparisons at the cluster level is predominant at left frontal regions, with a major cluster at the left inferior frontal gyrus (opercular area) and left premotor cortex. **(C)** Hypometabolism in CBS patients without dysarthria showing bilateral rBGM reduction, mainly at the temporoparietal areas, striatum, and thalamus, and without hemisphere predominance. **(D)** VBM analysis showing brain atrophy patterns in CBS patients compared to NC: widespread brain atrophy pattern with major clusters at the bilateral striatum, SMA, and posterior temporoparietal areas, mostly contralateral to the affected body side. **(E)** VBM showing brain atrophy patterns in CBS patients with dysarthria compared to NC: predominantly in the frontal areas and striatum. **(F)** VBM showing brain atrophy patterns in CBS patients without dysarthria compared to NC: posterior temporal and inferior parietal areas. Parametric maps were generated with an unpaired *t*-test ($p < 0.001$, uncorrected) in the SPM8 software and plotted on surface maps with the Surf Ice software—http://www.nitrc.org/projects/surfice/). Bars in the right side indicate *z* scores, ranging from $p = 10^{-3}$ (z-score = 3.0) to $p = 10^{-4}$ (z-score = 4.0).

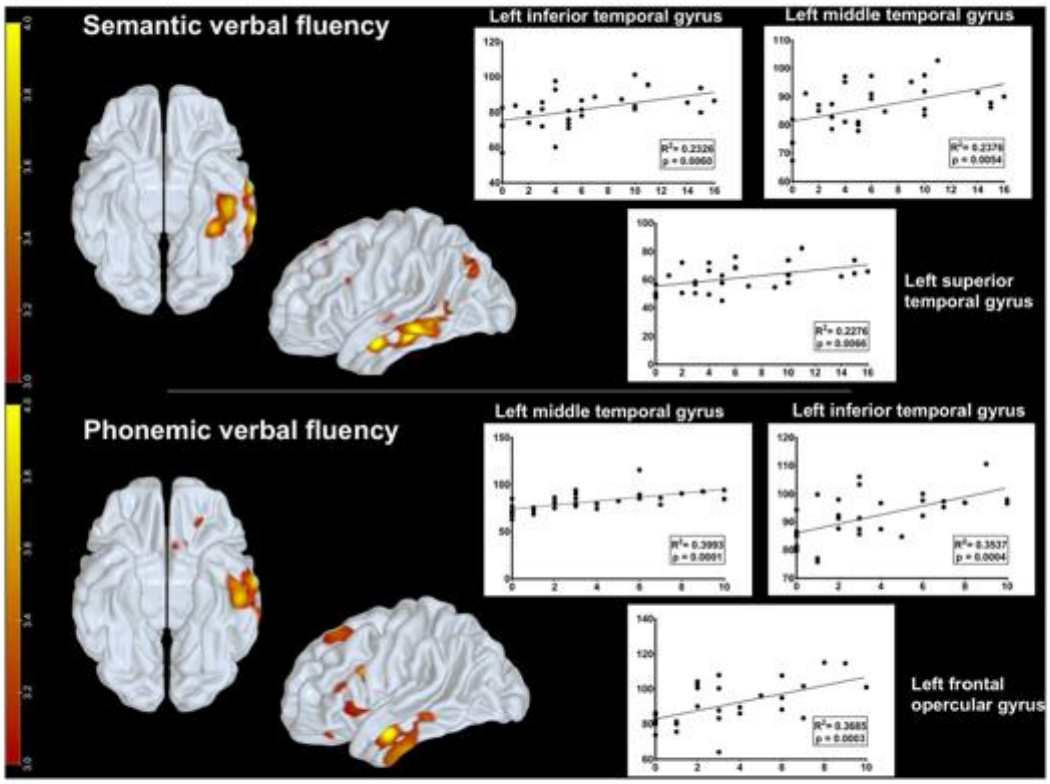

FIGURE 3 | Metabolic correlations between brain regions and verbal fluency tasks. Upper row: positive correlation between glucose uptake on FDG-PET and semantic verbal fluency at the left inferior, middle, and superior temporal gyri. Lower row: positive correlation between glucose uptake on FDG-PET and phonemic fluency at the left frontal opercular gyrus and the inferior and middle temporal gyri. Parametric maps were generated with an unpaired *t*-test (threshold: $p < 0.001$, uncorrected) in the SPM8 software and plotted on surface maps with the Surf Ice software http://www.nitrc.org/projects/surfice/). Bars in the left side indicate *z* scores, ranging from $p = 10^{-3}$ (*z*-score = 3.0) to $p = 10^{-4}$ (*z*-score = 4.0).

controls. Namely, CBS patients with dysarthria had a left-sided hypometabolism and bilateral brain atrophy pattern mainly at the opercular frontal region, premotor cortex, and SMA (see **Figures 2B,E**).

Motor speech production deficits such as dysarthria and AOS have been previously linked to CBS with underlying 4R tauopathy pathologies, such as CBD or PSP (9, 21, 22, 45). Dysarthria is considered a CBD and PSP frequent symptom from its first descriptions (2, 46) until their latest criteria (1, 47). Our results are in line with these previous studies. Furthermore, the regions with significant clusters of brain atrophy at MRI-based VBM in CBS patients with dysarthria were previously described to be anatomically involved in the motor speech production network (48). It is worth mentioning that AOS was also more commonly found in CBS-A– patients, although not achieving statistical significance.

In this cohort, aphasia was one of the most prominent cognitive impairments, present in 67.7% of the cases, second only to apraxia (96.8%). We identified a broad spectrum of the linguistic profile, ranging from the nfv-PPA phenotype to lexical-semantic deficits. The CBS-A+ group showed aphasia (77%) more often than did the CBS-A– group (61%) but without a statistically significant difference. Our data are congruent with a previous systematic literature review (1) and a recent clinicopathologic study (49) which demonstrated that aphasia occurred in more than 50% of CBS cases during the disease course.

Likewise, a prior retrospective study with a large cohort suggested that CBS consisted of a primarily language-motor disease with a predominant phenotype of mixed aphasia, thereby being the main cognitive feature (15). Our findings, along with these reports, strengthen the concept that language impairment, initially underscored in CBS, should be considered a cognitive hallmark of the disease.

In a previous study from our group with the same cohort, differences in rBGM in CBS patients were investigated according

to amyloid imaging status. A quantitative group analysis showed hypometabolism comprising the posterior temporoparietal areas, mainly contralateral to the most affected side, as the areas with the most consistent hypometabolism in amyloid-positive CBS patients. Amyloid-negative patients, conversely, showed more heterogeneous metabolic patterns and disclosed areas of rBGM reduction at the thalamus and SMA (36).

In this present study, patients with dysarthria showed clusters of rBGM reduction at frontal regions, mainly at the left opercular region, premotor cortex, and SMA, corroborating a previous finding that patients with nfv-PPA who later evolved into CBS shared a left-sided pattern involving the inferior frontal gyrus and the supplementary motor cortex (25). In this article, the authors provide further evidence that the topography of brain hypometabolism could reflect dysfunctional signatures of different language deficits. Although most patients with dysarthria in our cohort did not fulfill the criteria for nfv-PPA, they might pertain to the same language dysfunctional spectrum commonly found in the group with CBS with underlying 4R tauopathies.

It is acknowledged that the wide variety of aphasic syndromes in CBS probably derive from the diversity of underlying pathologies or is a function of the stage when the clinical assessment occurs (23). A logopenic-like aphasia phenotype, with poor sentence repetition, anomia, and word retrieval problems, has been associated with an underlying AD pathology in a previous clinicopathological series (49) and a study using amyloid-PET (26). However, we could not replicate these prior findings of logopenic-PPA phenotype in the CBS-A+ group from our cohort. Meanwhile, patients in the CBS-A+ group presented worse cognitive performances at MMSE and ACE-R attention, memory, and visuospatial subscores, findings earlier highlighted in *postmortem* (7, 45) and *in vivo* biomarkers-based (15, 36) research works. We hypothesize that the advanced functional stage and compromised cognition detected in the CBS-A+ group may have prevented us from obtaining this observation. Otherwise, one additional possibility is that the language profiles are too heterogeneous in CBS and it is often not possible to delineate a unique pattern.

The majority of our patients demonstrated phonemic and semantic verbal fluency impairment. It is recognized that verbal fluency performance relates not only to language dysfunction but also to other cognitive domains such as executive function and attention, reflecting initiation and processing speed. Notably, the CBS-A– group tended to show a more compromised phonemic verbal fluency, while the CBS-A+ group had a worse semantic verbal fluency performance, even though it did not reach statistical significance. Most studies have reported reduced word fluency in CBS patients (15, 50), especially concerning phonemic fluency. In line with our findings, a previous research work revealed significant impairment in the CBS-A– group regarding the phonemic verbal fluency task compared to the CBS-A+ group (51). As we consider that cases from the CBS-A– group probably encompass CBD and PSP pathologies and adding the fact that PSP studies have shown even more impairment related to phonemic verbal fluency, we might thus find a rationale to this pattern (23, 27).

Additionally, we assessed neural correlates from verbal fluency performance in CBS patients, a matter that has not been extensively investigated (23). Semantic verbal fluency correlated positively with glucose metabolism in the left superior, middle, and inferior temporal gyri, whereas phonemic verbal fluency correlated with metabolism in the left frontal areas, mainly at the left inferior frontal gyrus, and with left temporal areas, comprising the middle and inferior temporal gyri (see **Figure 3**). These findings are consistent with data from functional imaging in healthy adults (52).

The main limitation of our study was the lack of histopathological data or other pathology *in vivo* tracers, such as tau-PET. In its absence, we could not correctly distinguish the language profile concerning underlying pathologies in the group with negative amyloid deposition or investigate the influence of comorbid pathologies in language dysfunction. In a previous study, patients with nfv-PPA and underlying PSP pathology showed more dysarthria than those with nfv-PPA with CBD pathology (24). Therefore, there is a possibility that our patients in the CBS-A– group with dysarthria had more underlying PSP pathology than CBD. Positive aspects are a relatively significant number of CBS patients from a unique center, with standardized neurological, cognitive, and speech–language assessment, studied with multimodal imaging from the same protocols with blinded analysis for the diagnosis, including a specific ligand for amyloid pathology.

