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Corticobasal syndrome in Alzheimer's Disease: description of a pathological proven clinical case and review of the literature

Ana Sofia Santos Martins

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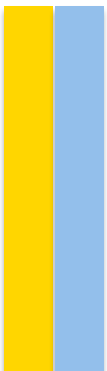

Corticobasal syndrome in Alzheimer´s Disease: description of a pathological proven clinical case and review of the literature

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Declaração da Integridade Científica

Eu, Ana Sofia Santos Martins, declaro solenemente que esta dissertação, intitulada "Corticobasal syndrome in Alzheimer´s Disease: description of a pathological proven clinical case and review of the literature", é um trabalho original e genuíno. Durante o seu processo de elaboração, segui estritamente os princípios éticos e as normas académicas estabelecidas pela comunidade científica. Assumo total responsabilidade pelo conteúdo desta dissertação e estou ciente das possíveis consequências de qualquer violação dos princípios de integridade científica.

Agradecimentos

Ao Professor Ricardo Taipa, pela sua inteira disponibilidade ao longo da redação deste trabalho e por toda a orientação e apoio prestados.

Aos meus pais, que sempre acreditaram em mim com uma confiança inabalável, e que sempre me dão coragem nos momentos mais difíceis. São e sempre serão a minha casa.

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Ao Dani, que trouxe um brilho especial à minha vida e me inspira todos os dias a ser melhor.

Resumo

Introdução: A Doença de Alzheimer (DA) constitui a forma mais prevalente de demência, manifestando-se principalmente por uma perturbação da memória episódica, frequentemente acompanhada por défices das capacidades visuo-espaciais e das funções executivas. Por outro lado, a Síndrome Corticobasal (SCB) é uma entidade clínica pouco comum, caracterizada por uma constelação de sinais e sintomas corticais e extrapiramidais, potencialmente decorrentes de múltiplas neuropatologias subjacentes. Relatamos o caso de um doente com diagnóstico neuropatológico confirmado de DA com fenótipo de SCB. Além disso, fazemos uma revisão concisa da literatura atual sobre este tema, abordando possíveis indicadores que poderão ajudar a diferenciar as várias neuropatologias subjacentes à SCB.

Material e Métodos: O caso clínico foi recolhido do Banco Português de Cérebros (BPC) e a informação clínica do doente foi obtida através do arquivo do BPC e dos registos das consultas realizadas pelo médico assistente do doente e orientador desta Tese de Mestrado. Foi obtida autorização do doente para a utilização dos tecidos e dados clínicos associados. Adicionalmente, foi efetuada uma revisão narrativa, não sistemática, da literatura publicada sobre esta variante atípica da Doença de Alzheimer, a qual foi identificada através de uma pesquisa na PubMed utilizando as seguintes palavras-chave: Alzheimer's Disease, Corticobasal Syndrome e Neuropathology. Não foram colocadas restrições quanto ao tipo de artigo e à data de publicação. As referências bibliográficas dos artigos selecionados foram também revistas de forma a garantir a integridade da informação recolhida para a revisão narrativa.

Conclusão: O diagnóstico exato da DA associada à SCB só tem sido possível através de uma análise neuropatológica post-mortem. É extremamente importante incentivar novos estudos com um maior número de casos clínicos desta variante rara, de modo a detetar indicadores que possam prever esta doença em vida. Ao longo desta revisão, foram registados alguns achados clínicos fortemente associados à DA, incluindo a presença de sinais piramidais numa fase inicial e a manifestação de mioclonias, perturbação da memória episódica e dificuldades visuo-espaciais durante o curso da doença. Assim, espera-se que, no futuro, sejam investigados e estabelecidos mais parâmetros clínicos, juntamente com biomarcadores de imagem e do líquido cefalorraquidiano, capazes de prever a patologia subjacente.

Palavras-chave**:**

Doença de Alzheimer – Síndrome Corticobasal – Neuropatologia – Biomarcadores

Abstract

Introduction: Alzheimer's disease (AD) represents the most prevalent form of dementia, primarily manifesting as episodic memory impairment, often accompanied by deficits in visuospatial abilities and executive function. Conversely, Corticobasal Syndrome (CBS) is an uncommon clinical entity characterized by a constellation of cortical and extrapyramidal signs and symptoms, potentially arising from multiple underlying neuropathologies. We report a case of a patient with a neuropatologically-proven diagnosis of AD, presenting with a CBS phenotype. Furthermore, we provide a concise review of the current literature on this subject, adressing possible indicators that could help differentiate the various neuropathologies underlying CBS.

Materials and Methods: The case report was sourced from the Portuguese Brain Bank (PBB), and pertinent clinical information was obtained from the PBB archive, medical appointment's records of the patient's attending physician and supervisor of this Master's Thesis. Permission for research use of tissue and associated clinical data was obtained from PBB patients. Additionally, we conducted a narrative, non-systematic review of the published literature on this atypical variant of AD, which was identified through a PubMed search using the keywords: Alzheimer's Disease, Corticobasal Syndrome, and Neuropathology. No restrictions were placed on the type of article and the date of publication. The bibliographical references of the selected articles were also reviewed in order to guarantee the information gathered for the narrative review was comprehensive.

Conclusion: An accurate diagnosis of AD within CBS presentations has only been possible through a post-mortem neuropathological analysis. It is extremely important to encourage new studies with a greater number of clinical cases of this rare variant, in order to detect indicators that could predict this disease in life. Throughout this review, some clinical findings strongly associated with AD were recorded, including the presence of pyramidal signs at presentation, and the manifestation of myoclonus, memory impairment and visuospatial difficulties over the course of the disease. Thus, clinical findings, together with imaging and cerebrospinal fluid biomarkers, capable of predicting the underlying pathology, are expected to be further investigated and established in the future.

Key words:
Alzheimer's Disease – Corticobasal Syndrome – Neuropathology – Biomarkers

Abbreviation List

AChEI - Acetylcholinesterase inhibitor
AD – Alzheimer's Disease
CBD – Corticobasal Degeneration
CBS - Corticobasal Syndrome
CJD - Creutzfeldt-Jakob Disease
CSF – Cerebrospinal Fluid
CT – Computed Tomography
IWG – International Working Group
LBD – Lewy Body Disease
MDS - Movement Disorders Society
MRI – Magnetic Resonance Imaging
NFT – Neurofibrillary Tangle
NIA – National Institute of Aging
PBB – Portuguese Brain Bank
PET – Positron Emission Tomography
PSP – Progressive Supranuclear Palsy
SN – Substantia Nigra
tAD - typical amnesic variant of Alzheimer's Disease
TDP-43 - TAR DNA binding protein of 43 kDa

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Introduction

Alzheimer's Disease (AD) is the most common cause of dementia and it is particularly associated with ageing, with its prevalence doubling every five years after the age of 65.[1] While AD predominantly exhibits a sporadic etiology, there are cases of familial AD, which represent less than 0.5% of cases and typically manifest earlier in adult life.[2]

The cardinal neuropathological findings of this disease include extracellular plaques of beta-amyloid 40 and 42 and the presence of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein. Additionally, signs of gliosis, indicative of a neuroinflammatory response, and the detection of cerebral amyloid angiopathy, predominantly with a posterior distribution, can also be observed.[3] These alterations result in macroscopically visible brain atrophy, predominantly characterized by symmetrical medial temporal atrophy.[4] This region is typically where NFTs are present at an early stage, subsequently extending to nearby association areas, usually the temporal and parietal association cortices.[3]

