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Clinical phenotypes associated to autopsy-proven corticobasal degeneration: 5 cases from the Portuguese Brain Bank and review of the literature

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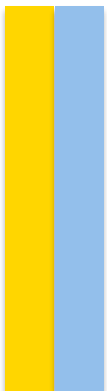

Clinical phenotypes associated to autopsy-proven corticobasal degeneration: 5 cases from the Portuguese Brain Bank and review of the literature

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Junho 2023

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Acknowledgments

I would like to express my sincere gratitude to all the patients and their families. Without their collaboration with the Portuguese Brain Bank this work would not be possible.

I extend my acknowledgment to the dedicated neurologists who diligently followed these patients over the years and meticulously gathered the essential information necessary for this research: Dr. Alexandre Mendes, Dr. Ana Paula Correia, Dr. Ernestina Santos, Dr. Marina Magalhães and Dr. Ricardo Taipa. Their tireless efforts in documenting and organizing the patient data have played a crucial role in the success of this work.

Lastly, I am sincerely thankful to my thesis advisor Dr. Ricardo Taipa for his valuable guidance and constant support throughout my research journey.

Resumo

Introdução

A degenerescência corticobasal (CBD) é uma doença neurodegenerativa rara e progressiva caracterizada pela predominância de depósito patológico de proteína tau em diferentes tipos celulares e regiões anatómicas do cérebro. Os primeiros relatos surgiram em meados da década de 1960 como uma "degenerescência corticodentatonigral com acromasia neuronal".[1,2] Vinte anos depois, Marsden e colaboradores introduziram o nome degenerescência corticobasal.[3]

Apesar de ser uma doença pouco estudada, desde as suas primeiras descrições ficou claro que não se tratava de uma única entidade clinicopatológica. A apresentação clínica de CBD inclui uma variedade de sintomas comportamentais, cognitivos e motores que se enquadram em diferentes fenótipos: síndrome corticobasal (CBS), afasia progressiva não fluente (NAV), demência frontotemporal variante comportamental (FBS) e síndrome de Richardson (PSPS). A maioria desses sintomas é semelhante a outras doenças neurodegenerativas, especialmente a síndrome corticobasal, que pode ser consequência de doença de Alzheimer, paralisia supranuclear progressiva, doença de Creutzfeldt-Jakob ou degenerescência lobar frontotemporal por TDP-43.[4]

Devido à variedade de entidades clínicas que se podem apresentar como CBD, a precisão do diagnóstico clínico é uma das mais baixas em comparação com outras doenças neurodegenerativas, prevendo apenas 25-56% dos casos por meio da aplicação de diretrizes clínicas. Essa diversidade de apresentações clínicas pode ser consequência das variações na localização da atrofia cerebral e da deposição de tau de 4 repetições. [4]

Embora já existam critérios clínicos para o diagnóstico de CBD, bem como para os fenótipos associados [5], é preciso o seu refinamento. Portanto, mais investigação é necessária para desenvolver ferramentas diagnósticas mais precisas para a CBD.

Objetivos

Com base na análise de cinco casos clínicos do Banco Português de Cérebros, esta tese tem como objetivo fornecer uma visão geral dos fenótipos clínicos associados à CBD comprovada por autópsia, juntamente com uma revisão detalhada da literatura existente. Dessa forma, pretende-se contribuir para um maior conhecimento clínico e patológico da doença e melhorar a acuidade diagnóstica e orientação terapêutica.

Métodos

Cinco casos de CBD patologicamente confirmados do Banco Português de Cérebros foram analisados retrospetivamente e avaliados quanto ao fenótipo clínico associado de acordo com os critérios de Armstrong. Em seguida, foi realizada uma revisão sistemática utilizando artigos em inglês publicados na base de dados Pubmed entre 2002 e 2022. Os termos de pesquisa incluíram "degenerescência corticobasal" e "fenótipos clínicos". Relatos de casos e séries pequenas e grandes de casos com CBD comprovada por autópsia foram selecionados e avaliados quanto ao fenótipo clínico específico. Artigos de revisão com dados patológicos extraíveis também foram incluídos.

Resultados

Dos cinco casos clínicos apresentados, dois cumpriam critérios para CBS, um para FBS, outro não preencheu os critérios para nenhum fenótipo. Um dos casos não tinha informações clínicas suficientes para estabelecer um fenótipo com segurança. Na revisão sistemática realizada, a CBS é o fenótipo clínico mais representado (24,2%), enquanto NAV foi o fenótipo menos representado (5,5%). Além disso, muitos casos foram incluídos no grupo "Outros" porque não atenderam aos critérios necessários para atribuir um fenótipo clínico (9,3%). A maior percentagem de casos pertence a casos sem informações clínicas suficientes (26,7%).

Conclusões

CBS foi o fenótipo clínico mais representado na nossa série, bem como na revisão realizada, portanto, confirmando que se trata da apresentação mais comum. NAV não estava presente na nossa série e foi o fenótipo clínico menos representado nos casos encontrados na literatura, o que o torna um fenótipo raro. Alguns casos não cumpriam critérios diagnóstico para nenhum dos fenótipos, sugerindo que haverá fenótipos a serem estabelecidos. Na maior parcela dos casos encontrados, as informações foram insuficientes para atribuir o fenótipo, o que implica melhores caracterizações clínicas, pesquisas e estudos.

Palavras-chave: degenerescência corticobasal; fenótipos clínicos; autópsia.