Finally, we could depict two groups (CBS-A+ and CBS-A–) with distinct motor speech features and cognitive performances, but without a clear difference concerning language profile. Our results shed light on dysarthria as an aspect related to the CBS-A– variant, and thus, it might be a helpful clinical clue suggesting the underlying CBS pathology. Also, we found metabolic and structural signatures related to the presence of dysarthria that provide insights into the motor speech production networks. Further longitudinal studies with larger samples are warranted to encompass the diversity of language impairment in distinct stages of CBS disease progression.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical committee of University of São Paulo under protocol number 2.046.113. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JP, IA, and AC: designed and conceptualized the study and data collection and drafted the manuscript for intellectual

content. MO: statistics, analyzed and interpreted the data, and revised the manuscript for intellectual content. AS-N, CG, and CO: data collection. MS, ER, RN, CB, and SB: revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.702052/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix F - Case report published in Movement Disorders Clinical Practice

Movement Disorders
CLINICAL PRACTICE

LETTERS: NEW OBSERVATIONS

Foot-Hand Synkinesis in Corticobasal Syndrome: Single Clinical Feature with Distinct Molecular Imaging Biomarkers

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Synkinesis is a subset of motor overflow in which voluntary movements of one part of the body are accompanied by involuntary activation of other, non-mirroring muscles.[1] This disorder has been observed in neurodegenerative diseases such as Parkinson's disease,[2] Creutzfeldt–Jakob disease,[3] and other parkinsonian disorders.[2,4] Moreover, it is also observed in healthy older subjects.[2] Their occurrence in patients with corticobasal syndrome (CBS) might be expected, but this phenomenon is still scarcely described in the literature. Here, we report 2 cases of patients with probable CBS[5] presenting ipsilateral and contralateral foot-hand synkinesis and distinct amyloid imaging biomarkers results.

A 52-year-old man (patient 1) was referred to our service with a 2-year history of progressive language impairment and limb rigidity. Neurological examination disclosed hypomimia, asymmetrical right-sided parkinsonism, cervical dystonia, ideomotor apraxia worse on the right side, right arm levitation, and nonfluent aphasia. A diagnosis of CBS was made. It was noteworthy that when we asked him to move his right foot, he started involuntarily to move his left hand, with a similar pattern and pace, presenting a contralateral and ipsilateral foot–hand synkinesis (Video 1, Segment 1).

Patient 2 was a 65-year-old man with a 4-year history of progressive cognitive impairment and asymmetric rigidity. His neurological examination demonstrated right-sided parkinsonism, bilateral myoclonus, and ideomotor apraxia (both worse on the right), and cortical sensory deficits. He was diagnosed with probable CBS. When we asked him to move his right foot, he developed involuntary movements in his right hand and later in his left hand (Video 1, Segment 2). Voluntary movements from the hands did not elicit synkinesis in both patients.

Both patients underwent a comprehensive investigation that included magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG)-positron emission tomography (PET), and Pittsburgh compound-B (PIB)-PET. Patient 1 showed an asymmetrical hypometabolism at the frontoparietal region contralateral to the affected side at FDG-PET (Fig. 1A) and negative PIB-PET (Fig. 1B). Conversely, patient 2 showed an asymmetrical hypometabolism predominantly at posterior temporoparietal regions at FDG-PET (Fig. 1D) and positive cortical amyloid deposition at PIB-PET (Fig. 1E).

Foot-hand synkinesis in corticobasal syndrome

Video 1. Segment 1: patient diagnosed with corticobasal syndrome is asked to move his right foot when, simultaneously, he performed involuntary movements in his left hand, with a similar pattern and pace. Despite explaining to him to only move his feet, seconds later both hands were involuntarily moving. The patient also presented bradykinesia and rigidity at both arms (worse on the right side) and bilateral ideomotor apraxia (also worse in the right arm). Segment 2: patient diagnosed with probable CBS developed involuntary movements in his right hand when asked to move his right foot and later demonstrated the same movements in his left hand. In this patient, myoclonus in both upper limbs is also notable (worse on the right side).

Patient 1 was diagnosed as CBS probably related to tauopathy, whereas patient 2 was diagnosed as CBS probably related to Alzheimer's disease. Both patients also revealed hypometabolism at the supplementary motor area (SMA) and premotor cortex, contralateral to the affected side where synkinesis occurred.

Although the brain networks involved in synkinesis are poorly understood, they are likely related to dysfunction in the secondary motor areas, such as the premotor cortex, SMA, cingulate, and their connections to the primary motor cortex.[1] A previous study using functional magnetic resonance imaging (fMRI) data

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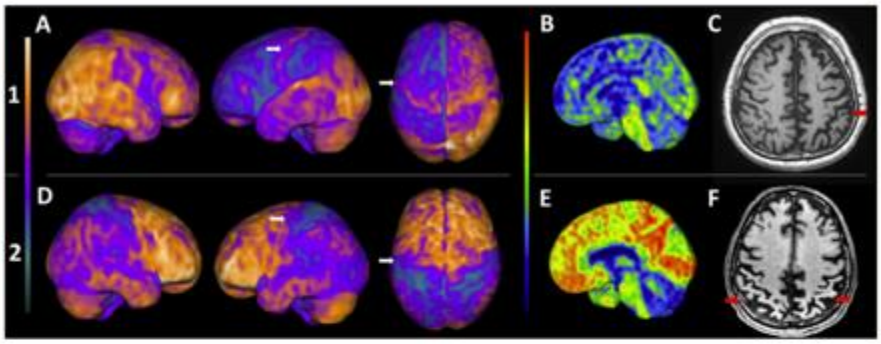

FIG. 1. Upper row (1) patient 1: (A) FDG-PET 3D-stereotactic surface projection (3D-SSP, software cortex ID suite, GE Healthcare): asymmetric frontoparietal hypometabolism, including the sensory and motor cortex, worst on the left side. PIB-PET 3D-SSP (B) negative for amyloid deposition, and T_1-weighted MRI (C) with asymmetric frontoparietal atrophy, also worst on the left (red arrows). Lower row (2) patient 2: (C) FDG-PET 3D-SSP: asymmetric posterior temporoparietal hypometabolism, also including the sensory and motor cortex, worst on the left side. PIB-PET 3D-SSP (E) positive for diffuse cortical amyloid deposition, and T_1-weighted MRI (F) showing bilateral parietal cortical atrophy (red arrows). The white arrows on A and D point to the supplementary motor cortex, probably related to the synkinesis.

in patients with hand–foot synkinesis showed that the SMA was activated during hand movements besides the foot motor cortex region. Therefore, the SMA might orchestrate the coordination of involuntary movements, probably being anatomically correlated with synkinesis.[4] Consonant with this, our cases revealed hypometabolism in this area (Fig. 1).

We demonstrate that synkinesis might be a motor finding of CBS and synkinesis are probably not related to its underlying pathology. Instead, synkinesis occur because of dysfunction of secondary motor areas, mainly the SMA, a typical anatomical affected site in CBS.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review, and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review, and Critique.

J.B.P.: 1A, 1B, 1C, 3A
S.M.D.B.: 3B
A.M.C.: 1A, 1B, 1C, 3B
R.N.: 3B

Disclosures

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Views & Reviews

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Corticobasal syndrome

A diagnostic conundrum

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ABSTRACT. Corticobasal syndrome (CBS) is an atypical parkinsonian syndrome of great interest to movement disorder specialists and behavioral neurologists. Although originally considered a primary motor disorder, it is now also recognized as a cognitive disorder, usually presenting cognitive deficits before the onset of motor symptoms. The term CBS denotes the clinical phenotype and is associated with a heterogeneous spectrum of pathologies. Given that disease-modifying agents are targeting the pathologic process, new diagnostic methods and biomarkers are being developed to predict the underlying pathology. The heterogeneity of this syndrome in terms of clinical, radiological, neuropsychological and pathological aspects poses the main challenge for evaluation.

Key words: corticobasal syndrome, corticobasal degeneration, dementia, atypical parkinsonism.

O ENIGMÁTICO DIAGNÓSTICO DA SÍNDROME CORTICOBASAL

RESUMO. A síndrome corticobasal é classificada dentro do grupo das síndromes parkinsonianas atípicas, e atualmente desperta interesse em neurologistas especialistas em distúrbios do movimento e neurologia cognitiva e comportamental. Inicialmente considerada como uma síndrome tipicamente motora, hoje se reconhece a importância dos achados cognitivos na apresentação, podendo ocorrer mesmo na ausência de alterações motoras. Tal designação refere-se à síndrome clínica e é associada a várias patologias subjacentes. Tendo em vista que drogas modificadoras da doença estão focando na patologia de base, novos métodos diagnósticos de imagem e outros biomarcadores estão sendo desenvolvidos para predizer o processo patológico específico antemortem. A heterogeneidade clínica e patológica desta entidade, portanto, é o maior desafio a ser desvendado.

Palavras-chave: síndrome corticobasal, degeneração corticobasal, demência, parkinsonismo atípico.

INTRODUCTION

In the vast group of neurodegenerative diseases, Corticobasal Syndrome was described particularly recently, in 1967 and 1968, when Rebeiz et al.[1,2] first reported clinical and neuropathological features of three patients with a syndrome that they called "corticodentatonigral degeneration with neuronal achromasia". Gibb and Marsden used the term Corticobasal degeneration (CBD) in 1989[3] and the term Corticobasal Ganglionic Degeneration has also been adopted by some authors. The clinical entity described by Rebeiz et al. is now considered an atypical parkinsonian syndrome of great interest to movement disorder specialists and behavioral neurologists and is referred to as Corticobasal Syndrome (CBS), denoting the clinical phenotype, and is associated with a heterogeneous spectrum of pathologies. The heterogeneity of this syndrome from clinical, radiological, neuropsychological and pathological aspects poses the main challenge for evaluation.

On the other hand, the pathologic entity CBD causes prominent focal cortical atrophy and subcortical damage and can be characterized with distinct clinical syndromes to CBS, such as Progressive Supranuclear Palsy

(PSP), Frontal Behavioral-Spatial Syndrome (FBS), nonfluent/agrammatic variant of Primary Progressive Aphasia (naPPA), also presenting with a wide range of neurologic signs and symptoms. This review is based on a PubMed literature search from 1967 to date, and aims to provide an overview of the current knowledge on the corticobasal syndrome, covering six aspects: clinical features, biomarkers, imaging, pathology, genetics and treatment.

CLINICAL FEATURES

The Corticobasal Syndrome is usually characterized by akinetic-rigid parkinsonism, dystonic and myoclonic movements, associated with cortical symptoms such as ideomotor apraxia, alien limb phenomena, aphasia or sensory neglect. There are many available criteria for CBS, and they differ considerably (Table 1).[4,5] In the latest criteria, probable CBS is characterized by an asymmetric presentation with at least two of: [a] limb rigidity or akinesia, [b] limb dystonia, [c] limb myoclonus, plus two of: [d] orobuccal or limb apraxia, [e] cortical sensory deficits, [f] alien limb phenomena.[4] In addition, other different cognitive deficits may coexist. Another study proposed a modified Cambridge criteria after comparing three previous criteria applied to a large group of 40 patients with a clinical diagnosis of CBS. As cognitive impairment was ubiquitous even at presentation, with speech and language impairment the commonest feature, the authors noted that all three criteria could be applied equally well at later stages, but in the earlier stages the Cambridge criteria had significantly wider applicability, almost certainly due to the weight given to cognitive and language dysfunction. Therefore, they suggested a minor modification to capture the high prevalence of aphasia (Table 1).[5]

With regard to motor presentation, including dystonia, rigidity, akinesia, myoclonus, tremor and levodopa-resistant parkinsonism, there is notable asymmetry. It is now recognized, however, that these motor features do not distinguish CBS underlying pathologies.[7-9] In a recent study, involving 296 pathologically-proven cases of Corticobasal Degeneration, only 37.5% had dystonia, where upper limb dystonia was the most common pattern (77.4%), followed by cervical dystonia (9.5%) and blepharospasm (8.3%). CBS was present in 202 patients (54%), and of these cases, 51% had myoclonus, 86.3%

Table 1. Current clinical criteria for CBS.