The most common presentation of AD consists of episodic memory impairment, often accompanied by difficulties in executive function and visuospatial deficit. The condition progresses gradually and insidiously, affecting other cognitive domains and interfering with the autonomy of patients, who frequently become dependent on assistance for daily living activities.[5]

The diagnostic criteria provided by the National Institute of Aging (NIA) and the International Working Group (IWG-2) include preclinical stages characterized by the absence of symptomatic evidence, mild cognitive impairment (classified into low, intermediate or high likelihood based on beta-amyloid positivity and/or the detection of neuronal injury biomarkers), and dementia due to AD, which can be probable or possible taking into consideration the same biomarkers (**Table 1**).[6,7]

In addition to a complete anamnesis and neurological examination, multiple diagnostic tests may be employed not only to confirm AD suspicion but also to exclude potential reversible causes of cognitive impairment, such as infectious, inflammatory and metabolic conditions. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain are recommended for investigating cognitive impairment, facilitating the exclusion of other neurodegenerative disorders and for the evaluation of cerebrovascular pathology.[8] On the other hand, cerebrospinal fluid (CSF) analysis serves as a valuable tool not only in ruling out reversible aetiologies (e.g., infectious, autoimmune, and inflammatory) but also in bolstering AD pathophysiology, showing decreased beta-amyloid 42 levels and elevated tau and phospho-tau protein levels.[9] While amyloid positron emission tomography (PET) and tau PET imaging represent valuable adjuncts for detecting these molecular abnormalities, their availability remains limited in most hospital settings.[10]

Although definitive disease-modifying therapies remain elusive, symptomatic treatments offer potential benefits for some patients, contingent upon disease severity and individual patient factors. Acetylcholinesterase inhibitors (AChEIs), comprising donepezil, galantamine, and rivastigmine, represent the cornerstone of treatment, demonstrating efficacy in patients with mild to moderate disease.[11] Conversely, memantine is indicated primarily for individuals with moderate to severe AD. As an N-methyl-D-aspartate receptor antagonist with low affinity, memantine mitigates excitatory neurotoxicity mediated by L-glutamate.[12]

In addition to the well-characterized amnesic variant of AD, multiple clinical syndromes underlying this disease have been identified, namely posterior cortical atrophy, primary progressive aphasia and the corticobasal syndrome (CBS).[13] The CBS is a rare clinical syndrome characterized by signs and symptoms of cortical and extrapyramidal damage, which evolve progressively and typically manifest asymmetrically.[14] Cortical signs include apraxia, alien limb phenomena, cortical sensory loss, myoclonus, pyramidal motor signs (hyperreflexia, spasticity, Babinski sign, loss of fine motor skills), agrammatic aphasia and visuospatial impairment. On the other hand, dystonia, rigidity, tremor and bradykinesia are the main extrapyramidal signs we can find in these patients.[14] These parkinsonism signs do not respond to levodopa, since CBS does not involve degeneration of the substantia nigra, but rather post-synaptic nigrostriatal dysfunction.[15] The neuropathological background to this syndrome is usually a tauopathy, most commonly Corticobasal Degeneration (CBD), followed by Progressive Supranuclear Palsy (PSP) and AD.[15-17] Other pathologies have also been registered, namely Lewy Body Disease (LBD)[18], frontotemporal lobar degeneration with TAR DNA binding protein of 43 kDa (TDP-43)[19], Creutzfeldt-Jakob Disease (CJD)[20], motor neuron disease[21], among others.

The first cases compatible with what is known today as CBS were reported by Rebeiz et al. in 1968 with an underlying pathology, now termed CBD.[22] The researchers studied three clinical cases of a distinct form of neurodegeneration, which they named “corticodentatonigral degeneration with neuronal achromasia” for the anatomapathologic findings they observed.

Over the years, there have been established multiple diagnostic criteria to define CBS, namely the Toronto criteria (1994)[23], the Mayo Clinic criteria (2003)[14], the modified Cambridge criteria (2012)[24], the Armstrong et al. criteria (2013)[25], and the criteria of the International Parkinson's Disease and Movement Disorders Society (MDS)[26]. Despite the differences in the specific characteristics outlined by each set of criteria, they all consistently identify the presence of apraxia and asymmetrical, progressive limb rigidity as core features of CBS. Conversely, there is debate regarding the inclusion of non-fluent aphasia, behavioural or personality change, visuospatial deficits, and other cognitive impairments, with the modified Cambridge criteria encompassing the broadest array of signs and symptoms (**Table 2**).

As stated before, AD presenting as CBS has increasingly been recognized as an atypical variant of this condition. To date, several clinicopathological studies have been conducted on this topic; however, these studies are based on a relatively small cohort of patients with this diagnosis.[17,27-34] Recognizing the different phenotypes of AD, including the CBS, is crucial in an era of approved disease-modifying pharmacotherapy. This differentiation allows for tailored treatment approaches that address the specific pathological and clinical characteristics of each phenotype, enhancing therapeutic efficacy. CBS and other atypical presentations may involve distinct underlying mechanisms or patterns of neurodegeneration, which need targeted interventions. Moreover, an accurate phenotype diagnosis ensures appropriate patient selection for clinical trials, optimizing the development and validation of new treatments.

In this dissertation, we report a clinico-pathological case of AD presenting with CBS and provide a comprehensive discussion of the existing literature on this subject.

Case Presentation

The patient was a right-handed 62-year-old man seen in the neurology outpatient clinic in 2015. The patient first noted difficulties with fine motor skills at approximately 58 years of age. Specifically, he reported changes in his handwriting and challenges in simple tasks such as manipulating cutlery or button up the shirt, with these changes being more prominent in his left hand. Subsequently, he developed visuospatial difficulties, particularly noticeable when parking his car, along with difficulties in performing calculations in the pharmacy he owned.

In the 9 to 6 months prior to his first medical appointment, he experienced progressive impairments in verbal expression and memory. In addition, a certain "forgetfulness" of his left upper limb, sometimes with involuntary movements, was noted by his family members, compatible with alien limb phenomena.

Shortly before the first medical appointment, he presented persecutory delusions. The patient denied experiencing sleep disturbances, and family members corroborated the absence of significant behavioural changes. His medical history was unremarkable, with no pertinent personal or family history. The patient had insight for his cognitive and motor difficulties.

Since the age of 62 that he had been living in a care home, due to his dependency on assistance for activities of daily living, including personal hygiene.

On the neurological examination, the patient exhibited a non-fluent speech, with anomic pauses, agrammatism and stuttering. Orobuccofacial apraxia was not evident. Further examination revealed gaze apraxia, with slow saccades and fragmented pursuit movements. Bilateral

appendicular apraxia was also present, more pronounced on the left side. The patient demonstrated an inability to mimic hand postures and exhibited significant visuospatial impairment throughout the consultation. Neurological examination also noted bilateral palmomental reflexes and a grasp reflex in the left hand, without the presence of a sucking reflex. Additionally, a cortical sensory deficit was observed on the left side, along with myoclonus of the left upper limb, the latter more pronounced when induced by action. No pyramidal signs were detected. An akinetic-rigid parkinsonian syndrome with a clear left-sided predominance was identified. Levitation of the left upper limb was also observed during the examination.