Abstract

Background

Corticobasal degeneration (CBD) is a rare and progressive neurodegenerative disease characterized by the predominance of pathological tau deposition in different cell types and anatomical brain regions. The first comprehensive reports emerged in the mid-1960s as a "corticodentatonigral degeneration with neuronal achromasia".[1,2] Twenty years later, Marsden and collaborators introduced the name Corticobasal Degeneration.[3]

Despite being a poorly studied disease, from its first descriptions it was clear that it was not a single clinicopathological entity. The clinical presentation of CBD includes a range of behavioural, cognitive and motor symptoms that fall into different phenotypes: corticobasal syndrome (CBS), progressive non-fluent aphasia (NAV), behavioural variant frontotemporal dementia (FBS) and Richardson syndrome (PSPS). Most of these symptoms are similar to other neurodegenerative diseases, especially corticobasal syndrome that can be the consequence of Alzheimer Disease, Progressive Supranuclear Palsy, Creutzfeldt-Jakob Disease or TDP-43 frontotemporal lobar degeneration. [4]

Due to the variety of clinical entities that can present as CBD, the clinical diagnostic accuracy is one of the lowest in comparison with other neurodegenerative diseases, predicting only 25-56% of cases through the application of clinical guidelines. This diversity of clinical presentations may be the consequence of the variances in the location of brain atrophy and 4-repeat-tau-pathology.[4]

Although there are already clinical criteria for the diagnosis of CBD as well as for the associated phenotypes[5], their refinement is needed. Therefore, further investigation is necessary to develop more accurate diagnostic tools for CBD.

Objectives

Based on the analysis of five CBD cases of the Portuguese Brain Bank, this thesis aims to provide an embracing overview of the clinical phenotypes associated with autopsy-proven CBD, along with a detailed review of the existing literature. In this way, it is intended to contribute to a greater clinical and pathological knowledge of the disease and to improve diagnostic accuracy and therapeutic management.

Methods

Five cases of pathologically confirmed CBD from the Portuguese Brain Bank were retrospectively analyzed and evaluated for the associated clinical phenotype according to Armstrong's criteria. Then, a systematic review using English Pubmed Database articles between 2002 and 2022. Search terms included “corticobasal degeneration” and “clinical phenotypes”. Case reports and short and large series of autopsy-proven corticobasal degeneration patients were selected and also evaluated for the specific clinical phenotype. Reviews with pathological extractable data were also included.

Results

Within the five presented clinical cases, two met criteria for CBS, 1 for FBS, another did not fulfill criteria for any phenotype and one did not have enough information for establishing a precise phenotype. In the carried out systematic review, Corticobasal Syndrome is the most represented clinical phenotype (24,2%), while NAV was the least represented phenotype (5,5%). Furthermore, many cases were included in the Others plot because they did not meet the criteria necessary for attributing a clinical phenotype (9,3%). The highest percentage of cases belongs to cases without sufficient clinical information. (26,7%).

Conclusions

CBS was the most represented clinical phenotype in our series as well as in the review carried out, confirming that is the most common presentation. NAV was not present in our series and it was the least represented clinical phenotype in the cases found in the literature, suggesting that is a rare phenotype. Some cases did not meet diagnostic criteria, so there will be phenotypes yet to be established. In most of the cases found, the information was insufficient to attribute the phenotype, which implies better clinical characterizations, searches and studies.

Keywords: corticobasal degeneration; clinical phenotypes; autopsy.

Abreviations list

AD - Alzheimer's Disease

CBS – Corticobasal Syndrome

CBD – Corticobasal Degeneration

FBS – Frontal-behavioural-spatial syndrome

FTD – Frontotemporal Dementia

NAV – Nonfluent/Agrammatic variant of primary progressive aphasia

PBB – Portuguese Brain Bank

PCA – Posterior Cortical Atrophy

PSP – Progressive supranuclear palsy

PSPS – Progressive supranuclear palsy syndrome

RP – Rapid global cognitive decline

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Table list

Background

CBD is a progressive neurodegenerative disease characterized by abnormal 4-repeat tau deposition in neurons and glial cells.[6] The first description of CBS was in 1925 when a 72-years-old carpenter presented with a clumsy useless arm with rigidity, ideomotor apraxia, abnormal flexed posture, "jerky"contractions, alien limb phenomenon and cortical parietal sensory disfunction.[7]

In the mid-60's, Rebeiz and colleagues introduced the term "corticonigral degeneration with neuronal achromasia" after describing three patients with slowly progressive clumsiness and a variety of assymetric extrapyramidal signs with few cognitive impairment.[1,2] Later, in 1989, Marsden and collaborators named this entity as "corticobasal degeneration for the first time".[3]

It´s consider a rare disease with an estimate incidence of less that 1 per 100 000 cases per year. The symptoms commonly start between the fifth to seventh decade of life, but the first features of the youngest case with a pathologic confirmation of CBD were reported at age 45. The gender distribution of the disease is not well defined, but some authors concluded a women predominance.[8]

In 2002, Dickson et al. established pathological criteria to identify CBD which included four key features: neuronal loss and gliosis (degeneration of neurons and the proliferation of glial cells particularly in cortex and basal ganglia); presence of protein tau in the form of neurofibrillary tangles; astrocytic plaques (clumps of abnormal protein tau that accumulate in astrocytes) and focal cortical atrophy.[9] The macroscopic, histopathological and immunohistochemical findings are presented in the following figures, from the Portuguese Brain Bank archive:

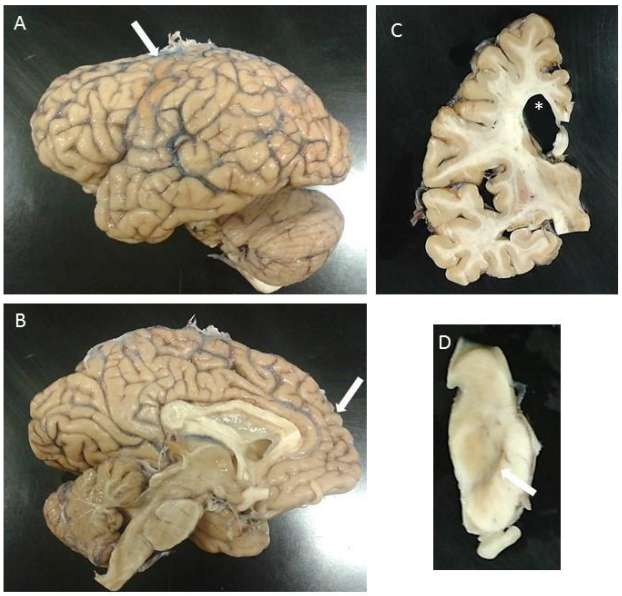


Fig.1 - Macroscopic findings of CBD-CBS. (A) Frontal cortical atrophy that extends to the premotor superior frontal gyrus (arrow). (B) Medial view of hemisphere showing superior frontal atrophy (arrow). (C) Coronal section showing enlargement of the frontal horn of the lateral ventricle (asterisk), thinning of the corpus callosum, atrophy of the superior frontal gyrus with preservation of the inferior frontal and temporal lobe structures. (D) Transverse section at the level of the superior colliculus showing pigment loss of the substantia nigra (arrow).

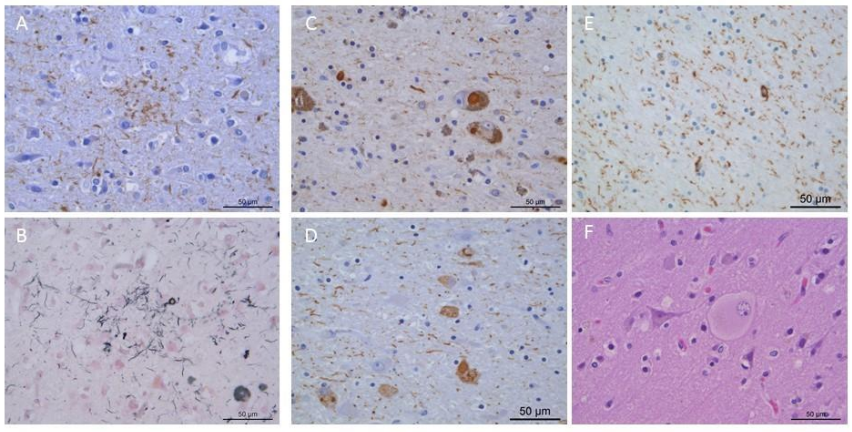


Fig.2 - Histopathology findings of CBD. (A and B) Typical astrocytic plaque characteristic of CBD. Neurofibrillary tangles and pre-tangles in substantia nigra (C) and subthalamic nucleus (D), some

densely packed into small inclusion body to some extent reminiscent of Pick bodies. (E) Dense neuropil threads in frontal white matter with oligodendroglial coiled bodies. (F) Ballooned neurons in motor frontal cortex, one of the histological hallmarks of CBD. A, C, D and E – Tau (AT8) immunohistochemistry; B –Gallyas silver stain; F – H&E stain

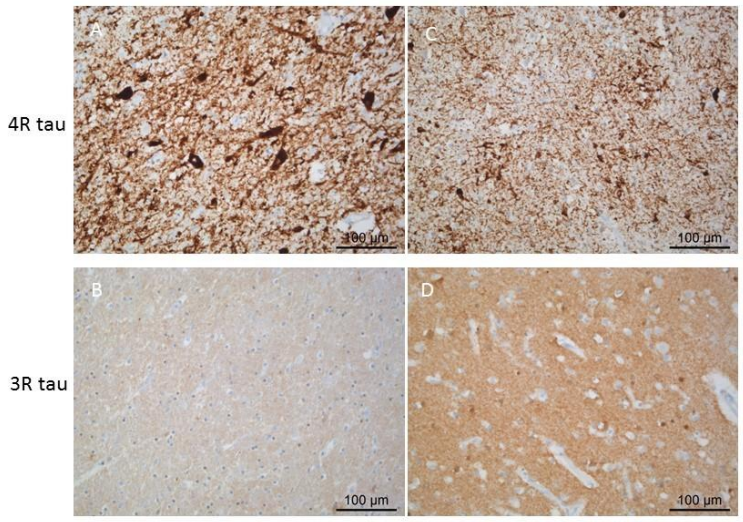


Fig.3 - Tau immunohistochemistry isoforms. The tau pathology is almost exclusively 4R. A and B, globus pallidus; C and D, frontal cortex.

Due do widely distributed neuronal loss and tau pathology in the brain, this disorder can present with a wide range of symptoms including: motor symptoms (for example limb rigidity, bradykinesia, postural instability, tremor, myoclonus) which are related to the damage that CBD causes to the basal ganglia; higher cortical symptoms (for example cognitive impairment, behavioural changes, cortical sensory loss, alien limb phenomenon), related with cortex involvement; and other features as abnormal eye movements, hyperreflexia or speech changes.[10]

Considering the clinical heterogeneity of the different phenotypes, the antemortem clinical diagnoses is difficult. There are some brain imaging tests findings described as supportive of the diagnosis, namely: asymmetric cortical atrophy on structural neuroimaging, asymmetric cortical or basal ganglia hypometabolism on PET imaging. [10]

In order to improve the accuracy of CBD diagnosis, Armstrong et al. developed a new set of criteria using pooled neuropathologically-proven cases to determine the clinical phenotype of CBD. In these criteria, they proposed categories of probable and possible CBD, trying to

differentiate the level of certainty of the disease. Additionally, they defined four clinical phenotypes based on clinical features: Corticobasal Syndrome (CBS), Frontal-behavioural-spatial (FBS), Nonfluent/agrammatic variant of primary progressive aphasia (NAV), Progressive supranuclear palsy syndrome (PSPS). [5]

The next table summarizes the clinical features required to meet criteria for clinical phenotypes of CBD according to Armstrong et al.