Modified Bak and Hodges criteria (Cambridge criteria) Mathew et al.[10]	**Armstrong et al.[4]**	
Mandatory criteria*	**Probable**	**Possible**
• Insidious onset and gradual progression	• Insidious onset/gradual progression	• Insidious onset/gradual progression
• No sustained response to levodopa treatment	• Asymmetric presentation	• May be symmetric
↓	↓	↓
Major criteria	**Cortical dysfunction**	**Cortical dysfunction**
Motor features	At least 2 of:	At least 1 of:
• *Akinetic rigid syndrome*	• Orobuccal/limb apraxia	• Orobuccal/limb apraxia
Cortical motor sensory features	• Cortical sensory deficit	• Cortical sensory deficit
• *Limb apraxia*	• Alien limb phenomena	• Alien limb phenomena
Cognitive features		
• *Speech and language impairment*		
Minor criteria	**Extrapyramidal dysfunction**	**Extrapyramidal dysfunction**
Motor features	At least 2 of:	At least 1 of:
• Focal or segmental myoclonus	• Limb rigidity or akinesia	• Limb rigidity or akinesia
• Asymmetrical dystonia	• Limb dystonia	• Limb dystonia
Cortical motor sensory features	• Limb myoclonia	• Limb myoclonia
• Alien limb phenomenon		
• Cortical sensory loss or dyscalculia		
Cognitive features		
• Frontal executive dysfunction		
• Visuospatial deficits		

*For a diagnosis of CBS, the patient should satisfy all mandatory criteria, two major criteria (in italics) and two minor criteria.

apraxia and 100% had an akinetic-rigid syndrome. Considering this, despite dystonia being included in clinical criteria for CBS and CBD, this aspect does not seem to predict a clinicopathological correlation.[9] Another study sought to investigate the frequency and pattern of dystonia in a group of patients with atypical parkinsonism. The series demonstrated dystonia as a common feature with overall frequency of 50%, and in the CBD group of 100% (8 patients). Dystonia was not the first complaint in any of these patients. Levodopa therapy did not influence the pattern of dystonia.[10]

Most studies describe myoclonus in the presentation of patients with CBS, occurring in 55% to 93% of cases,[11-13] where terms used are "focal myoclonus" or "stimulus-sensitive myoclonus". This occurs commonly in upper extremities and can also be present in the face. They are typically spontaneous or triggered by sensory stimulation, and usually considered of cortical origin. Limb rigidity is commonly asymmetric and described as severe, but the nature is uncertain, and could be related to parkinsonism, dystonia or paratonia.[4]

Although commonly described as a "Parkinson-plus" syndrome, it is clear that behavioral and cognitive changes prevail in the clinical course, which may affect quality of life as much as the movement disorders. Initially considered an entity with primary damage to the basal ganglia and the frontal-parietal cortex, with parkinsonism and apraxia, recent investigations have shown variable involvement of frontal, parietal and temporal cortices, resulting in combinations of parkinsonism and other cognitive impairments. Higher cortical features include apraxia, alien limb phenomena, cortical sensory loss, global cognitive impairment, behavioral changes and aphasia.

Previously, cognitive deficits were considered a late-stage phenomenon.[14] It is now known that these features are present from the outset of the illness, even in cases secondary to underlying CBD pathology, leading to their incorporation into most diagnostic criteria (Table 1). Occasionally, motor features emerge and patients later develop cognitive and language disturbances. The opposite is also observed; some patients with dementia syndrome criteria such as probable primary progressive aphasia (PPA), behavioral-variant frontotemporal dementia or posterior cortical atrophy, may develop motor features of CBS later in the course of the disease.

There is a bias in the frequency of reports on cognitive deficits, probable because these cases are commonly not evaluated by behavioral specialists, even though multidomain cognitive impairment is extensively reported in CBS patients. Patients can sometimes start the presentation with impairment in executive function and memory,[15] but these symptoms are also commonly seen in other neurodegenerative diseases.

Deficits in language and visuospatial dysfunction seem to be much more characteristic. In some cases, language dysfunction is the first symptom, and most studies have reported reduced word fluency, speech apraxia and also syntactic deficits, when the CBS overlaps with the naPPA phenotype.[16,17] A recent study using ligand Pittsburgh compound B-Positron Emission tomography (PiB- PET) imaging demonstrated a tendency for greater impairment of sentence repetition, also observed in logopenic progressive aphasia in PiB-Positive cases (PiB-positive 75%, PiB-negative 22.2%). Thus, the study suggested that impaired sentence repetition in CBS cases could predict AD pathology.[18,19]

Another large cohort study of 45 CBS patients demonstrated a frequent start with language impairment (69% of patients) compared to apraxia (29%), unlike most studies which highlight apraxia as the major cognitive sign of CBS. The predominant language impairment was coherent with asymmetrical hypoperfusion of left frontal-parietal and posterior temporal cortices. However, it is unclear whether there is a specific aphasia phenotype. There are findings of a phenotype suggestive of a "mixed" progressive aphasia, presenting with agrammatism and speech disorders, as well as with anomia and sentence repetition impairment (such as the logopenic variant of PPA) and disorders of single word comprehension (such as the semantic variant).[28]

Visuospatial dysfunction is also an alteration included in most diagnostic criteria for CBS.[7,17,18] Some patients, who later go on to develop CBS, present Posterior Cortical Atrophy in the initial evaluation, and these deficits can be quite severe. They can develop Balint's Syndrome or only one of the components of the syndrome (simultanagnosia, oculomotor apraxia and optic ataxia),[22] and can also develop Gerstmann's syndrome (dyscalculia, dysgraphia, finger agnosia and left-right disorientation) or visual agnosia. A cohort study demonstrated the existence of Gerstmann's syndrome as a frequent finding in CBS cases related to a probable AD underlying cerebrospinal fluid (CSF) signature, with considerable sensitivity (75%) and specificity (75%).[28]

The assessment of visuospatial functions in CBS and atypical parkinsonism syndromes has to overcome a wide range of confounding variables.[23] The exact frequency of visuospatial deficits and the interpretation of existing studies are complicated by the possible influence of motor and frontal executive deficits, and are therefore difficult to measure, because these motor

deficits and other higher cortical dysfunction sometimes can render the examination almost impossible. A test called the Visual Object and Space Perception Battery (VOSP) was used in one study to minimize the influence of motor and executive dysfunction and to distinguish between object and space processing alterations (ventral and dorsal streams, respectively). The percentage of patients impaired ranged from 28% to 52%, with spatial tests more often impaired (44-52%) than object-based tests (28-38%), suggesting early involvement of the "dorsal stream" with its anatomical substrate in parietal lobe pathology.[24] Another study using PiB binding has shown a correlation of performance on the VOSP in CBS with underlying Alzheimer's pathology.[19]

There are two disorders of voluntary action included in diagnostic criteria and normally present in clinical features of CBS, namely, alien limb and apraxia. Both archetypical disorders of volition, the first represents a performance of semi-purposeful movements in the absence of volition.[24] The phenomenon of alien hand syndrome is complex and has various clinical manifestations related to different lesion sites, such as supplementary motor area, anterior cingulate, corpus callosum, anterior prefrontal cortex, posterior parietal cortex and thalamus.[26]

Case studies have associated lesions in the anterior corpus callosum with volitional disorders of alien limb and apraxia in the non-dominant hand. Damage to this tract could lead to compromised transition of sensorimotor signals from the dominant to the non-dominant hemisphere. Thus, apraxia and alien limb could represent a "disconnection syndrome", as sensorimotor representations for voluntary movements are disconnected from motor areas.[25] There is evidence from studies regarding volitional deficits of alien limb and apraxia, considering that they both can occur in the same patient but are dissociable, and correlating focal structural changes in gray and white matter of the medial frontal-prefrontal network and its connectivity with the pre-supplementary motor area.[22] Another study utilizing functional magnetic resonance imaging showed an association of alien limb and a broader network of brain regions related to movement execution and planning as well as areas linked to inhibition control, the inferior frontal gyrus and the precuneus. Behavioral symptoms similar to those observed in patients with behavioral variant[26] frontotemporal dementia may be present, typically apathy rather than disinhibition.[18]

Akin to motor features, there are no cognitive or language manifestations that reliably distinguish between underlying pathologies in patients with CBS.[11]

Other symptoms not usually related to CBS but likely important to quality of life have also been studied. Swallowing and speech disturbances are common in these patients and differ from the same symptoms in other parkinsonian syndromes such as PSP. Speech apraxia and piecemeal deglutition is also a characteristic feature in CBS.[27]

PATHOLOGY

The constellation of CBS is associated with a variety of underlying pathologies other than CBD. Many patients with post-mortem diagnosis of CBD are never suspected of having the disease during life.[1,6,8,35] Additionally, CBD pathology was found in only 50% of all clinically diagnosed patients, with others showing PSP, Pick's disease, FTLD- TDP43, AD, dementia with Lewy bodies, and Creutzfeldt-Jakob disease at autopsy.[2,6,8,35-37] Due to this clinical-pathologic diversity, Boeve et al. (2003) introduced the term CBS to distinguish the clinical syndrome from the pathologic entity, CBD.[38]

Diagnosis of the underlying cause of CBS is only possible through postmortem brain analysis due to the degree of clinical-pathologic mismatch that exists. The majority of causes of CBS are tauopathies.[39] In the 1990s, the neuronal aggregates in CBD[40] were shown to consist of the microtubule associated protein (MAPT). The tau protein exists in 6 isoforms as a result of alternative mRNA splicing of the exons 2, 3 and 10. The inclusion of exon 10 generates an isoform with four microtubule-binding domains (4R), while the absence of this inclusion produces an isoform with three microtubule-binding domains (3R). The different neurodegenerative disorders that can cause CBS have been associated with specific tau isoforms. CBD features predominant deposition of 4R-tau, and likewise PSP, while AD is characterized by the simultaneous presence of 3R and 4R-tau protein, and Pick's disease by 3R-tau.[41]