The patient underwent two brain magnetic ressonance imaging (MRI) scans, which revealed significant cortical atrophy (**Figure 1**). The atrophy was relatively asymmetrical, being more pronounced in the right cerebral hemisphere. The asymmetry was more marked in the parietal and anterior temporal regions, with notable involvement of the hippocampus and parahippocampal cortex.

A comprehensive neuropsychological assessment was also performed. Although the assessment was not able to pinpoint very specific results due to already severe cognitive deterioration, it identified impairments across multiple cognitive domains, including ideomotor and ideational apraxia.

The patient's pharmacological treatment included sertraline 100 mg daily, memantine 20 mg daily, and rivastigmine 4.6 mg/24 hours transdermal patch. Additionally, the patient was prescribed risperidone 1 mg daily.

The symptoms gradually worsened and the patient passed away at the age of 63 years. The family provided informed consent and signed the terms of agreement to participate as a donor for the Portuguese Brain Bank.

Pathologic Findings

The fixed brain weighed 1246 grams and showed frontal and parietal atrophy on gross examination at autopsy **(Figure 2)**. Sequential coronal sections of the cerebral hemispheres revealed slight enlargement of the lateral ventricles, parietal cortical atrophy and a slight atrophy of the hippocampus. The basal ganglia and thalamus were normal in size and had no macroscopic changes. A horizontal section of the brainstem showed depigmentation of the substantia nigra (SN) and locus coeruleus was normal. The medulla oblongata and cerebellum did not show macroscopic changes.

Histological examination revealed neurodegenerative features with neuronal loss, gliosis and superficial microvacuolation of the frontal and parietal regions (**Figure 3**). Amyloid plaques and NFTs were already evident on Hematoxil & Eosin stain in cortical and on hippocampal formation. There was mild small vessel disease on the basal ganglia, without microinfarcts. The substantia nigra of the midbrain showed neuronal loss on the lateral tier, with occasional Lewy bodies in some of the remaining neurons. The locus coeruleus was severely depleted. The immunohistochemistry study revealed extensive tau pathology (NFTs, neuritic plaques and dystrophic neurites) in the cortical regions, extending to the associative areas of the occipital cortex, amygdala and hippocampal formation and moderate involvement of the brainstem (particularly in the substantia nigra of the midbrain). The study for amyloid β revealed mature plaques in all cortical regions and hippocampal formation. There was also diffuse amyloid deposition on the basal ganglia, brainstem and cerebellar cortex. There was mild cerebral amyloid angiopathy. Additionally, there was moderate Lewy body pathology (α-synuclein) in the cingulate cortex and hippocampal formation. There was severe involvement of the amygdala and brainstem (substantia nigra, reticular formation and dorsal motor nucleus of the X cranial nerve). There was no TDP43 pathology.

Overall, the neuropathological study was consistent with the diagnosis of Alzheimer´s disease (AD neuropathological change high likelihood: A3, B3, C3; Braak & Braak estadio V; Thal Aβ stage 5; CERAD: frequent neuritic plaques; NIA-AA guidelines, 2012).

Discussion

AD presenting with CBS is rare, however in previous reports on the underlying pathology of CBS, it was frequently the third most common, representing up to 24% of cases of CBS.[15-17,34] Nonetheless, this percentage can vary widely among different studies and populations. **Table 3** presents a summary of the demographic and clinical characteristics of four different studies that include multiple cases of AD-CBS, in addition to our case report.[35-38] **Table 4** summarizes the purposes and conclusions of these studies, which aimed to identify clinical and demographic characteristics that could predict an ante-mortem diagnosis of AD presenting with CBS.[35-38]

Comparing to CBD-CBS, AD-CBS is more commonly associated with a younger age of onset, memory impairment (particularly at an early stage), pyramidal signs, visuospatial difficulties and myoclonus.[35,36,38] The age of onset was in agreement of the previous descriptions. Regarding clinical features, according to a study by Sakae N et al.[36], cognitive signs were the most common presentation in 85% of AD-CBS cases, with memory impairment observed in 23% of them. In fact, although memory impairment is not a feature as frequent in AD-CBS as it is in the typical amnesic

variant of AD (tAD)[36], other studies have reported early memory problems in patients with a pathological bioprofile of AD (CSF and SPECT imaging consistent with AD) associated with CBS.[40] In our patient, memory problems were not a major complaint at presentation, however the patient was only observed with four years of disease duration. Despite a recent study[37] associated AD-CBS to pyramidal signs at presentation, this was not present in our patient. On the other hand, myclonia was observed ant it has been suggested by multiple studies as an extremely important indicator of AD-CBS. [28,35,36,41]

Subsequently, the patient developed visuospatial difficulties, which, as reported by studies conducted by Hassan et al.[35] and Sakae N et al.[36], are more strongly associated with AD-CBS. Additionally, it is important to note that Boyd et al[39]. have previously suggested that visuospatial impairment may serve as a distinguishing feature to differentiate AD-CBS from non-AD-related CBS.

In the disease course the patient began exhibiting psychiatric symptoms, specifically persecutory delusions. Hallucinations together with delusions were more commonly associated with AD-CBS than with CBD-CBS in Sakae N et al.'s study.[36] Throughout the course of the disease, the patient exhibited additional signs and symptoms characteristic of CBS. Many of them had an asymmetrical manifestation, which is seen in CBS. Specifically, alien limb phenomena and sensory cortical deficit were limited to the left side, while appendicular apraxia, fine motor skill difficulties, and parkinsonian syndrome happened to manifest bilaterally, however with a predominance on the left side. Furthermore, the patient demonstrated non-fluent aphasia, characterized by agrammatism and annomic pauses, which is considered a core feature of CBS in two of the five CBS diagnostic criteria, as stated in **Table 2**. Regarding aphasia and language disorders, findings are somewhat contradictory, with Shelley et al. suggesting that initial non-fluent language impairment is more associated with CBD, while Sakae N et al. suggest that aphasia occurs significantly more frequently in AD-CBS during the disease course. Conversely, Aiba I et al. found that having dysarthria at presentation and an age at onset older than 61 years suggested PSP. The patient did not manifest any behavioural or personality changes during the course of the disease according to his family. This is consistent with Shelley et al.'s study, which correlate CBD to frontal-lobe type behavioural symptoms. These symptoms include apathy, irritability, socially inappropriate disinhibited behaviour, emotional lability, stereotypic behaviour and loss of insight. The last one was not present as well, since our patient had insight for his cognitive and motor difficulties.