Table I – Diagnostic criteria of clinical phenotypes of CBD[5]

Clinical phenotypes of CBD	Clinical features
Probable CBS	Asymmetric presentation of 2 of: limb rigidity or akinesia; limb dystonia; limb myoclonus plus 2 of: Orobuccal or limb apraxia; cortical sensory deficit; alien limb phenomena
Possible CBS	May be symmetric. One of: limb rigidity or akinesia; limb dystonia; limb myoclonus plus 1 of Orobuccal or limb apraxia; cortical sensory deficit; alien limb phenomena
FBS	Two of: Executive dysfunction; Behavioural or personality changes; Visuospatial deficits
NAV	Effortful, agrammatic speech plus at least one of: Impaired grammar/sentence comprehension with relatively preserved single word comprehension; groping, distorted speech production (apraxia of speech)
PSPS	Three of: Axial or symmetric limb rigidity or akinesia; Postural instability or falls; Urinary incontinence; Behavioural changes; Supranuclear vertical gaze palsy or decreased velocity of vertical saccades

CBS is the most common phenotype for CBD pathology[11], but at the same time, can be the presentation of a patient with other underlying pathologies such as AD, PSP and FTD.[12]

Using clinical criteria, only 25-56% of cases of CBS is predicted antemortem.[4] Many patients who were diagnosed with CBS or clinical CBD ended up receiving another pathological diagnosis, most commonly AD and FTD.[13]

In order to develop more specific and accurate diagnostic tools, it is important to understand the pathophysiological mechanisms of the disease. Consequently, the autopsy plays a leading role, not only in the definitive diagnoses, but also in the examination of the specific cells and brain regions affected.

Based on the analysis of five CBD cases of the Portuguese Brain Bank and a detailed review of the existing literature, this thesis aims to provide an embracing overview of the clinical phenotypes associated with autopsy-proven CBD. In this way, it is intended to contribute to a greater clinical and pathological knowledge of the disease and to improve diagnostic accuracy and therapeutic management.

Methods

Cases from the Portuguese Brain Bank with pathological diagnoses of CBD were collected and their demographic and clinical data were obtained. The study captured clinical features of patients in two different time points – at the initial presentation and at any point during the course of the disease. Initial presentation was considered in the first three years after the symptoms onset. It was consider an absent clinical feature if it was not explicitly described in the files. To calculate the percentage frequencies, the documented presence or absence of each feature was added together in Table III, similar to the methodology used by Armstrong et al. The criteria for CBD phenotypes was applied to each patient considering the initial presentation (Tables IV-VII). One patient has been previously described (Case 5)[14].

Additionally, a systematic literature search using Pubmed database identified English-language articles (2002 to 2022). The year of 2002 was decided to capture case reports and case series after the publication of the pathological criteria for CBD. Search terms included "corticobasal degeneration" and "clinical phenotypes". Case reports, short and large series of autopsy-proven corticobasal degeneration patients were selected. Reviews with pathological extractable data were also included. All retrospective clinical studies of pathologically confirmed cases were collected and the frequency of each specific clinical phenotype was assessed. Repeated cases were excluded.

Results

In the retrospective evaluation of the 110 cases of the PBB, CBD was identified in 5 individuals (4,55%). Demographic and clinical data are summarized in Table II. The female-to-male ratio in our cohort is 3:2. The age at disease onset ranges from 49 to 76 years, with a mean of approximately 61.4 years. The age of death ranges from 53 to 81 years, with a mean of approximately 65,8 years and the disease duration varies from 3 to 6 years, with a mean of approximately 4.4 years. The clinical diagnoses include FTD, CBS, probable CBS, probable PSP, and autoimmune encephalitis.

Table II - Overview of demographic data and clinical diagnosis of our cohort cases

	Sex (M/F)	Age at disease onset (years)	Age of death (years)	Disease duration (years)	Clinical Diagnosis
Case 1.	M	64	70	6	FTD
Case 2.	F	76	81	5	CBS
Case 3.	F	67	71	4	Probable CBS
Case 4.	F	49	53	4	Probable PSP
Case 5.	M	51	54	3	Autoimmune Encephalitis

In the following section a brief clinical vignette of each case is described. Clinical data are also summarized in the appendix table IA.

Clinical Cases

Case 1.

A 65-years-old man presented with a one year history of progressive behavioural changes including marked irritability, apathy, coprolalia, social disinhibition, obsessive conduct and change in the diet patterns with greater preference for sweets. The patient had no insight to the behaviour changes and neurology examination was normal except for the presence of a right palmar grasp reflex. The neuropsychological study showed predominant executive dysfunction and the MRI study showed cortical atrophy with a slight bilateral frontotemporal/perisylvian predominance, which also involved the hippocampus bilaterally. The CSF biomarkers for Alzheimer's pathophysiology were negative. The patient’s symptoms rapidly progressed with hyperphagia and marked apathy with aggressive periods. There was no evidence of oculomotor dysfunction, extrapyramidal signs or corticobasal syndrome. He died at 70 with a pneumonia. The clinical diagnosis was of behaviour variant of Frontotemporal Dementia.