Besides these distinct biochemical features, microscopically some findings could help to distinguish the different pathologic causes of CBS. Neuropathological diagnostic criteria for CBD require tau inclusions in neurons and glia with astrocytic plaques and extensive thread-like pathology.[42] Like CBD, PSP has threads in gray and white matter, but in CBD the boundary between gray and white matter may be indistinct due to the severity of threads in both compartments (Figure 1).[39,44,45]

Astrocytic plaques are the hallmark glial lesion of CBD and the most distinguishing histopathological feature of CBD and PSP. Astrocytic plaques represent tau accumulation in the distal segments of astrocytes with minimal accumulation in the cell body, creating a

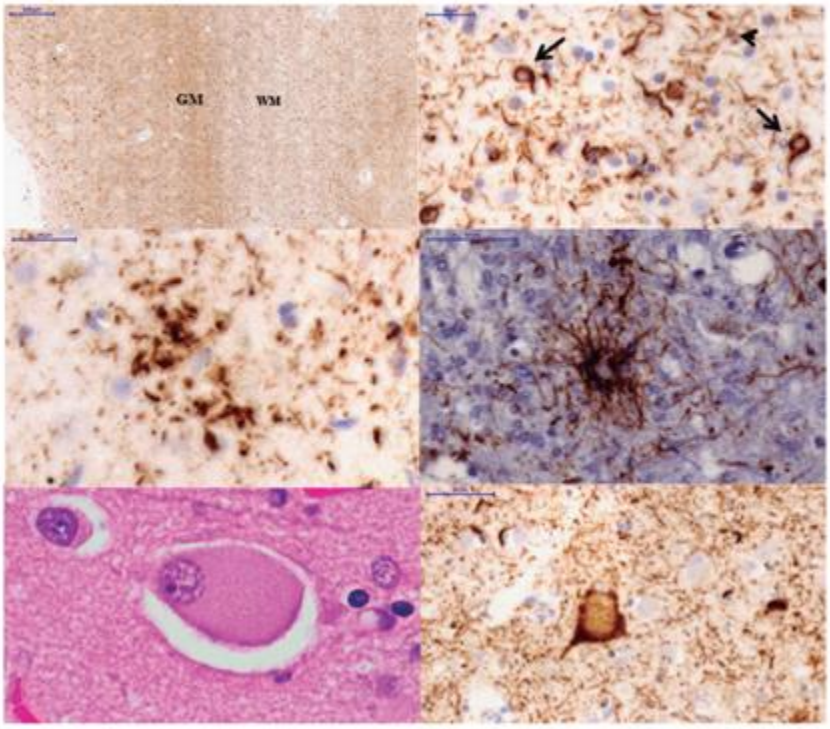

Figure 1. Microscopic findings of CBD and PSP: [A] boundary between GM and WM in the inferior temporal gyrus of a CBD case. Note the severe involvement of both compartments (tau immunostain, CP13 antibody); [B] oligodendroglial coiled bodies (arrows) and thread-like pathology (arrowhead) in white matter in CBD case (tau immunostain, CP13 antibody); [C] astrocytic plaque, a hallmark of CBD (tau immunostain, CP13 antibody); [D] tufted-astrocyte, the characteristic glial lesion of PSP (tau immunostain, CP13 antibody); [E] ballooned neuron in temporal cortex (hematoxylin eosin); [F] tau-positive ballooned neuron in temporal cortex. Scale bars represent 500 µm in A; 20 µm in B, C; 50 µm in [D, E]; and 10 µm in [F]. GM: gray matter; WM: white matter.

central clear zone (Figure 1). They are more numerous in cortex, but can also be seen in caudate and putamen and less often in thalamus and midbrain tectum.[39,43-45] By contrast, in PSP the characteristic glial lesion is the tufted astrocyte (Figure 1). They are seen especially in the precentral gyrus, striatum and superior colliculus, being more variable in the thalamus, subthalamic nucleus and red nucleus yet rare or absent in the lower brainstem. A third neuropathological lesion highly suggestive of CBD is the ballooned neuron (BN) (Figure 1). These are swollen cortical neurons, most often found in the third, fifth and sixth cortical layers, and have been linked to chromatolysis. Cingulate gyrus, amygdala, insular cortex and claustrum are the most common locations.[39,44,45] Unlike in argyrophilic grain disease, limbic and paralimbic distribution of BN should not be considered specific of CBD. In addition, the presence of BN in convexity cortical areas is of much more diagnostic significance. BN are rare or absent in PSP.[39,44,45,47]

In addition, the presence of oligodendroglial tau inclusions called coiled bodies are common in CBD, but are much more frequent in PSP than CBD (Figure 1). In PSP they tend to be parallel to the distribution of neuropil threads and can be numerous in white matter tracts in the basal ganglia, thalamus and brainstem.[39,44,45,47]

Predicting underlying pathology in CBS is difficult, because of the multitude of etiologies. The sensitivity of clinical findings for predicting underlying CBD pathology ranges from 26% to 56 %.[45-47] Lee et al. (2011) observed a 35% prevalence of CBD post-mortem in 40 patients meeting CBS criteria, followed by 23% AD, 13% PSP and 13% FTLD-TDP43.[8]

Table 2. CBS: Pathologic correlations.

Study Pathology	Boeve, 2003[37]	Hodges, 2004[38]	Josephs, 2006[39]	McMonagle, 2006[28]	Shelley, 2009[8]	Ling, 2010[34]	Lee, 2011[7]	Total, n (%)
CBS cases, n	34	9	21	19	12	21	40	156 (100)
CBD	18	7	10	11	6	5	14	71 (45.5)
PSP	6	0	10	1	0	6	5	28 (18.0)
AD	3	0	0	1	6	5	9	24 (15.4)
Pick's disease	2	0	1	3	0	0	1	7 (4.5)
DLDH	2	1	0	0	0	1	0	4 (2.6)
PD	0	0	0	0	0	2	0	2 (1.3)
FTLD-TDP43	0	1	0	2	0	1	5	9 (5.8)
FTLD-TDP43 + MND	0	0	0	0	0	1	0	1 (0.6)
CJD	3	0	0	1	0	0	0	4 (2.6)
MST	0	0	0	0	0		1	1 (0.6)
Mixed disease[a]	0	0	0	0	0	0	5	5 (3.2)

[a] Mixed cases: 2 PSP, 1 CBD, 1 FTLD-TDP; all mixed with intermediate probability of Alzheimer's disease. CBD: Corticobasal degeneration; PSP: Progressive supranuclear palsy; AD: Alzheimer's disease; DLDH: Dementia lacking specific histology; PD: Parkinson's disease; FTLD-TDP43: Frontotemporal lobar degeneration with TDP-43 inclusions; MND: Motor neuron disease; CJD: Creutzfeldt-Jacob disease; MST: Multiple system tauopathy without argyrophilia.

Another study of Ling et al. (2010) involving a movement disorder-focused series, found a frequency of 53% CBD or PSP, and 24% AD in 21 cases clinically diagnosed with CBS. The clinical presentation and progression of symptoms reflect the distribution of the pathology more than the specific underlying histology (Table 2).[35]

The better characterization of clinical, neuropsychological and imaging features is important to improve antemortem diagnosis and crucial for designing therapies.

IMAGING AND BIOMARKERS

There is growing interest in developing disease-specific biomarkers to aid the prediction of pathology in the antemortem diagnosis of neurodegenerative disorders. Tau and Alzheimer disease pathology-targeted therapies are currently being developed and undergoing clinical trials. Therefore, determining the nature of the underlying pathology ought now to be considered of great importance and not only a matter of purely academic interest. The possible future biomarkers include CSF testing and imaging modalities.[11] Although the pathophysiology of CBS is largely unknown, recent advances in neuroimaging have shed light on specific structural neuroanatomical changes that occur as a result of this disorder.[31]

A recent study assessed gray matter and white matter changes using a more advanced technique than voxel-based morphometry (VBM), the surface-based morphometry, which evaluates cortical thickness and surface area, by also using diffusion tensor imaging (DTI) to evaluate white matter. The results showed that cortical thinning, subcortical volume loss and fiber tract degeneration prominently involved the hemisphere contralateral to the more affected limb. These findings corroborate other data suggesting that the asymmetric distribution affecting frontostriatal connectivity is closely associated with asymmetric motor and non-motor symptoms.[31] The patterns of white matter damage in bvFTD and CBS have been contrasted using DTI. They showed greater damage to the uncinated fasciculus, genu of corpus callosum and forceps minor. In contrast, CBS patients had greater damage to the midbody of the corpus callosum and perirolandic corona radiata, thus the distribution and degree of white matter damage differed between them.[32]

Apparently, specific patterns of atrophy may suggest underlying pathology. Volumetric Magnetic Resonance Imaging (MRI) using VBM was used to compared groups of CBS with different postmortem diagnosed pathologies, such as CBS-AD (6 cases), CBS-CBD (7 cases), CBS-PSP (6 cases) and CBS-FTLD-TDP43 (frontotemporal lobar degeneration with TDP-43 inclusions; 5 cases), revealing that imaging patterns of gray matter loss differ according to the underlying pathology. All CBS

pathologic groups showed gray matter loss in premotor cortices, the supplemental motor area and insula on imaging. CBS-TDP43 and CBS-AD were associated with a more widespread pattern of gray matter loss, and in CBS-TDP43 cases there was predominantly loss in the prefrontal cortex and posterior temporal lobes. The CBS-AD group was associated with a posterior pattern of gray matter imaging loss, involving parietal, posterior temporal and occipital lobes.[33,34]

Also, a representative cohort population of 45 CBS patients was analyzed for AD profile in CSF with biomarkers, a possible useful tool to distinguish between underlying pathologies, together with brain perfusion imaging (Spect). It disclosed two distinct anatomo-clinical variants, both related (18% of cases) and unrelated (82%) to probable underlying AD. AD-CBS cases were more frequently characterized by myoclonus and Gerstmann syndrome, whereas non-AD CBS more frequently had orobuccal apraxia and severe aphasia. Spect imaging showed that AD-CBS involved posterior parietal-temporal cortices, pre-cuneus and posterior cingulate, while non-AD CBS had more anterior damage to left-sided frontal cortices impacting language. These findings raised the question as to whether some CBS should be considered atypical AD.[28] Tau/Abeta ratio in CSF, as used in this study, may represent a useful way of detecting CBS-AD in vivo, although neuropathological confirmation is not yet forthcoming and the technique's sensitivity for detecting CBS-AD at an early stage has yet to be determined.[48]

Recently, the use of specific ligand-based nuclear imaging modalities such as PiB-PET, which was developed to detect fibrillary b-amyloid peptide and is a sensitive and specific biomarker of AD pathology, can be used to detect pathology in vivo in patients with dementia syndromes and can distinguish different neurodegenerative disorders.[18] Amyloid imaging may be of value to determine which cases are related to AD, although it is known that 15%-30% of cognitively-normal older individuals can have a positive amyloid PET.[47] Tau-ligand imaging is also the subject of current research and probably will be incorporated in the future to predict pathology. Reflecting the rarity of the disease, the number of participants in these studies of ligands to amyloid or tau typically remains small.