Regarding the cerebral MRI findings, it was recorded an asymmetrical cortical atrophy, more evident in the right cerebral hemisphere. This asymmetry accounts for the contralateral manifestation of most clinical signs observed on the left side. Topographically, the atrophy was predominantly located in the anterior temporal and parietal regions, including the hippocampus and parahippocampal cortex. While tAD is generally characterized by symmetrical medial temporal

atrophy, including the entorhinal cortex, it is well-documented that the brain regions involved in AD-CBS differ significantly.[35] Several authors have reported that frontal, temporal, and parietal involvement is common in AD-CBS.[42,43] Furthermore, some studies suggest that temporoparietal atrophy serves as a sensitive and specific marker for predicting AD-CBS.[44] It is also important to note that even though our patient did not exhibit occipital cortex atrophy, in Sakae N. et al.'s study[36], AD-CBS demonstrated more pronounced atrophy in the occipital cortex compared to CBD-CBS. In fact, investigators suggest that posterior cortical atrophy might help distinguish AD-CBS from CBD-CBS.[45]

Neuropathological examination revealed significant neurodegeneration features of AD. Tau pathology was extensively distributed in the cortical regions, extending to the associative areas of the occipital cortex, amygdala, and hippocampal formation, with moderate involvement of the brainstem. The extent of neocortical involvement classified the brain as Braak stage V. **Figure 4** illustrates the Braak classification in AD based on the topographical distribution of NFTs.[46] In addition to the topographical differences between AD-CBS and tAD concerning cortical atrophy, the topography of NFT deposition also differs between these two variants. In fact, AD-CBS seems to have higher levels of NFTs in the motor cortex and lower in the superior temporal cortex and hippocampus, which may explain the clinical differences between these two forms of AD.[36] Beta-amyloid mature plaques were observed in all regions of the cerebral cortex, hippocampal formation, basal ganglia, brainstem and cerebellar cortex. The involvement of these last two structures leads to a Thal stage 5 classification. In **Figure 5** we can see the different stages of this classification, which depends on the topography of the beta-amyloid burden.[47]

Additionaly, depigmentation of the substantia nigra was also observed, possibily correlating with the patient's parkinsonian signs.

It should be also noted that moderate Lewy body pathology (alpha-synuclein) was detected in the cingulate cortex and hippocampal formation, with severe involvement of the amygdala and brainstem. In a study comparing neuropathologically confirmed cases of AD with early-onset (before the age of 65) and late-onset, it was concluded that Lewy body disease (LBD) is as prevalent in sporadic early-onset AD as it is in late-onset AD.[48] However, in about a quarter of early-onset AD cases, LBD co-pathology was predominantly confined to the amygdala. These results are quite interesting since our patient had an early age of onset (58 years old) and there was severe Lewy Body pathology on the amygdala. Furthermore, Lewy body disease is associated with frequent psychotic features, particularly visual hallucionations.[49] We can speculate that this pathology could have contributed to these symptoms in our patient. Furthermore, studies indicate that coexistent LBD pathology significantly worsens the severity of the clinical presentation of AD.[50]

Despite the absence of amyloid PET or CSF analysis in our patient's diagnostic evaluation, it is well-established that the combination of these modalities serves as a robust tool for AD diagnosis.[51,52] Therefore, their integration is highly advantageous in clinical practice.

Given that, to date, an accurate diagnosis of AD within CBS presentations has only been possible through a post-mortem neuropathological analysis, it is extremely important to encourage new studies with a greater number of clinical cases of AD-CBS, in order to detect indicators that could predict this disease in life. In fact, throughout this review, some patterns most strongly associated with AD were recorded: the manifestation of pyramidal signs at presentation, as well as the presence of myoclonus, memory impairment, and visuospatial difficulties during the course of the disease. On the other hand, it was found that frontal-lobe type behavioral symptoms and utilization behaviour may predict CBD-CBS rather than AD-CBS. The established fluid biomarkers for AD are now valubale tools for predicting AD pathology in CBS cases. However, they do not exclude the presence of additional pathologies as seen in our patient. Thus, clinical findings, together with imaging (brain MRI, amyloid PET, tau PET) and cerebrospinal fluid biomarkers, capable of predicting the underlying pathology, are expected to be further investigated and established in the future. Such developments are pivotal for implementing targeted therapeutic interventions capable of modulating disease progression.

Appendix

Tables

Table 1 – An overview of the diagnostic criteria provided by the National Institute of Aging (NIA) and the International Working Group (IWG-2)[6,7]

		NIA criteria	IWG-2 criteria
Asymptomatic individulas	Individuals who have evidence of early AD pathological changes but do not meet clinical criteria for mild cognitive impairment (MCI) or dementia	**Stage 1** – asymptomatic cerebral amyloidosis. **Defined by**: reductions in CSF β-amyloid 42 or increased amyloid tracer retention on PET imaging **Stage 2** – amyloidosis + neurodegeneration. **Defined by:** reductions in CSF β-amyloid 42 or increased amyloid tracer retention on PET imaging <u>plus</u> positive markers of neuronal injury* **Stage 3** - amyloidosis + neurodegeneration + subtle cognitive/behavioural decline. **Defined by:** reductions in CSF β-amyloid 42 or increased amyloid tracer retention on PET imaging <u>plus</u> positive markers of neuronal injury* <u>plus</u> evidence of subtle cognitive change but does not yet meet criteria for MCI	**Asymptomatic at-risk for AD** Individuals with biomarkers of Alzheimer's pathology but without clinical signs or symptoms. Not all individuals in these conditions will progress to symptomatic stages. **Criteria (A plus B):** **A** - Absence of specific clinical phenotype (both are required): • Absence of amnestic syndrome of the hippocampal type • Absence of any clinical phenotype of atypical AD **B** - In-vivo evidence of Alzheimer's pathology (one of the following): • Decreased Aβ1–42 + increased total-tau or phosphorylated-tau in CSF • Increased retention on fibrillar amyloid PET **Presymptomatic AD** Applies to individuals who carry an autosomal dominant monogenic AD mutation with virtually full penetrance. They will inevitably develop clinical AD. **Criteria (A plus B):** **A** - Absence of specific clinical phenotype (both are required):

			• Absence of amnestic syndrome of the hippocampal type • Absence of any clinical phenotype of atypical AD **B** - Proven AD autosomal dominant mutation in PSEN1, PSEN2, or APP, or other proven genes (including Down's syndrome trisomy 21)
Symptomatic individuals	Symptoms that do not meet criteria for dementia	**MCI due to AD** • High likelihood (requires positive beta-amyloid and neuronal injury biomarkers*) • Intermediate likelihood (requires either positive beta-amyloid or neuronal injury biomarkers) • Unlikely (negative beta-amyloid and neuronal injury biomarkers) • Uninformative (biomarkers ambiguous or conflict with each other)	-
	Symptoms that meet criteria for dementia	**Dementia due to AD** • Probable (no biomarker evidence required, based on clinical picture) • Possible (no biomarker evidence required, based on clinical picture) • Probable or possible with evidence of AD pathophysiological process (beta-amyloid and/or neuronal injury biomarker evidence – high likelihood,	**Typical AD** **Criteria (A plus B):** **A** – Presence of early and significant episodic memory impairment: Gradual and progressive memory decline reported over more than 6 months + objective evidence of hippocampal-type amnestic syndrome, shown by poor performance on a specific episodic memory test, such as cued recall with control of encoding test.

		intermediate likelihood, unlikely and uninformative)	**B** - In-vivo evidence of Alzheimer's pathology (one of the following): • Decreased Aβ1–42 + increased total-tau or phosphorylated-tau in CSF • Increased tracer retention on amyloid PET • AD autosomal dominant mutation present (in PSEN1, PSEN2, or APP) **Atypical AD** **Criteria (A plus B):** **A** - Clinical manifestations consistent with each specific clinical phenotype (Posterior/Logopenic/Frontal/Down's syndrome variants of AD). **B** - In-vivo evidence of Alzheimer's pathology (one of the following): • Decreased Aβ1–42 + increased total-tau or phosphorylated-tau in CSF • Increased tracer retention on amyloid PET • AD autosomal dominant mutation present (in PSEN1, PSEN2, or APP) **Mixed AD** **Criteria (A plus B):** **A -** Amnestic syndrome of the hippocampal type or one of the clinical phenotypes of atypical AD **and** decreased Aβ1–42 together with increased total-

			tau or phosphorylated-tau in CSF / increased tracer retention on amyloid PET **B** - <u>For cerebrovascular disease</u>: Documented history of stroke, or focal neurological features, or both **and** MRI evidence of one or more of the following: corresponding vascular lesions, small vessel disease, strategic lacunar infarcts, or cerebral haemorrhages <u>For Lewy body disease</u>: One of the following: extrapyramidal signs, early hallucinations, or cognitive fluctuations **and** abnormal dopamine transporter PET scan

*Markers of neuroinjury include elevated CSF tau, decreased fluorodeoxyglucose 18F (FDG) uptake on PET with a temporoparietal pattern of hypometabolism or brain atrophy on MRI in a characteristic pattern involving the medial temporal lobes, paralimbic and temporoparietal cortices.