Case 2.

A 81-years-old woman with history of hypertension, dyslipidaemia, thyroidectomy and a depressive syndrome presented with a five-year history of left hand tremor, predominantly at rest, associated with slowed movements and the perception that his hand moved by itself. She was on venlafaxine for the depressive syndrome. There was a positive family history of

Parkinson´s disease noticed in her mother and sister. On her first examination, the patient had no signs of cognitive dysfunction. There was a left-hand tremor, irregular, presented in rest, posture and action, associated with rigidity, myoclonus and movement apraxia. No evidence of agraphesthesia or astereognosis. She was medicated with levodopa with no improvement. One year later she developed agraphestesia, astereognosia and slight bilateral rigidity. The symptoms progressed and started to involve the right hand, causing apraxia and dystonia, together with cognitive decline. The patient became more hypomymic, bradykinetic, hypophonic with rigidity in the upper limbs and gait instability. A few months later, she became speechless and dependent of others, with no capacity to walk. There were no hallucinations, constipation, urinary changes or sleep changes suggestive of REM behaviour disorder (RBD). The MRI revealed brain atrophy with predominance in the parietal regions, particular post-central gyri involved symmetrically, as well as multiple subcortical hyperintensities suggestive of old ischemic lesions. A study for the C9orf72 gene did not show pathological expansions. The clinical diagnosis was of a CBS.

Case 3.

A 71-years-old woman presented with a four-year gait instability and ideomotor apraxia, predominantly on the left. The symptoms progressed, becoming unable to walk and to use the upper limbs. At the neurological examination, the patient revealed right palmar grasping, buccofacial and upper limb apraxia, worse on the left, left alien limb phenomenon, astereognosis and bilateral agraphesthesia. Furthermore, the upper limbs presented a myoclonic tremor, osteotendinous reflexes were brisk and there was severe impairment of the postural reflexes. The gait was impossible without support (flexed posture, wide base, small steps). There was no dysarthria, oculomotor abnormalities or motor deficits. There was no language or other major cognitive changes. She was medicated with levodopa without improvement. The MRI study was normal and a DaT Scan (Ioflupane - 123I) study revealed bilateral presynaptic degeneration. The clinical diagnosis was of a CBS.

Case 4.

A 49-years-old woman, with history of alcohol abuse, was admitted in a psychiatric hospital due to progressive behavioural and speech changes, with severe cognitive decline. In the following three years there was a description of blefarospasm and rapidly progress of the symptoms, becoming dependent for basic activities such to eat without assistance.

At 52 years-old the neurological examination revealed severe dementia with marked apathy, without verbal or motor initiative, pre-tarsal blepharospasm, a supranuclear ophthalmoparesis, a left palmomentonian reflex and a bilateral palmar grasping. There was a mixed of rigidity,

paratonia and global bradykinesia. The gait was possible without support, with flexed posture, small steps and difficulties in turnings. No tremor or ataxia. She was treated with levodopa and botulin toxin but without improvement.

The MRI showed diffuse cerebral atrophy with frontal and temporal polar predominance. The blood and cerebrospinal fluid analysis were normal. The EEG revealed slow activity in the frontotemporal region. The genetic test, including MAPT, C9orf72 and progranulin, was negative.

The clinical diagnosis was of a neurodegenerative condition under the umbrella of Pick´s complex, probably a PSP.

Case 5.

A 51-years-old man presented in neurology appointment with 6-month history of diplopia, eyelid ptosis and dysphagia with progressive worsening. Furthermore, the patient developed cognitive dysfunction and slowed movements. Examinations were performed to exclude myasthenic syndromes. Due to a positive result of anti-PNMA2 (Ma2/Ta) antibodies and a T2 hyperintensity involving the midbrain and pons, the diagnosis of immune-mediated brainstem encephalitis was considered. The patient was treated with immunoglobulins and plasmapheresis with no results. One year later, the patient developed horizontal and vertical gaze limitation and an akinetic/rigid parkinsonian syndrome with axial predominance, disinhibited behaviour and speech "stuttering". He became fully dependent at age 53 and died at 54 years old with a sepsis due to a pneumonia.

The following table summarizes the clinical features at presentation and during the entire course of the disease. The larger cohort of patients from Armstrong et al. study[3] that led to the criteria for the diagnosis of corticobasal degeneration is represented for comparison.

Table III - Frequency of individual clinical features in our patient cohort compared with the data of Armstrong et al.[5]

Feature	At presentation, n (%)		During entire course, n (%)	
	PBB cohort	Armstrong	PBB cohort	Armstrong
Motor features				
Limb rigidity	3/5 (60)	65/114 (57)	4/5 (80)	153/180 (85)
Bradykinesia/clumsy limb	2/5 (40)	53/111 (48)	3/5 (60)	126/165 (76)
Postural instability	1/5 (20)	20/49 (41)	2/5 (40)	73/94 (78)
Falls	1/5 (20)	27/76 (36)	1/5 (20)	83/111 (75)
Abnormal Gait	1/5 (20)	30/92 (33)	2/5 (40)	102/140 (73)
Axial Rigidity	1/5 (20)	18/67 (27)	2/5 (40)	68/98 (69)
Tremor	1/5 (20)	17/83 (20)	1/5 (20)	50/127 (39)
Limb dystonia	1/5 (20)	18/91 (20)	3/5 (60)	47/123 (38)
Myoclonus	2/5 (40)	14/94 (15)	2/5 (40)	34/128 (28)
Higher cortical features				
Cognitive impairment (general)	4/5 (80)	59/114 (52)	4/5 (80)	123/175 (70)
Behavioural changes	3/5 (60)	52/113 (46)	3/5 (60)	82/150 (55)
Limb apraxia	2/5 (40)	46/102 (45)	2/5 (40)	81/142 (57)
Aphasia	0/5 (0)	40/101 (40)	1/5 (20)	80/155 (52)
Depression	1/5 (20)	21/80 (26)	1/5 (20)	42/82 (51)
Cortical sensory loss	2/5 (40)	20/81 (25)	2/5 (40)	29/107 (27)
Alien limb	2/5 (40)	20/90 (22)	2/5 (40)	24/81 (30)
Others				
Abnormal eye movements	1/5 (20)	29/88 (33)	2/5 (40)	90/150 (60)
Hyperreflexia	1/5 (20)	17/57 (30)	3/5 (60)	58/116 (50)
Speech changes	1/5 (20)	18/77 (23)	2/5 (40)	59/112 (53)