The first study to use amyloid imaging in CBS included 14 CBS patients to undergo PiB-PET imaging, four (28.6%) were PiB-positive –patients with high PiB binding, a standardized uptake ratio >1.5- and the remaining were PiB-negative (71.4%). There were no significant differences in motor examination findings between the two groups, though sentence repetition impairment revealed a tendency for greater impairment in PiB-positive cases, and also for visuospatial function, memory impairment and everyday skills domains. VBM analyses showed atrophy affecting the posterior part of the left superior temporal gyrus, distinguishing PiB-positive cases.[18]

Another more recent study using amyloid imaging split CBS into frontal and temporoparietal clinical variants based on modified clinical criteria, MRI and FDG-PET and compared with PiB-PET results. In total, 25 patients underwent amyloid imaging, and nine out of the fourteen patients classified as temporoparietal variant were PiB-positive (82% sensitivity and 71% specificity). Cognitive testing demonstrating greater episodic memory and visuospatial impairment than executive dysfunction had the strongest association with PiB status.[29]

Temporoparietal-predominant neuroimaging patterns with FDG-PET hypometabolism proved sensitive but not specific for AD. One autopsy-proven patient with a positive amyloid PET scan had the presence of CBD pathology, indicating that the possibility of co-pathology must be considered.[30] Amyloid PET scans, although an optimal modality for detecting AD pathology in CBS patients, is not widely available and further knowledge about more accessible neuroimaging modalities is still required.

GENETICS

The genetics of cases of CBS is largely unknown and the majority are sporadic. CBS, when genetically related, is frequently observed in patients who have mutations in the gene that encodes progranulin (PGRN).[50] There have been reports of families with autosomal-dominant frontotemporal lobar degeneration linked to PGRN gene mutations that could represent 5-7.9% cases in large series of CBS.[52]

Mutation in the MAPT gene has also been demonstrated in a CBS-like presentation[52] as well as pathogenic C9orf72 repeat expansion, particularly when there is a positive family history of FTD and amyotrophic lateral sclerosis (ALS).[53]

A recent case report described a family with pathologically-confirmed cases of early-onset, autosomal-dominant familial AD (EOFAD) linked to a Met233Leu mutation of the presenilin-1 gene (PSEN-1), and one family member developed prominent CBS combined with severe neuropsychiatric and behavioral disturbances resembling those often found in EOFAD. The authors concluded that CBS may represent an atypical clinical presentation in autosomal-dominant EOFAD

and that the PSEN-1 gene could be an opportunity to predict AD pathology. They also suggested testing for PSEN-1, PGRN, MAPT and C9orf72 gene mutations when there is a positive family history of neurodegenerative conditions.[54]

Another study suggested testing genetic mutation in FTLD with movement disorders as a motor presentation, and when CBS is present, testing first for PGRN and after, if the first is negative, testing for MAPT, C9orf72, CHMP2B (which encodes charged multivesicular body protein 2b), VCP (valosin-containing protein), FUS (which encodes RNA-binding protein FUS- fused in sarcoma), TARDBP (TAR DNA-binding protein 43) and NIFID (neuronal intermediate filament inclusion disease).[50]

TREATMENT

There is no specific treatment for CBS, but the ability to accurately detect underlying pathology early in the course of CBS will be crucial when effective therapies are developed.[18]

Symptomatic treatment of CBS is used to improve motor and cognitive-behavioral symptoms, but in general these are largely based on Class IV evidence, due to lack of randomized clinical trials.[55] Levodopa can be helpful in CBS, as demonstrated in an observational study which showed that 56% of pathologically-confirmed CBD patients had slight improvement in bradykinesia and rigidity. To consider a subject as a non-responder, it is recommended to treat the individual with a dosage of 1000 mg daily for at least 2 months before withdrawal.[35,36] Although no definitive data are available regarding the efficacy of botulinum toxin (BoNT) type A and B, it may be helpful for CBS-associated limb dystonia and may be used to alleviate abnormal posture, pain and for maintaining hand hygiene.[55,57] Usual therapeutic strategies for myoclonus include levetiracetam (up to 3000 mg/day) or benzodiazepines (clonazepam, up to 15mg/day).[55]

With regard to cognitive and behavioral symptoms, acetylcholinesterase inhibitors can be considered for patients with CBS that may have underlying AD pathology. For psychosis, agitation and aggression, anti-psychotics (atypical agents) are employed despite adverse effects that include extrapyramidal symptoms. Mood stabilizers, such as carbamazepine and valproic acid, can be used to control agitation. Trazodone has been employed for behavioral symptoms in FTLD, but in CBS no clear data on its effectiveness are available, and selective serotonin reuptake inhibitors (SSRIs) provide effective treatment in these subjects.[55] In a case report, alien hand syndrome was highly responsive to amantadine.[58]

Non-pharmacological therapies, such as cognitive behavioral therapy, physiotherapy, occupational therapy, are employed in CBS patients, improving quality of life, as well as motor, speech and language symptoms.

Disease-modifying agents targeting the pathologic process are undergoing development, highlighting the importance of accurate pathological diagnosis in the near future.

CONCLUSION

CBS is an enigmatic diagnosis, as a syndrome with many motor and non-motor symptoms due to different underlying pathologies, still not accurately diagnosed in vivo. The wide range of cognitive, behavioral and motor aspects is extremely variable between patients.

Further characterization of the clinical, imaging and neuropsychological hallmarks of CBS patients related to specific pathology is very important, considering the new recent advances in treatment. Patients with underlying AD pathology and tauopathies correctly diagnosed in the future may benefit from symptomatic therapies and future disease-modifying agents.

Author contribution. Jacy Bezerra Parmera: project review, conception, organization, and execution. Roberta Diehl Rodriguez: conception of the pathology issue. Adalberto Studart: review. Ricardo Nitrini: review and critique. Sonia Dozzi Brucki: review and critique.

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Appendix H – Review article published on Dementia & Neuropsychologia.

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Original Article

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Language in corticobasal syndrome: a systematic review

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ABSTRACT. Language is commonly impacted in corticobasal syndrome (CBS). However, the profile and type of language assessment in CBS are poorly studied. **Objective:** To identify language impairments in CBS. **Methods:** A search was performed in the Medline/PubMed database, according to the PRISMA criteria, using the keywords "corticobasal syndrome" OR "corticobasal degeneration" AND "language". Articles on CBS covering language assessment that were written in English were included, with no constraints on the publication date. **Results:** A total of 259 articles were found and 35 were analyzed, consisting of 531 participants. Twenty-eight studies showed heterogeneous language deficits and seven mentioned nonfluent primary progressive aphasia. The most used tests were the Western Aphasia Battery (8 studies) and the Boston Naming Test (8 studies). **Conclusion:** It was not possible to identify a unique linguistic profile in CBS.

Keywords: corticobasal syndrome, language, neurocognitive disorders, language tests.

LINGUAGEM NA SÍNDROME CORTICOBASAL: UMA REVISÃO SISTEMÁTICA

RESUMO. A linguagem encontra-se comumente alterada na síndrome corticobasal (SCB). No entanto, o perfil e a forma de avaliação da linguagem na SCB são pouco estudados. **Objetivo:** identificar as alterações de linguagem na SCB. **Método:** Realizou-se uma busca na base de dados Medline/PubMed, com as palavras-chave "síndrome corticobasal" OU "degeneração corticobasal" E "linguagem". Artigos sobre SCB envolvendo avaliação de linguagem, escritos em inglês, foram incluídos, sem restrição de data de publicação. **Resultados:** Foram encontrados 259 artigos, e 35 estudos foram analisados, abrangendo 531 sujeitos. Um total de 28 estudos mostraram déficits heterogêneos de linguagem, e sete mencionaram afasia progressiva primária não-fluente. Os testes mais utilizados foram Western Aphasia Battery (8 estudos) e o Teste de Nomeação de Boston (8 estudos). **Conclusão:** Não foi possível identificar um perfil linguístico único em pacientes com SCB.

Palavras-chave: síndrome corticobasal, linguagem, transtornos neurocognitivos, testes de linguagem.

INTRODUCTION

Corticobasal syndrome (CBS) is a progressive, neurodegenerative disease classified amongst atypical parkinsonian syndromes. The syndrome was first described in 1967 by Rebeiz, Kolodny, and Richardson, who presented three cases of patients with initial significant motor impairments followed by final stage cognitive impairments.[1] The initial description focused on motor deficits and showed that cognitive impairments only occurred in the final stage, but it is now known that both can occur in equal proportion in CBS and may manifest as the first symptom.[2-6]

The terms "corticobasal syndrome" and "corticobasal degeneration" (CBD) represent distinct entities. The former denotes the clinical phenotype, whereas CBD is a pathological entity affecting cortical and subcortical regions, whose diagnosis can

only be confirmed by *postmortem* anatomopathological analysis.[5] An estimated 50% of patients with clinical symptoms of CBS are diagnosed with CBD at *postmortem*. In the remaining patients, tauopathies or amyloid pathology are generally found, such as Alzheimer's disease (AD). CBD is often found in patients clinically diagnosed with other syndromes.[5,7-9]

In CBS, classically, motor symptoms occur asymmetrically and include akinetic-rigid parkinsonism, dystonia, and myoclonic movements. Cognitive symptoms include apraxia, aphasia, cortical sensory deficits, and the alien hand phenomenon.[5,10,11] This syndrome is generally challenging to diagnose owing to its clinical, pathological, radiological, and neuropsychological heterogeneity.[5]

Few studies have thoroughly investigated the profile of speech and language impairments in CBS. Some studies show a pattern similar to the nonfluent variant of primary progressive aphasia (nf-PPA), i.e., deficits at a morphosyntactic level, reduced fluency and apraxia of speech.[3,12-14] However, other studies focusing on language assessment reveal a mixed pattern encompassing characteristics of more than one type of primary progressive aphasia (PPA).[15,16]

This heterogeneity found in the literature on speech and language in CBS may be explained by multiple factors: disease stage at the time of assessment, different underlying pathologies[6] or lack of consensus on linguistic aspects to be assessed in these patients. Gorno-Tempini et al.[17] recommended that language assessment in PPA cover the following domains: naming, word and sentence comprehension, word and sentence repetition, syntactic processing, semantic memory, reading, and motor aspects of speech.

The present review aimed to identify the language impairments in CBS patients.

METHODS

The writing of this manuscript is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (www.prisma-statement.org), according to the following recommendations: introduction containing the description of the rationale and objectives of the review; methods containing the eligibility criteria, the information sources, the process for selecting studies, the data collection process, the definition of all variables for which data were sought, the methods used for assessing risk of bias of the studies, and how the results were analyzed; and discussion containing the summary of evidence, the limitations and the conclusions of the review.