Table 2 – Comparison of five different diagnostic criteria for CBS

	Imbalance and falls Urinary incontinence Behavioural changes	Vertical gaze palsy Slow saccades	Akinetic rigid syndrome Myoclonus Dystonia Limb apraxia Alien limb phenomena Cortical sensory loss	Apraxia of speech Non-fluent aphasia	Frontal executive dysfunction Visuospatial deficits Behavioural or personality change
Toronto (1994)			**CBS**		
Mayo Clinic (2003)			**CBS**		
Modified Cambridge (2012)			**CBS**		
Armstrong* (2013)	**PSPS**		**CBS**	**PNFA**	**FBS**
MDS PSP** (2017)		**PSP-CBS**			

*Armstrong et al. proposed four clinical phenotypes of CBD, namely CBS, PSP syndrome (PSPS), frontal behavioural-spatial syndrome (FBS) and progressive non-fluent aphasia (PNFA).[25]
**The International Parkinson and Movement Disorder Society (MDS) proposed diagnostic criteria for PSP, which included eight phenotypes, one of them being PSP with CBS.[26]

Table 3 – Summary of the demographic and clinical features of AD-CBS cases reported by five different studies

Author	Sex (%) / Median age at onset / Median disease duration (years)	Initial signs and symptoms	Signs and symptoms during the disease course
B. P. Shelley et al. (n=6)	33% M, 67% F 69.5* 12	Limb apraxia, extrapyramidal signs, dysarthria, alien hand phenomena, visuospatial syndrome, episodic memory impairment	Limb apraxia, extrapyramidal signs, myoclonus, oculomotor apraxia, dysarthria, gait/postural instability, alien hand phenomena, cortical sensory loss, visuospatial syndrome, frontal release signs, episodic memory impairment, language impairment, personality and behaviour changes, visual spatial deficits, signs of frontal-executive dysfunction
Hassan A et al. (n = 29)	41% M, 59% F 60 (50, 75) 9	-	Apraxia (nonspecified), alien limb, aphasia, memory impairment, dressing apraxia, personality/behaviour change, cortical sensory loss, visuospatial disturbance, constructional apraxia, hemisensory neglect, frontal release signs, extraocular disturbance, parkinsonism, bradykinesia, rigidity, dystonia, tremor, myoclonus, postural instability/gait change, fisted hand, dysarthria, dysphagia, pyramidal signs
Sakae N et al. (n = 43)	40% M, 60% F 61 (55, 69) 9	Language impairment, limb apraxia, memory impairment, gait abnormalities, visual problems, myoclonus, tremor	Apraxia (nonspecified), myoclonus, gait disorder, aphasia, visuospatial problems, memory impairment, behaviour or personality changes, tremor, hallucinations or delusions, alien limb, visual neglect, cortical sensory loss, dystonia, falls
Aiba I et al. (n = 6)	- 69.5* 8.5*	Gait disturbance (including slow gate, short stapes gait and unstable gait), apraxia nonspecified, bradykinesia, clumsy limbs, memory impairment, speech disturbance, lack of insight, tremor, irritability, personality change, falls	Limb rigidity or bradykinesia, cognitive impairment (general), executive dysfunction, limb apraxia, pyramidal sign, speech and language impairment, gait disturbance (including unstable gait, slow gait, short-step gate and frozen gait), myoclonus (with or without asymmetric presentation), limb rigidity or bradykinesia with asymmetric presentation, postural instability or falls, personality change, behavioural change, tremor, supranuclear vertical gaze palsy or decreased velocity of vertical saccades, urinary incontinence, dysarthria, groping distorted speech production
Case report of this text	M 58 5	Fine motor skills difficulties	Fine motor skills difficulties, visuospatial impairment, difficulties in performing calculations, verbal expression and memory impairment, alien limb, persecutory delusions, gaze apraxia, cortical sensory deficit, myoclonus, parkinsoninan syndrome

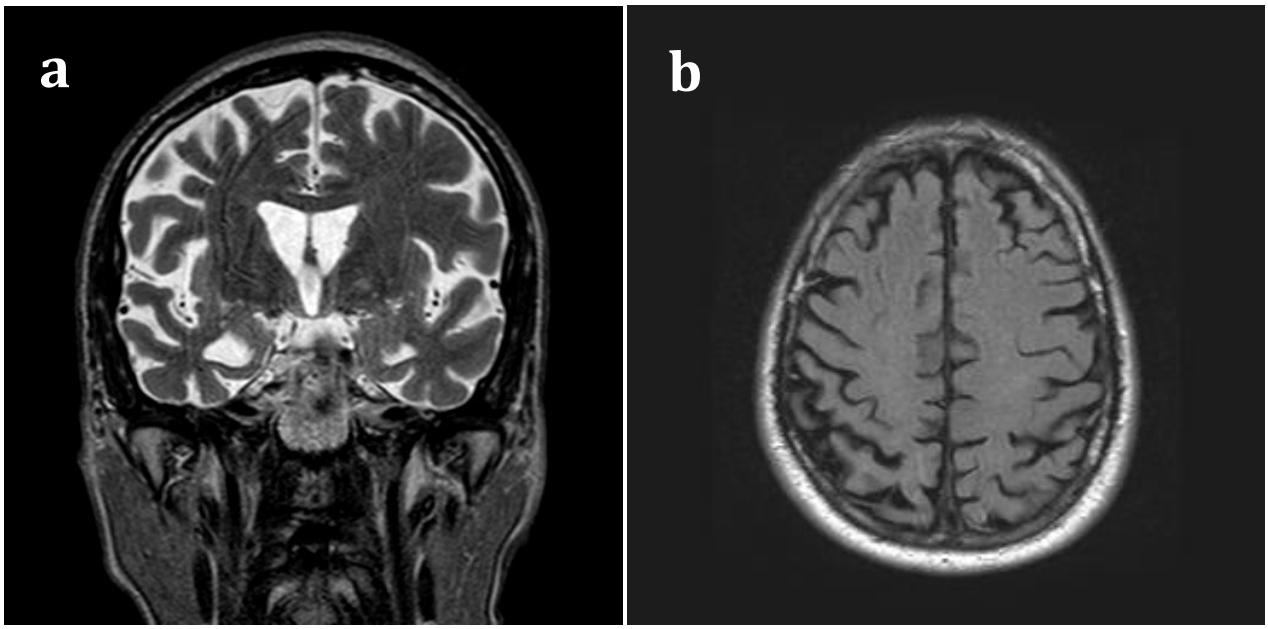
M – masculine , F – feminine ; *in this study data was presented as mean