At presentation, the most common motor feature was limb rigidity (60%), followed by bradykinesia/clumsy limb (40%) and myoclonus (40%). During the entire course of the disease, limb rigidity remained the most frequent motor symptom (80%), followed by bradykinesia/clumsy limb (60%) and limb dystonia (60%). Postural instability, abnormal gait, axial rigidity and myoclonus (40%) were also common motor features during the entire course of the disease.

Regarding higher cortical features, cognitive impairment was the most common at presentation (80%), followed by behavioural changes (60%). During the disease course, those symptoms were also the most frequent ones.

In these following tables, the diagnostic criteria for each clinical phenotype were applied to the cases. Two cases comprise criteria for CBS and one case for FBS. Two cases did not meet criteria for any phenotype considered in Armstrong et al. diagnostic criteria.

Table IV – CBS phenotype criteria application in our cohort

	Case 1	Case 2	Case 3	Case 4	Case 5
Limb rigidity or akinesia	-	+	+	-	+
Lymb distonia	-	+	+	-	-
Limb myoclonus	-	+	+	-	-
Apraxia (orobuccal or limb)	-	+	+	-	-
Cortical sensory deficit	-	+	+	-	-
Alien Limb Phenomenon	-	+	+	-	-
CBS syndrome	No	Probable CBS	Probable CBS	No	No

Table V – PSPS phenotype criteria application in our cohort

At least 3 of:	Case 1	Case 2	Case 3	Case 4	Case 5
Axial or symmetric limb rigidity or akinesia	-	-	+	-	-
Postural instability or falls	-	+	+	-	-
Urinary incontinence	-	-	-	-	-
Behavioural changes	+	-	-	+	+
Supranuclear vertical gaze palsy or decreased velocity of vertical saccades	-	-	-	-	+
PSP syndrome	No	No	No	No	No

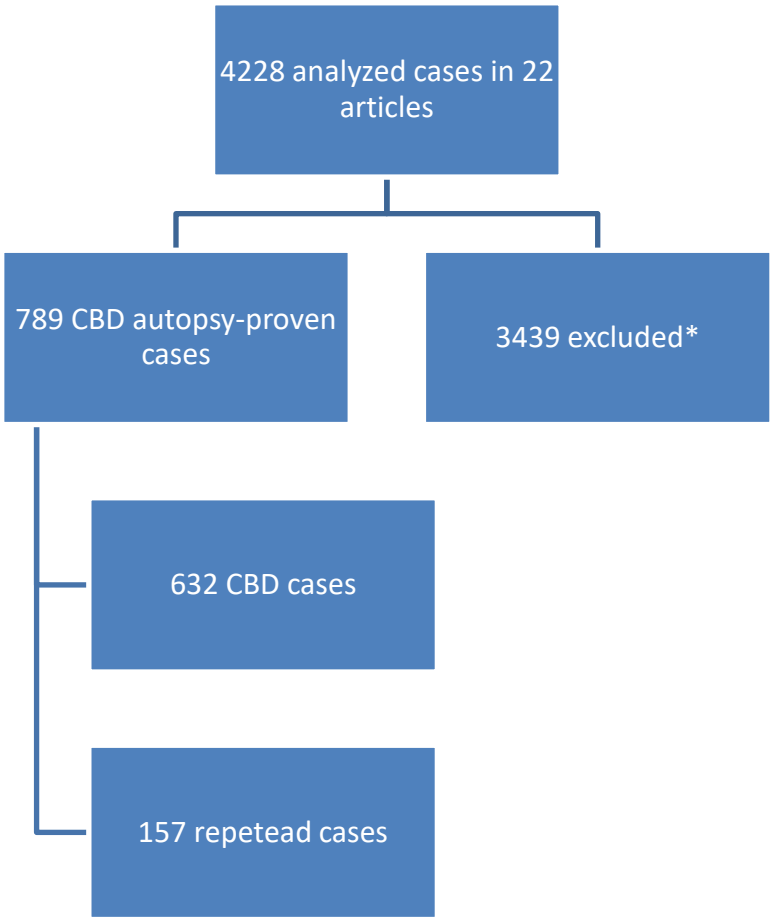
Table VI – FBS phenotype criteria application in our cohort

At least 2 of:	Case 1	Case 2	Case 3	Case 4	Case 5
Executive dysfunction	+	+	+	-	-
Behavioural or personality changes	+	-	-	+	+
Visuospatial deficits	-	-	-	-	-
Frontal behavioural-spatial syndrome	Yes	No	No	No	No

Table VII – NAV phenotype criteria application in our cohort

	Case 1	Case 2	Case 3	Case 4	Case 5
Effortful, agramatic speech	-	-	-	-	-
Impaired grammar/sentence comprehension with relatively spared single word comprehension	-	-	-	-	-
Groping, distorted speech production (apraxia of speech)	-	-	-	-	-
Nonfluent/agrammatic variant of primary progressive aphasia	No	No	No	No	No

In order to analyze the phenotypic variation of CBD, the clinical cases reviewed were grouped together with the clinical cases from the Portuguese Brain Bank, after framing the associated clinical phenotype. A final number of 632 autopsy proven CBD cases published in the period considered for this review were analyzed.