The outcome of interest of this review is the profile of language in patients with CBS. Articles on CBS covering speech and language assessment were included, with no constraints on the publication date. Exclusion criteria were: 1) studies on CBD associated with syndromes other than CBS; 2) intervention studies in CBS; 3) studies written in languages other than Portuguese or English; 4) studies that could not be accessed via our University and were not open access.

The literature search was conducted using the electronic database Medline/PubMed, and it was based on manuscripts published up to February 2020. The keywords used were the following: "corticobasal syndrome" AND "language", "corticobasal degeneration" AND "language". The search was guided by the Population, Intervention, Comparison and Outcome (PICO) strategy. The population refers to the CBS patients, the intervention refers to the language assessment, the comparison is related to intragroup or between group comparisons, and the outcomes are the results from the language assessment.

All titles and abstracts were independently screened by two authors (IJA and MLS), according to the eligibility criteria previously established. The articles that were not excluded in this screening stage were fully read. A disagreement between the authors was resolved by consensus.

One author (IJA) extracted data from included studies and a second author (MLS) checked the information. Data were transferred to a data extraction sheet (using Microsoft Excel®) and included: 1) first author's name and year of publication; 2) sample size; 3) clinical and demographic data (gender, age, disease duration); 4) main speech and language results; and 5) speech and language tests used in the evaluation or speech and language abilities evaluated (when tests not mentioned). We classified the studies into three categories based on language evaluation:

- Comprehensive assessment: evaluation included all language domains recommended for testing PPA patients.[17]
- Restricted assessment: evaluation included some of the language domains recommended for testing PPA patients.[17]
- No tests or language skills mentioned: the tests or language skills evaluated were not reported.

Two authors (IJA and MLS) independently assessed the methodological quality and the risk of bias of the manuscripts included in this review through the JBI Critical Appraisal tool for cross-sectional studies.[18] This tool has eight questions regarding the criteria for inclusion of the sample, the clarity of the description of the sample and the setting, the validity and reliability of the outcomes' measurement, the appropriateness of statistical analysis and four questions that refer

exclusively to clinical trial studies. Each question must be answered as "yes", "no", "unclear" or "not applicable". All the questions regarding clinical trials were marked as "not applicable". Each question that was marked as "yes" received 1 point. The question that refers to the outcome measurement was answered exclusively on the basis of the language evaluation described in each study. For most studies included, language was only one of the clinical characteristics assessed.

Discrepancies between the two authors were discussed until consensus was reached. All manuscripts were then classified into one of three groups, according to the score obtained on the JBI Critical Appraisal tool: "low quality", if the study had less than 50% of the maximum score; "moderate quality", for studies with 50 to 80% of the maximum score; and "high quality", for studies with at least 80% of the maximum score.

Finally, confidence in the overall findings of the present review was assessed through the Confidence in the Evidence from Reviews of Qualitative Research (GRADE CERQual).[19] This instrument is based on four components: 1) methodological limitations of the primary studies, 2) relevance of those studies to the review question, 3) coherence of results among primary studies, and 4) adequacy of data, i.e., the degree to which data support the review finding. From the analysis of these four components, the review may be classified as high confidence ("it is highly likely that the review finding is a reasonable representation of the phenomenon of interest"), moderate confidence ("it is likely that the review finding is a reasonable representation of the phenomenon of interest"), low confidence ("it is possible that the review finding is a reasonable representation of the phenomenon of interest"), and very low confidence ("it is not clear whether the review finding is a reasonable representation of the phenomenon of interest).[19]

The first component, methodological limitations, was judged using the JBI Critical Appraisal tool. Relevance, coherence and adequacy of data were judged exclusively on the basis of the language evaluations of primary studies.

Two authors (IJA and MLS) independently scored each component of the CERQual tool and its final classification. Discrepancies were discussed until consensus was reached.

RESULTS

The search on the Medline/PubMed database led to the retrieval of 259 articles, of which 79 were duplicate articles, giving a total of 180. After a screening of titles and abstracts, another 128 articles were excluded (literature reviews, letters to editor, articles in Japanese, studies on unrelated topics and inaccessible articles). A total of 52 articles were read in full, of which 17 were subsequently excluded (studies on CBD associated with syndromes other than CBS and studies on unrelated topics). We included 35 manuscripts in the present review (Figure 1).

Due to the heterogeneity of the population and outcomes of the studies included, it was not possible to perform a meta-analysis.

The demographic and clinical data of the studies are given in Table 1. The sample size was very heterogeneous, ranging from 1 to 55 CBS patients, with a median value of 11 and a mean of 15.2. CBS patient age ranged from 47 to 76 years, with a median of 66.2 and mean of 65.31 years. The mean number of female patients in the studies was slightly higher than that of male patients (12.14 and 8.9, respectively). Disease duration at the time of assessment ranged from 3 months to 8.08 years, with a median of 3.32 and mean of 3.46 years.

The profile of language impairments is given in Table 2. Seven studies (20%) cited nf-PPA as the predominant language deficit profile in patients with CBS.[4,12-14,20-22] Twelve studies (34.28%) investigated specific aspects of language.[23-34] In two (5.71%) studies, the language impairments were not described in detail.[26-35] The remaining studies mentioned a variety of different symptoms, including agraphia[15,23,31,36-39] speech apraxia,[2,23,36,37,39,40] dysarthria,[36,41] a mixed type of PPA,[16] logopenic variant of PPA (L-PPA),[15,21] anomic aphasia,[3,4,42] transcortical motor aphasia[42] and Broca's aphasia.[42]

The tests used for assessment and classification of type of evaluation are also given in Table 2. The most

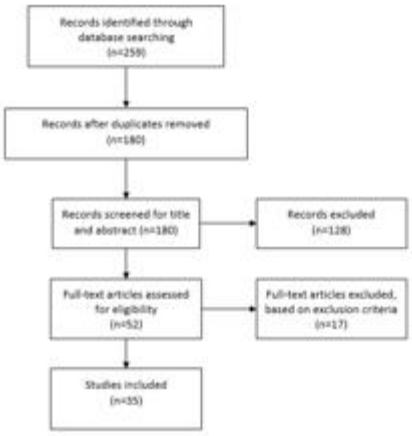

Figure 1. Literature search flow diagram.

Table 1. Sociodemographic and clinical characteristics of studies selected.

Authors, year of publication	Sample size	Gender (male/female)	Age (years)	Disease duration (years)
Kertesz et al., 2000[2]	35	movement disorder=5/10 cognitive disorder=14/6	movement disorder=61.9 cognitive disorder=63.6	movement disorder=5.4 cognitive disorder=7.1
Frattali et al., 2000[42]	15	8/7	67.7	4.5
Graham et al., 2003[50]	10	7/3	67.6	3.35
Frattali et al., 2003[26]	prospective study=34 retrospective study=9	prospective study=18/16 retrospective study=4/5	prospective study=67.91 retrospective study=71.3	prospective study=3.8 retrospective study=2.78
Gorno-Tempini et al., 2004[20]	1	0/1	not applicable	not applicable
McMonagle et al., 2006[3]	55	motor onset=10/9 cognitive onset=16/20	n/a	motor onset=2.7 cognitive onset=3.6
McMillan et al., 2006[32]	16	n/a	66.3	n/a
Cotelli et al., 2006[29]	10	n/a	63.8	n/a
Cotelli et al., 2007[30]	11	n/a	64.6	n/a
Donovan et al., 2007[23]	1	0/1	60	4
Koenig et al., 2007[28]	experiment 1=8 experiment 2=9	experiment 1=3/5 experiment 2=5/4	experiment 1=64.5 experiment 2=70.1	n/a
Silveri and Ciccarelli, 2007[31]	5	2/3	63.8	1.6
Halpern et al., 2007[27]	16	9/7	67.07	3.9
Kim et al., 2008[45]	1	1/0	55	n/a
Shelley et al., 2009[12]	12	6/6	75.5	8.08
Gross et al., 2010[24]	20	9/11	67.4	3.9
Valverde et al., 2011[35]	1	0/1	74	0,25
Borroni et al., 2011[47]	30	21/9	63.5	2.5
Troiani et al., 2011[33]	11	n/a	65.5	n/a
Passov et al., 2011[36]	1	0/1	49	2
Dopper et al., 2011[41]	1	1/0	61	2
Caso et al., 2012[21]	2	0/2	case 1=64 case 2=70	case 1=2 case 2=4
Assal et al., 2012[37]	1	0/1	64	n/a
Mathew et al., 2012[4]	40	22/18	70	initial assessment=3 follow-up=4.9
Sakurai et al., 2013[38]	1	0/1	65	n/a
Burrell et al., 2013[15]	14	7/7	66.1	2.9
Turaga et al., 2013[51]	17	11/6	66.35	4.06
Marshall et al., 2015[40]	1	0/1	47	1
Abe et al., 2016[13]	26	9/17	76	2.3
Di Stefano et al., 2016[16]	45	23/22	69.2	3.2
Ash et al., 2016[34]	33	15/18	65.3	4.2
Kim et al., 2016[22]	1	0/1	58	4
Magdalinou et al., 2018[25]	4	n/a	n/a	n/a
Mazzon et al., 2018[39]	1	1/0	74	1
Dodich et al., 2019[14]	33	15/18	70.4	3.06

n/a: not available.

Table 2. Profile of speech-language impairments, tests used for assessment, type of evaluation employed, and quality of studies included.

Authors, year of publication	Main speech/language results	Speech and language tests or abilities tested	Classification of the language evaluation	Quality of studies
Kertesz et al., 2000[9]	Initially, only word finding difficulties; verbal apraxia in 3/35 patients	WAB	Comprehensive assessment	High
Frattali et al., 2000[42]	Anomic, Broca's and transcortical motor aphasia	WAB (1st section)	Restricted assessment	Moderate
Graham et al., 2003[30]	Specific linguistic deficit involving phonologic processing	Letter fluency (FAS), semantic fluency, picture naming, word-picture matching, PPT, Single-word reading (The surface list), nonword reading, oral spelling, phoneme blending and phoneme segmentation	Restricted assessment	Moderate
Frattali et al., 2003[24]	Aphasia, without details	WAB (1st section)	Restricted assessment	Moderate
Gorno-Tempini et al., 2004[20]	nf-PPA	Motor speech evaluation, BDAE (verbal agility component, repetition), WAB (spontaneous speech section, written picture description, repetition, auditory word recognition, sequential command), BNT, PPT, CYCLE-R, PALPA (Regularity and Reading, Lexical Morphology and Grammatical Class, Homophone Decision), Gathercole and Baddeley's Non-Word Repetition task	Comprehensive assessment	High
McMonagle; Blair; Kertesz, 2006[7]	Majority classification of anomic aphasia (55%) in both groups (cognitive and motor onset), but more motor onset patients were normal and more cognitive onset patients had severe aphasias	WAB (1st section)	Restricted assessment	Moderate
McMillan et al., 2006[32]	Non-aphasic patients with CBD are significantly impaired in their comprehension of quantifiers	Sentence comprehension task	Restricted assessment	Moderate
Cotelli et al., 2006[29]	Action naming is impaired in FTD, PSP and CBS in comparison to object naming	Token Test, phonemic and semantic verbal fluency, action and object naming, Battery for Analysis of the Aphasic Deficits (action–object comprehension tasks)	Restricted assessment	Moderate
Cotelli et al., 2007[30]	CBS patients present with syntactic knowledge deficits	AAT (repetition, naming, writing and comprehension), BADA (sentence comprehension tasks)	Comprehensive assessment	Moderate
Donovan et al., 2007[23]	Aphasia, speech apraxia, alexia, agraphia, social language usage deficits	Pragmatic Protocol, Revised Token Test, WAB, BNT, Battery of Adult Reading Function, Woodcock Reading Mastery Tests, Comprehensive Test of Phonological Processing	Comprehensive assessment	High
Koenig et al., 2007[28]	CBS patients were impaired in similarity-based categorization process	Semantic decision task	Restricted assessment	Moderate
Silveri and Ciccarelli, 2007[31]	Hypofluent speech, agrammatism, anomia, word-finding difficulties, agraphia	Confrontation naming task of objects and verbs, semantic and phonemic fluency	Restricted assessment	Moderate

Continue...