Table 4 - Overview of the reviewed sources

Authors	Country	Purpose	Type of source	Summary points
B. P. Shelley et al. (2009)	UK	Comparing pathologically-confirmed cases of AD-CBS and CBD-CBS to identify clinical and cognitive variables that may assist in determining the pathological substrate of CBS in vivo	Article	Two independent predictors were identified to accurately distinguish AD from CBD: initial episodic memory complaints for the AD group and frontal-lobe type behavioral symptoms for the CBD group. Initial non-fluent language impairment, orobuccal apraxia and the presence of utilization behaviour were also significantly associated with CBD.
Hassan et al. (2011)	USA	Reviewing the literature for AD-CBS case reports and series and comparing them to CBD-CBS, in order to examine factors that might predict the antemortem diagnosis of AD	Article	AD seemed to be strongly associated with longer disease duration, younger age at onset, hemisensory neglect, memory impairment, visuospatial difficulties, dressing apraxia and myoclonus. Even though there were no significant associations with CBS-CBD, utilization behaviour, rigidity and extraocular dysfunction were more frequently associated with it
Sakae N et al. (2019)	USA	Comparing pathologically-proven cases of AD-CBS with CBD-CBS, as well as with tAD	Article	Presenting with episodic memory impairment was significantly less frequent in AD-CBS than in tAD. Comparing AD-CBS to CBD-CBS, myoclonus, aphasia and behavioural problems were significantly more frequent in AD-CBS during the disease course. On the other hand, dystonia and falls were more frequent in CBD-CBS cases. Aditionally, AD-CBS had significantly greater atrophy in the paracentral lobule, compared to tAD and also greater atrophy in the occipital cortex compared to CBD-CBS. AD-CBS showed significantly higher levels of neurofibrillary tangles in the motor cortex and fewer in the superior temporal cortex and hippocampus, compared to tAD. The neuronal loss in substantia nigra was greater in CBD-CBS, followed by AD-CBS and tAD
Aiba I et al. (2023)	Japan	Analyzing clinical findings and course of pathologically, genetically and biochemically confirmed CBD and CBS with background pathology to determine findings suggestive of CBD-CBS, PSP-CBS and AD-CBS	Article	Presenting with gait freezing or not having dysarthria and gait freezing at presentation, with an age at onset <66 years old seemed to predict CBD. On the other hand, having dysarthria at presentation and age at onset older than 61 years suggested PSP, while a pyramidal sign at presentation, together with personality change during the entire course implied AD.

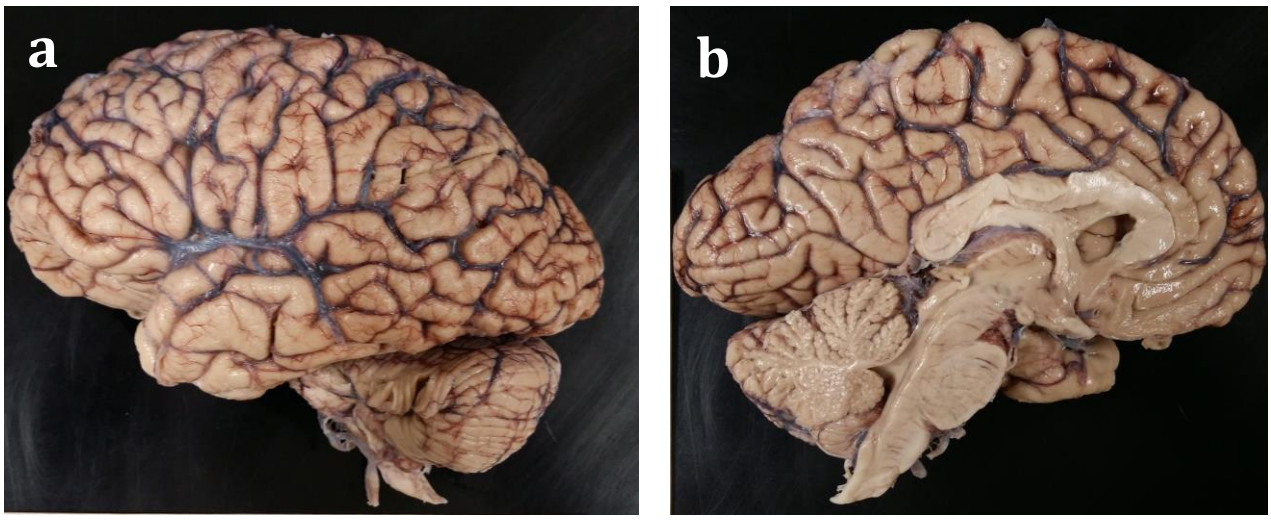
Figures

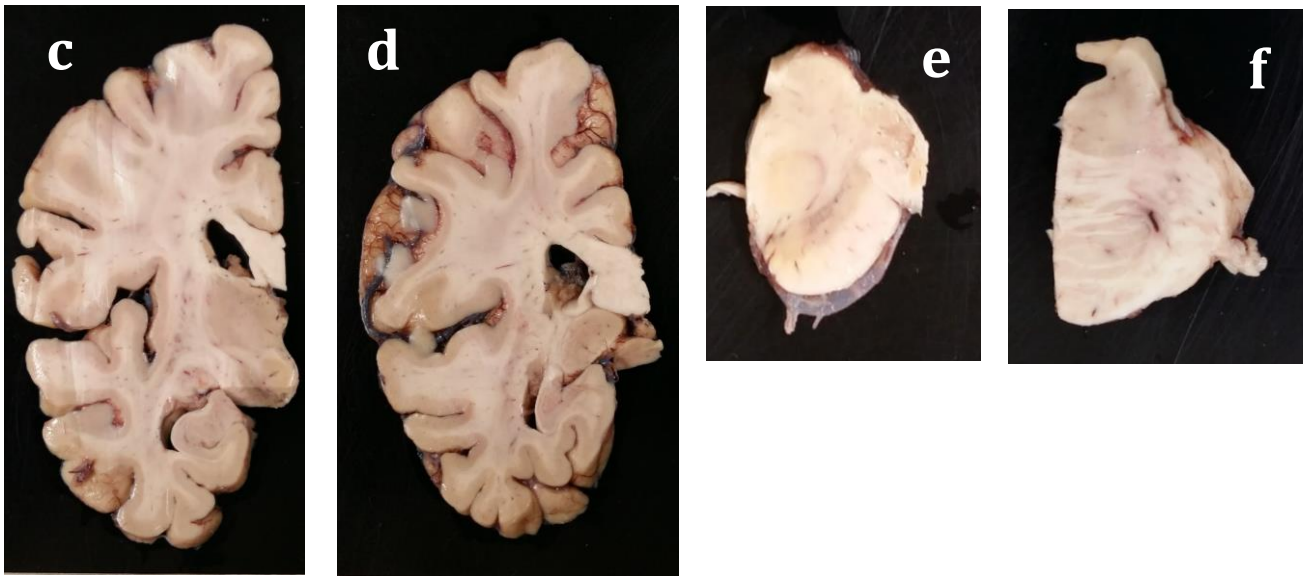
Figure 1 – Brain MRI scans using T2-weighted image and FLAIR



MRI showing hippocampal and cortical atrophy, more pronounced on the right temporal and parietal regions (a - coronal T2-weighted image; b – Axial Fluid-attenuated inversion recovery (FLAIR) weighted image).