*Other pathologies or no autopsy-proven CBD cases

Table VIII - Frequency of clinical CBD phenotypes in retrospective clinical studies of pathologically confirmed cases

	Cases	CBS	PSPS	NAV	FBS	Overlap	Others*	No details**
Armstrong et al.[5]	267	78	49	10	29	12	32	57
Helen Ling et al.[15]	124	25	16	13	20	18	11	21
Alexander S.K[13]	19	10	1	2	4	0	2	0
Naoki Nishida et al.[4]	3	0	0	0	1	0	2	0
Rana A. Eser et al.[16]	10	0	0	0	0	0	0	10
Mark S. Forman et al.[17]	12	0	0	0	0	0	0	12
Katherine P. Rankin et al.[18]	17	5	2	4	5	0	1	0
Julie S. Snowden et al.[19]	10	6	0	0	4	0	0	0
Naomi Kouri et al.[20]	108	21	41	0	0	0	0	46
Jonathan Vöglein et al.[21]	20	0	0	0	0	0	0	20
Gregory S. Day et al.[22]	17	2	0	3	3	0	9	0
Albert Lladó et al.[23]	8	0	0	2	3	0	0	3
Mar Guasp et al.[24]	8	4	0	0	0	4	0	0
PBB	5	2	0	0	1	0	1	1
Case Reports								
Ece Bayram et al.[11]	2	0	2	0	0	0	0	0
Hans H. Jung et al.[25]	2	1	1	0	0	0	0	0
Chun-Feng Tan et al.[26]	2	0	0	0	1	1	0	0
Kurt A. Jellinger et al.[27]	1	0	0	0	0	0	1	0
Yasushi Iwasaki et al.[28]	1	0	0	0	1	0	0	0
Shinsuke Fujioka et al.[29]	1	0	0	1	0	0	0	0
Total	637	154	112	35	72	35	59	170
Total (%)	100,0%	24,2%	17,6%	5,5%	11,3%	5,5%	9,3%	26,7%

*Including Rapid Progressive (RP), Posterior Cortical Atrophy (PCA), Motor Predominance Disease, Alzheimer disease (AD) dementia–like syndrome, Parkinson Disease, Multiple Esclerosis and Unclassified Cases; ** no clinical details available

Discussion

Since the establishment of the pathological criteria for CBD, we were able to identify 22 papers with autopsy proven CBD cases. Altogether, 632 patients were described, including case reports, small and large series. The larger series published has 267 patients.

Age at onset

In our study, the age at disease onset ranged from 49 to 76 years, with a mean of approximately 61,4 years. This is consistent with previous reports in the literature: Armstrong et.al reported a mean symptom onset of 63.7 years and an age at onset that ranged from 45 to 77.2 years[5].

Disease duration

In terms of duration of the disease, in our cohort the mean was 4.4 years, slightly less time than the reported average. In Armstrong study, mean CBD disease duration was 6.6 years[5]. We had a case with 3 years of disease duration which is rare, being described in the literature as a rapid progressive CBD (RP-CBD)[14]. This phenotype may represent a distinct aggressive variant of CBD with characteristic neuropathological substrates resulting in a fulminant disease process as evident both clinically and pathologically[14]. On the other side and supporting our study, Alexander SK et al. in their research of validation of the Armstrong criteria, noted a 4 years mean disease in a pool of 19 patients[13]. In both cases in which the duration of disease was shorter, the number of patients involved was significantly lower, which may indicate compromised external validity. It is important to note that disease duration can also depend on the specific CBD phenotype and the individual patient's characteristics, such as age at onset and rate of disease progression. These results reinforce that CBD is a relatively rapid progressive neurodegenerative disorder.

Clinical Features

Comparing clinical features of our cohort to the described by Armstrong et al., there is some overlap, as both studies report limb rigidity and cognitive impairment as the most common features of CBD. Six motor symptoms showed an increasing appearance during the course of the disease in the PBB cohort: limb rigidity, bradykinesia/clumsy limb, postural instability, abnormal gait, axial rigidity, and limb dystonia and only one cortical higher symptom showed that increase during the course of the disease in the PBB cohort: aphasia.

These findings support that motor symptoms tended to appear over the course of the disease, while the higher cortical symptoms such as cognitive impairment, behavioural changes, limb

apraxia, cortical sensory loss and alien limb if not present at the beginning it is infrequent their development during the disease course.

Clinical Phenotypes

Based on our cohort of 5 patients with CBD, 2 of them have criteria for CBS, 1 have criteria for FBS, 1 does not fit in either phenotype and 1 there was not enough information to classify with certainty. This suggests that even within this relatively rare and well-defined proposed diagnostic criteria of CBD, there may be significant heterogeneity in clinical presentation and subtypes. According to the table VIII, CBS is identified as the most common phenotype in the larger studies (Armstrong et al., Helen Ling et al)[5,15], being also the most common phenotype accounting for all cases analyzed (24,2%). In our cohort, CBS was the most represented clinical phenotype, in accordance with the existing literature. Despite the most common phenotype associated to CBD, it is known that CBS can occur in many diseases in addition to CBD, so the definitive diagnosis becomes uncertain.