Table 2. Continuation.

Authors, year of publication	Main speech/language results	Speech and language tests or abilities tested	Classification of the language evaluation	Quality of studies
Halpern et al., 2007[27]	CBS patients were less accurate and slower at judging smaller Arabic numeral dot array compared to FTD patients and controls	PPT	Restricted assessment	Moderate
Kim et al., 2008[45]	Language functions relatively preserved	BNT	Restricted assessment	Low
Shelley et al., 2009[12]	nf-PPA	n/a	No tests or language skills are mentioned	Low
Gross et al., 2010[24]	CBS patients have a higher-level deficit integrating described events into a coherent narrative	BNT, PPT	Restricted assessment	Moderate
Valverde et al., 2011[30]	Aphasic, without details	n/a	No tests or language skills are mentioned	Moderate
Borroni et al., 2011[42]	The AD-like group showed greater impairment of memory performances, language and psychomotor speed while the nAD-like group had more severe extrapyramidal syndrome	Semantic and phonemic verbal fluency, Token Test,	Restricted assessment	Moderate
Troiani et al., 2011[32]	CBS patients were significantly impaired in their judgments of quantified statements	Philadelphia Brief Assessment of Cognition (used to exclude aphasic patients), BNT, phonemic verbal fluency (FAS), Oral Sentence Comprehension Test, short sentence comprehension task	Restricted assessment	Moderate
Passov et al., 2011[36]	Mild apraxia of speech, mild hypokinetic dysarthria, apraxic agraphia	"Formal speech pathology evaluation"; picture description task; confrontation naming task; comprehension of simple and complex commands; writing; spelling; motor speech disorders	Comprehensive assessment	High
Dopper et al., 2011[41]	nonfluent speech with perseverations, word-finding difficulties and comprehension deficits, hypokinetic dysarthria	n/a	No tests or language skills are mentioned	Moderate
Caso et al., 2012[21]	nf-PPA, L-PPA	AAT, Token Test, phonemic and semantic verbal fluency	Comprehensive assessment	High
Assal et al., 2012[37]	crossed-PAOS followed by peripheral agraphia	Bachy 90-item battery (confrontation naming), MTL (auditory and written language comprehension, and writing), written descriptions of the Bank Robbery Picture, and the Cookie Theft Picture, and oral spelling with the French version of the WAIS III	Comprehensive assessment	Moderate
Mathew et al., 2012[4]	nf-PPA (60%) and anomic aphasia (40%)	n/a	No tests or language skills are mentioned	Moderate
Sakurai et al., 2013[38]	Progressive apraxic agraphia with micrographia, and acalculia	WAB, reading and writing test with 100 single-character kanji and kana transcription	Comprehensive assessment	Moderate

Continua...

Table 2. Continuation.

Authors, year of publication	Main speech/language results	Speech and language tests or abilities tested	Classification of the language evaluation	Quality of studies
Burrell et al., 2013[15]	Impaired single word repetition (61.5%), dysgraphia (58.3%), phonological errors in spontaneous speech (46.2%), impaired sentence repetition (38.5%), and word-finding difficulty (30.8%). Agrammatism and anomia were only occasionally identified. There was a trend for greater impairment of sentence repetition in PiB-positive cases	Motor speech disorder, phonological errors, agrammatism, word-finding difficulty, anomia, word and sentence repetition	Restricted assessment	Moderate
Turaga et al., 2013[33]	phonemic verbal fluency impairment	ACE-R (phonemic verbal fluency, semantic verbal fluency, naming)	Restricted assessment	Moderate
Marshall et al., 2015[40]	PAOS	n/a	No tests or language skills are mentioned	Moderate
Abe et al., 2016[13]	nf-PPA (34,61%)	Standard Language Test of Aphasia	Comprehensive assessment	High
Di Stefano et al., 2016[14]	Mixed progressive aphasia, including disorders of L-PPA (anomia, sentence repetition impairment) and S-PPA (deficits in single-word comprehension)	BDAE, picture naming test, single-word comprehension task, semantic and phonemic verbal fluency, sentence repetition test, assessment of motor speech disorders and agrammatism	Comprehensive assessment	High
Ash et al., 2016[34]	CBS were significantly impaired in the production of quantifiers	BNT, semantic verbal fluency, semi-structured speech sample (description of the Cookie Theft picture from the BDAE)	Restricted assessment	Moderate
Kim et al., 2016[22]	nf-PPA	WAB, BNT, semantic and phonemic verbal fluency	Comprehensive assessment	High
Magdalinou et al., 2018[25]	Impaired verbal fluency and sentence generation	BNT, Graded Naming Test, Verb Naming Task, PALPA (sentence comprehension), Sentence Production Program for Aphasia (expressive grammar), phonemic and semantic verbal fluency, National Adult Reading Test, sentence completion tasks	Restricted assessment	Moderate
Mazzon et al., 2018[39]	Apraxia of speech, characterized by slow overall speech rate, mild dysphonia, abnormal prosody, distorted and inconsistent speech sound substitutions, segmentation of syllables in words productions, mild dysgraphia with letter substitutions and omissions	Motor Speech Evaluation, AAT, Cookie Thief Test	Comprehensive assessment	High
Dodich et al., 2019[14]	nf-PPA, other language disorders	Connected speech production (speech apraxia and articulation difficulties, anomia, circumlocutions, agrammatism), CAGI battery (naming and word-picture matching), phonemic and semantic controlled associations, AAT (repetition), Token Test, BADA (sentence comprehension) phonemic (P-F-L) and semantic (animals-fruits-cars) verbal fluency	Comprehensive assessment	High

AAT: Aachen Aphasia Test; ACE-R: Addenbrooke's Cognitive Examination – revised; AD: Alzheimer's disease; BADA: Batteria per l'Analisi dei Deficit Afasici; BDAE: Boston Diagnostic Aphasia Examination; BNT: Boston Naming Test; CBD: corticobasal degeneration; CBS: Corticobasal syndrome; CYCLE-R: Curtiss-Yamada Comprehensive Language Evaluation-Receptive; FTD: frontotemporal degeneration; L-PPA: logopenic variant of primary progressive aphasia; MTL: Montreal-Toulouse Language Assessment Battery; n/a: not available; nAD: non-Alzheimer's disease; nf-PPA: Nonfluent variant of primary progressive aphasia; PALPA: Psycholinguistic Assessments of Language Processing in Aphasia; PAOS: Progressive apraxia of speech; PP: Pragmatic Protocol; PPA: primary progressive aphasia; PPT: Pyramids and Palm Trees; WAB: Western Aphasia Battery.

frequently used tests in the studies were the Western Aphasia Battery (WAB)[2,3,20,22,23,26,38,42,43] and the Boston Naming Test (BNT),[20,22-25,33,34,44,45] both mentioned by eight studies (22.85%). The Token Test[46] was used in five studies (14.28%)[14,21,23,29,47] and the Aachen Aphasia Test (AAT[48])[14,21,30,39] and Pyramids and Palm Trees (PPT)[20,24,27,49,50] featured in four articles (11.42%).

Regarding the type of evaluation employed in the studies, 13 (37.14%) used a comprehension speech/language assessment,[2,13,14,16,20-23,30,36-39] 17 (48.57%) used a restricted assessment,[3,15,24,29,31-34,42,45,47,50,51] while five (14.28%) failed to mention the tests or language skills evaluated.[4,12,35,40,41]

The assessment of methodological quality of the manuscripts is shown in Table 2. Ten studies (28.57%) were classified as "high quality",[2,13,14,16,20-23,36,39] 23 (65.71%) as "moderate quality",[3,4,15,24-35,37,38,40-42,47,50,51] and two (5.71%) as "low quality".[12,45]

GRADE CERQual analysis was carried out for three separate review findings: comprehensive language impairments, impairment in isolated language processing, and absence of language impairment. The overall CERQual assessment of confidence in the results was considered low for the first two review findings and very low for the last one (Table 3).

DISCUSSION

The purpose of the present literature review was to identify a possible language impairment profile in patients with CBS.

First, regarding the demographic and clinical characteristics of the sample, the mean age of patients was 65.31 years. The slight predominance of more women in studies is in line with the literature,[7] though some studies found no evidence of gender differences.[9,52,53] The sample size was relatively small, with a median value of 11 subjects. This may be explained by the rarity of the syndrome.

Regarding the language profile in CBS, many studies cited the nf-PPA phenotype as a common feature. This profile was found in 20% of the articles.[4,12-14,20-22] Although not a high rate, this phenotype appears to be the most common. Other studies cited a broad range of profiles, which are discussed below.

Frattali and colleagues[42] sought to characterize language profiles in 15 CBS patients. They were classified as having anomic aphasia, Broca's aphasia, or transcortical motor aphasia.

Another study with a similar objective, conducted by Graham,[50] detected language deficits mainly in phonological awareness, spelling and verbal fluency tests,

Table 3. Confidence in the Evidence from Reviews of Qualitative Research assessment of review findings.