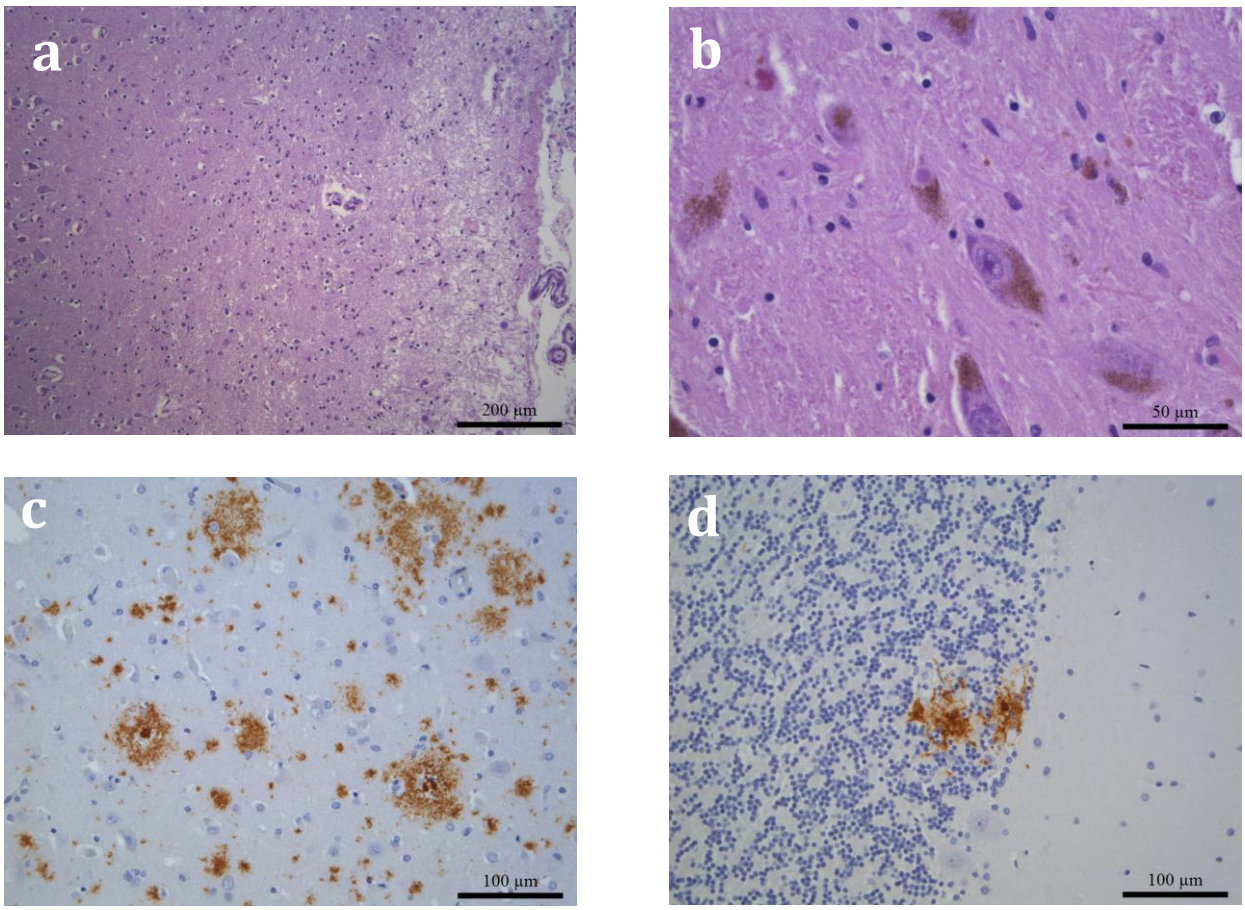
Figure 2 – Macroscopic findings of brain tissue

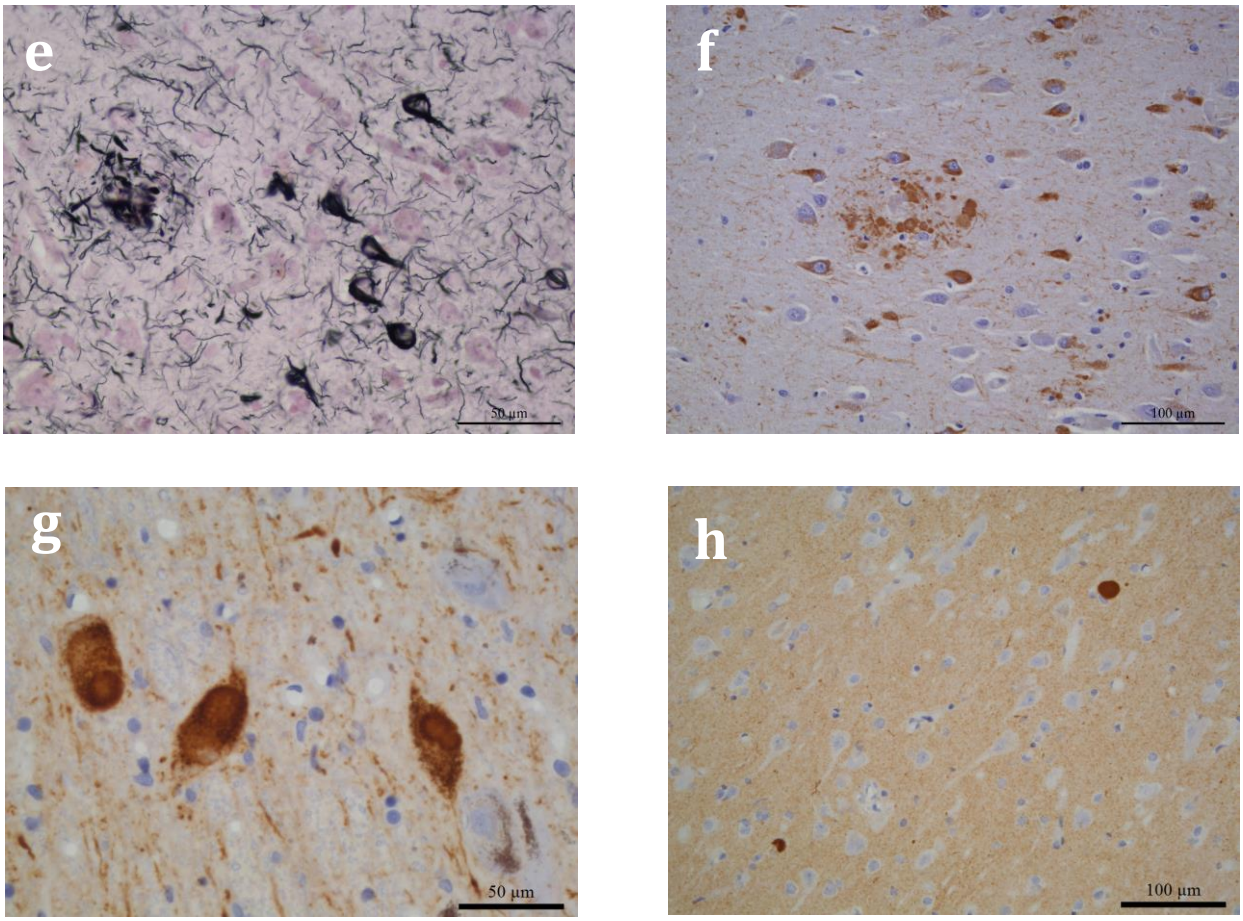




Lateral (a) and medial (b) views of the left hemibrain showing mild frontal atrophy, with relatively sparing of the premotor and motor area. Coronal section showing mild atrophy of the hippocampus (c) and parietal atrophy (d). Transverse sections of the brainstem showing pigment loss of the substantia nigra of the midbrain (e) and normal pons (f).