Although being a very representative clinical phenotype in Armstrong et al. study[5] with such a large sample, none of the presented patients met criteria for PSPS. It was the second most common clinical phenotype found in our review of the pool of cases (17,6%). A few patients presented with clinical features associated with PSPS phenotype but did not meet the diagnostic criteria. However, we cannot exclude that patient four from our cohort, who had supranuclear vertical gaze palsy on examination, could meet those diagnostic criteria if fully clinical details were available for analysis regarding the first years of the disease.

FBS was the clinical phenotype presented by one of the patients involved in our cohort. Within our reviewed cases from the literature, FBS was the third most commonly encountered clinical phenotype (11,3%). Interestingly, our case did not develop during disease progression motor features commonly associated to CBD.

In general, NAV was the least frequent phenotype (5,5%). For instance, only 10 out of 267 cases in the study by Armstrong et al.[5] and only 13 out of 124 patients in the study by Helen Ling et al. satisfied the criteria for NAV[15], respectively. In our cohort, none of the patients met criteria for NAV. This may be because NAV is a relatively rare clinical phenotype in CBD.

The table VIII shows an overlap between the various clinical phenotypes of CBD in a few investigations. For example, in the study of Armstrong et al., 12 cases met criteria for more than one clinical phenotype[5] and Helen Ling et al. identify 18 overlap cases[15]. Although, none of the patients of our cohort met criteria for more than one phenotype. These findings suggest that

overlap between clinical phenotypes exists in CBD and highlights the need for a more rigorous approach to diagnosis.

One of the cases did not meet criteria for any clinical phenotype associated with CBD. Although this case presented with some common symptoms as limb rigidity and bradykinesia, cognitive dysfunction, and supranuclear ophthalmoplegia, the patient revealed different features that are not included in Armstrong criteria like diplopia, eyelid ptosis, and dysphagia. These findings suggest that there may be additional clinical phenotypes associated with CBD that have yet to be fully characterized in the literature.

There is a lack of clinical information available for 170 patients, making it difficult to assign them to a specific phenotype or category based on their symptoms or characteristics. Gathering more information about these 170 patients through further investigation and retrospective studies would allow us to identify patterns or associations that could lead to improved diagnosis, treatment, and management of the disease.

This work has limitations, namely the small number of cases and retrospective nature of the clinical information collected. The fact that we consider a clinical feature absent if not explicit, takes the risk of underestimating each feature. For example, case 4, where clinical information regarding the first 3 years of the disease is very scarce, did not allow classifying in any of the phenotypes.

Conclusion

CBD is a neurodegenerative disorder with a variable disease course, with some patients experiencing a rapid and fulminant progression, while others have a more slowly progressive disease course. Furthermore, this pathology can have many clinical presentations.

In summary, this work highlights the significant variability in clinical presentation and subtypes of CBD, even within well-defined diagnostic criteria. Our cohort including at least one patient that dit not fit into recognized CBD phenotypes. This observation suggests that CBD's clinical presentation may be even more heterogeneous and complex, making it challenging to make definitive diagnoses.

The findings also showed that CBS was the most common clinical phenotype, followed by PSPS and FBS. The NAV presentation seems to be rare. However, there is an overlap between clinical phenotypes in CBD, which is common and emphasizes the need for a more rigorous approach to diagnosis. Therefore, it is critical to obtain a comprehensive clinical assessment and conduct further investigations to ensure accurate diagnosis.

Future research should aim to better understand the various clinical subtypes of CBD and their associated features to improve diagnostic accuracy and optimize management approaches. Additionally, neurobiological basis of different clinical presentations and progression will be important to understand pathophysiology, develop treatment and monitoring treatment response.

Appendix

Table IA - Summary of the clinical data of the five Portuguese Brain Bank cases

	Clinical Diagnosis	First symptoms (within the first three years of onset)	Other symptoms/signs Symptoms/signs in disease progression	Others and negative symptoms/signs
Case 1	Frontotemporal dementia	Behavioural and personality change; executive cognitive dysfunction	Palmar grasp reflex	No parkinsonism; no other features suggestive of CBS; No dysautonomia, hallucinations or RBD; normal ocular movements
Case 2	Corticobasal syndrome	Asymmetrical parkinsonism, left limb apraxia, agraphestesia, astereognosis, myoclonus	Cognitive disfunction with predominant non-fluent aphasia, limb dystonia, parkinsonian gait	No dysautonomia, hallucinations or RBD; normal ocular movements
Case 3	Corticobasal syndrome	left limb apraxia, alien limb and dystonia, right agraphesthesia and astereognosis, myoclonus, gait instability	Orobuccal apraxia, bilateral agraphesthesia and astereognosis, right palmar grasping, dysphagia, left Babinski sign and impairment of postural reflexes	No dysautonomia, hallucinations or RBD; normal ocular movements
Case 4	Progressive Supranuclear Palsy	Behavioural and speech changes, cognitive deterioration	Severe cognitive deterioration, severe apathy, supranuclear ophthalmoparesis, palmar grasping, left palmomental reflex, brisk reflexes, parkinsonism	No dysautonomia, hallucinations or RBD
Case 5	Autoimmune Rhomboencephalitis	Diplopia, eyelid ptosis, dysphagia, dysarthria, apathy; 6 months later: supranuclear ophthalmoplegia, cognitive decline, asymmetric right predominant akinetic-rigid parkinsonism	Echolalia, complete bilateral ptosis, severe ophthalmoplegia (abducted left eye on primary gaze and no right eye movement).	No dysautonomia, hallucinations or RBD

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