Review findings	Studies contributing to the review finding	Methodological limitation	Relevance	Coherence	Adequacy of data	Overall CERQual assessment of confidence
Comprehensive language impairments (presence of aphasia)	2; 3; 4; 12; 13; 14; 15; 16; 20; 21; 22; 23; 35; 41; 42; 47; 50	minor methodological limitation (8 studies with moderate methodological quality and 1 study with low methodological quality)	moderate concerns about relevance (only 8 studies carried out a comprehensive language assessment)	moderate concerns about coherence (inconsistent data across studies regarding language outcomes)	substantial concerns about adequacy of data (6 studies are case reports or case series and 4 have up to 15 participants)	Low confidence
Impairments in isolated language processing	24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 36; 37; 38; 39; 40; 51	moderate methodological limitation (15 studies with moderate methodological quality)	moderate concerns about relevance (only 5 studies carried out a comprehensive language assessment)	moderate concerns about coherence (inconsistent data across studies regarding language outcomes)	substantial concerns about adequacy of data (7 studies are case reports or case series)	Low confidence
Absence of language impairments	45	substantial concerns (low methodological quality)	substantial concerns about relevance (restricted language assessment)	not applicable	substantial concerns about adequacy of data (case report)	Very low confidence

CERQual: Confidence in the Evidence from Reviews of Qualitative Research.

suggesting language impairments related to phonological processing.

Three studies that explored the relationship between clinical aspects and the underlying pathology found different language profiles. Borroni and colleagues[47] assessed 30 patients with CBS, divided into two groups according to results on cerebral spinal fluid (CSF) examination (suggestive of AD and not suggestive of AD). The probable AD group showed more significant impairment on tests of episodic memory and language comprehension, whereas the other group showed more severe extrapyramidal abnormalities. However, language assessment was restricted to a sentence comprehension test (Token Test) and verbal fluency tests.

Burrell and colleagues[15] assessed 14 CBS patients, divided into two groups according to the probable underlying pathology based on amyloid positron emission tomography (PET). The authors found language impairments in the following decreasing order of frequency: word repetition, dysgraphia, sound substitution in spontaneous speech, sentence repetition, and word-finding difficulties. The group with probable AD had a more marked problem on sentence repetition, a characteristic of L-PPA, whose underlying pathology is typically AD. The authors correlated difficulty in sentence repetition with a higher likelihood of AD being the underlying pathology.

In the study by Di Stefano and colleagues,[16] 45 CBS patients were assessed with a comprehensive language battery. Language impairment was the most prevalent cognitive deficit in the sample. Language deficits were found in the following tasks: phonemic and semantic verbal fluency, sentence repetition, and word comprehension. Patients with CSF biomarkers indicating probable AD as underlying pathology showed a positive correlation with Gerstmann syndrome, and the group without AD presented more severe language deficits, especially in picture naming and word comprehension. The authors suggested a mixed aphasia phenotype, including characteristics of L-PPA and the semantic variant of PPA (S-PPA).

The language heterogeneity in CBS was also illustrated in some case reports. Sakurai et al.[38] reported the case of a patient with CBS and apraxic agraphia and micrographia, without other language impairments, detected using a comprehensive language assessment.

Mazzon and colleagues[39] reported the case of a 74-year-old man, who evolved with language impairments, compatible with nf-PPA and apraxic agraphia.

Another case of apraxic agraphia was reported by Passov and colleagues.[36] In this case, apraxic agraphia was the onset symptom. The patient evolved with motor and speech disturbances (hypokinetic dysarthria and speech apraxia).

Assal and colleagues[37] reported the case of a patient with progressive apraxia of speech who evolved with peripheral agraphia and, subsequently, with characteristic CBS symptoms. Imaging scans disclosed hypometabolism and atrophy in the right hemisphere, confirming a case of crossed-apraxia of speech.

In summary, although the nf-PPA phenotype seems to be the most common language profile in CBS, it is possible to find characteristics of L-PPA as well as S-PPA. Other language characteristics, such as writing impairments, difficulty in comprehension and expression of quantifiers (words preceding nouns that convey quantity information), syntactic processing impairment, and deficits in narrative skills may also be present in CBS patients. A review of language in CBS also reported a wide array of language profiles.[6]

Regarding the tests used in the assessment of language impairments in CBS, WAB was the most utilized comprehensive language test in the studies reviewed.[2,3,20,22-3,26,38,42] WAB assesses the following linguistic abilities: speech content, fluency, auditory comprehension, repetition, naming, reading, and writing. It also includes the assessment of non-linguistic skills in its second part: apraxia, calculation, and constructional and visuospatial abilities. Three composite scores can be obtained from WAB: Aphasia Quotient (AQ), Language Quotient (LQ), and Cortical Quotient (CQ). AQ is derived from spontaneous speech, auditory verbal comprehension, repetition, and naming and word-finding tests. It is a widely used measure of aphasia severity. LQ includes, in addition to the abilities covered in AQ, reading and writing, and CQ is derived from the whole test.

A study[54] investigated the use of the revised version of WAB (WAB-R)[55] for detecting PPA subtypes. A total of 169 patients were included, with different PPA subtypes and progressive apraxia of speech (PAOS). On group comparisons, the AQ proved satisfactory for distinguishing PPA subtypes from PAOS. At the individual level, however, sensitivity for detecting aphasia proved low, as 20% of the PPA participants had AQ in the normal range. The authors concluded that, for PPA, WAB-R should be used together with other tests, including an assessment for motor speech disorders.

Another widely used test for language evaluation on CBS was the BNT, mentioned in eight studies.[20,22-25,33,34,45] BNT is a visual confrontation naming test that assesses lexical access and the semantic system.

In one[45] of the eight studies that used BNT, this test was used alone to evaluate language abilities. In other studies, BNT was used as part of a larger battery of language tests.

The Token Test, which was utilized in five studies,[14,21,23,29,47] also assesses a specific language ability,

i.e., verbal comprehension, including simple and complex sentences. Again, except for one study,[47] the others used the Token Test as part of a larger language battery.[14,21,23,29]

AAT, like WAB, is a comprehensive language assessment battery, initially developed in German. AAT includes the assessment of spontaneous language, verbal comprehension, repetition (words and phrases of increasing length), reading and writing, and naming abilities. The four studies that included this test were conducted in Italian universities, and used the Italian version.[14,21,30,39]

PPT is a semantic access test. It consists of pictures of objects presented in triads, in which the one on the top must be matched to one of two others (the distractor or the target picture), on the basis of some type of association, which varies across the triads. The distractor and the target pictures are always semantic coordinates. PPT comprises 52 triads. This test has the advantage of not requiring a verbal response, which is very useful to assess semantic knowledge in patients with severe aphasia or motor speech disorders.

PPT was part of a larger language battery in three of the four studies that utilized it.[20,24,50] In the survey conducted by Halpern et al.,[27] the language assessment, however, was based exclusively on the PPT score. Nevertheless, this study aimed to assess the semantic knowledge of numbers.

Regarding the type of evaluation used in the assessment of language impairments in CBS, results showed that just over a third of the studies included in this review performed a comprehensive assessment,[2,13,14,16,20-3,30,36-39] in strict compliance with recommended guidelines for assessing PPA.[17]

Of the studies performing a restricted assessment, some sought to analyze specific aspects of language. Frattali and colleagues[26] investigated the occurrence of yes/no reversal phenomenon in CBS; in other words, when a patient verbalizes or gestures "no" when meaning "yes", or vice versa. This error was found in almost half of the sample and was attributed to deficits in inhibitory control and mental flexibility.

Three studies by the same group[32-34] investigated comprehension and expression of quantifiers, showing that CBS patients had significantly worse performance in comprehension and expression of quantifiers compared to controls. In all of those three studies, patients were non-aphasic as inclusion criteria, and they were tested on only a few linguistic abilities.

Three other studies focused on verb and syntactic processing in CBS.[29-31] CBS patients had more significant impairment in processing verbs than nouns and in syntactic knowledge.

One study[28] investigated semantic memory processing in AD patients, comparing them with CBS patients. The task consisted of similarity-based and rule-based processes for teaching names of non-existent, but biologically plausible animals. CBS patients were impaired in both learning strategies, with disadvantages in the similarity-based processing, as they tended to focus on a single element of the picture.

The narrative skills of CBS patients were investigated by Gross et al.,[24] using a story-telling task based on a book of images. CBS patients displayed impaired discursive abilities, with deficits in organization and coherence, having difficulties integrating elements described into a coherent narrative. The formal aspects of language were not specified in the study.

Another study[25] was based on the notion that patients with CBS, PSP and Parkinson's disease (PD) have reduced verbal output and decreased ability to produce new information, in the absence of other language deficits, a condition referred to as "dynamic aphasia". The authors used tasks that involved generating new information in different situations with an increasing level of difficulty. All patients were impaired in producing sentences from a context and describing pictures.

Halpern et al.[27] compared the number knowledge of CBS patients with those with frontotemporal degeneration (FTD). Patients had to state whether a given Arabic numeral matched the number of black circles displayed on a screen. The stimuli were divided into "low numbers" (2–4) and "high numbers" (5–9). Patients with CBS had worse performance compared to the FTD group, particularly for low numbers, showing impairment in semantic knowledge of numeric values. The patients were described as non-aphasics.

Finally, this diversity of linguistic profiles in CBS is partly due to its clinical-pathological heterogeneity.[6] Some recent articles aimed to identify clinical characteristics indicative of the underlying pathology of CBS, including language characteristics. These articles may call attention to the importance of a comprehensive language assessment, since, in some of these studies, correlations were found between specific language deficits and the biomarker for AD, showing that the linguistic profile may be useful in the identification of the underlying pathology.

However, this review shows that there are still few studies that comprise a complete assessment of language. Moreover, part of the studies included in this review were case reports or studies with a small sample. A higher number of studies with comprehensive language

assessment are necessary to clarify the language profile of CBS patients.

The assessment of the methodological quality of the studies showed that less than a third were classified as "high quality".[2,13-14,16,20-23,36,39] Among the studies classified as "moderate quality",[3,4,15,24-35,37,38,40-42,47,50,51] the majority lost points on the item regarding outcome evaluation, which, here, refers to the language evaluation. This is in line with the classification of the type of evaluation discussed above.

The overall CERQual assessment of confidence in the outcomes of this review was considered low for the findings concerning comprehensive language impairments (presence of aphasia) and impairments in isolated language processing, and very low for the findings concerning absence of language impairments. This is mainly due to the adequacy of data. Fourteen studies were case reports or case series, and some included less than 15 patients. There were also concerns about relevance, as few studies carried out a comprehensive language assessment, and coherence, as the results regarding language were inconsistent across studies. Some studies had methodological limitations.

The main limitation of this review refers to the search, which was performed in only one database. A more exhaustive search would possibly result in more studies with comprehensive language assessment, that could help in delineating the language profile of CBS patients. One possible future direction for a primary study is a more detailed analysis of the motor speech disorders and their form of assessment in CBS. It is well documented that patients with CBS may present with dysarthria and/or apraxia of speech.

The results of the present review showed that the language impairments found in patients with CBS were heterogeneous. Concerning the language assessment, the most used tests for evaluation were WAB and BNT. Finally, most publications were based on restricted language assessments and had moderate methodological quality. Therefore, the data available in the relevant literature are insufficient to identify a single language profile in CBS patients.

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