Figure 3 – Microscopic findings of brain tissue using multiple staining techniques





a) Parietal cortex with severe neuronal loss, gliosis and microvacuolation in the superficial layers. b) Neuronal loss with extracellular pigment and occasional Lewy bodies in the substantia nigra. c) Amyloid deposition with mature plaques in the neocortex (d), extending to the cerebellum (e). Neurofibrillary tangles and neuritic plaques in the neocortex (f and g). Lewy bodies and Lewy neurites in the substantia nigra (g) and rare Lewy bodies in the cingulate cortex.
Haematoxylin & Eosin (a, b); Amyloid β immunohistochemistry (c, d); Gallyas silver stain (e); Tau (AT8) immunohistochemistry (f); α-synuclein immunohistochemistry (g, h).

Figure 4 - Braak staging of neurofibrillary changes in prodromal and clinical Alzheimer's disease

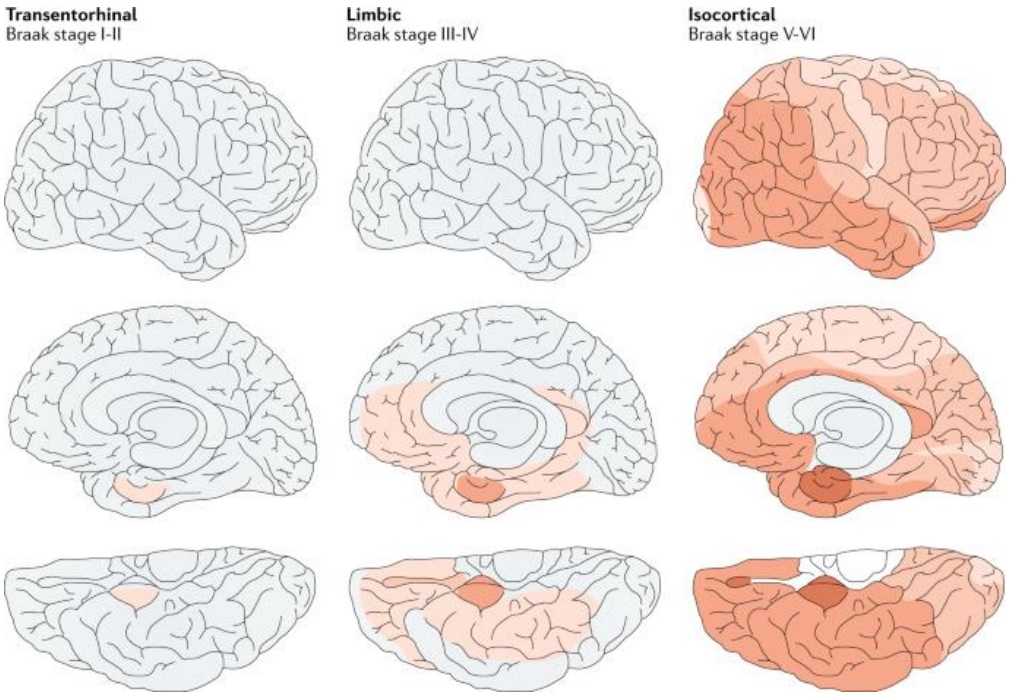


Image retrived from Murphy C. Olfactory and other sensory impairments in Alzheimer disease. Nat Rev Neurol. 2019;15:11-24

Braak stages I and II are characterized by neurofibrillary tangles primarily located in the entorhinal cortex. In Braak stages III and IV, these tangles extend to the limbic regions, including the hippocampus. Braak stages V and VI signify moderate to severe involvement of the neocortex.

Figure 5 - Neuropathological stages of β-amyloid accumulation in Alzheimer's disease

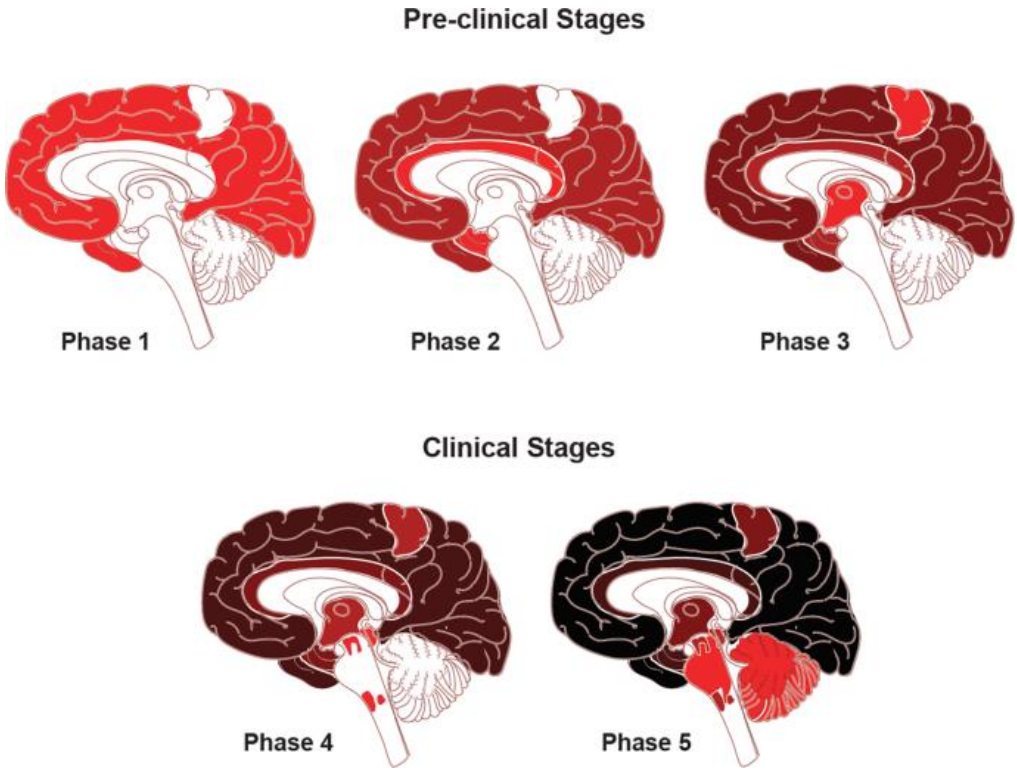


Image retrived from Hampel H, Hardy J, Blennow K, et al. The Amyloid-β Pathway in Alzheimer's Disease. Mol Psychiatry. 2021;26:5481-5503

The red regions show the accumulation of beta-amyloid in several structures of the brain. The change to a darker tone indicates the continuous accumulation of beta-amyloid. Phase 1 represents the early pre-clinical stage, in which there is beta-amyloid deposition in the neocortex. Additional accumulation is seen in allocortical regions (phase 2), extending to the midbrain in phase 3. In late phase clinical stages, there is further deposition at the brain stem, affecting the cerebellum in phase 5.

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