ARTIGO ORIGINAL/ORIGINAL ARTICLE

The Profile of Cognitive Complaints Associated with Neurodegenerative Dementia: A Single Centre Retrospective Analysis in Northern Portugal

O Perfil das Queixas Cognitivas Associadas à Demência Neurodegenerativa: Análise Retrospetiva Unicêntrica no Norte de Portugal

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Abstract

Introduction: The detection of early phases of neurodegenerative cognitive disorders is challenging. Differentiating these from non-neurodegenerative conditions is increasingly important, especially with the recent approval of disease-modifying treatments for early Alzheimer's in Europe (lecanemab and donanemab). This study aimed to identify the clinical profile of patients presenting for the first time at a general Neurology clinic with cognitive complaints due to neurodegenerative conditions, i.e. Alzheimer's disease and related disorders.

Methods: We conducted a retrospective, single-centre study of patients referred by primary care to a general neurology outpatient clinic for cognitive complaints. Sociodemographic and clinical data were collected from primary care records and the first neurology appointment. Diagnoses of a "neurodegenerative disorder" or "non-degenerative disorder" were established per the judgment of the attending physician according to established guidelines. Patients with overt dementia (moderate/advanced stages) were excluded.

Results: Among 283 patients, 169 (59.7%) had a non-degenerative condition, 108 (38.2%) a neurodegenerative disorder and six (2.1%) were lost to follow-up. Characteristics associated with a diagnosis of a neurodegenerative disorder were: age >76 years (OR 1.05); retirement (OR 3.42); absence of psychiatric pathology (OR 0.54); apathy (OR 3.36); major cognitive complaints (i.e. cognitive impairment likely to cause harm or requiring assistance) (OR 2.27); absence of responsibility demanding tasks (OR 0.50); presence of head turning sign (OR 2.89); cognitive bedside scores below the established cut-off (OR 7.88); focal/asymmetrical atrophy in imaging reports (OR 2.40). After multivariate analysis, failure to recall any words on delayed recall and focal/asymmetrical atrophy on imaging reports remained significant predictors of neurodegeneration. The model achieved 93.4% accuracy, 87.4% sensitivity, and 88% specificity in distinguishing degenerative from non-degenerative cognitive disorders, although these results should be interpreted with caution. Diagnostic changes occurred in older individuals (OR 1.04), those with lower bedside scores (OR 4.17), parkinsonian features (OR 4.05), and apathy (OR 4.40).

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Conclusion: Our study provides a profile of patients presenting for the first time to a general neurology clinic who might be on the early stages of a neurodegenerative process (older, major complaints, cognitive bedside testing below established thresholds, focal and/or asymmetrical atrophy in brain imaging, impaired delayed recall tasks, and parkinsonism), and who may benefit from further testing. Prospective validation of these criteria in primary care and other neurology clinics is advised.

Resumo

Introdução: A deteção de fases iniciais de perturbações cognitivas neurodegenerativas é desafiante. É cada vez mais importante diferenciá-las das doenças não neurodegenerativas, especialmente com a recente aprovação de tratamentos modificadores da doença para estadios iniciais da doença de Alzheimer na Europa. Este estudo teve como objetivo identificar o perfil clínico de doentes que se apresentaram pela primeira vez a uma consulta externa de Neurologia com queixas cognitivas devido a condições neurodegenerativas, como doença de Alzheimer e distúrbios relacionados.

Métodos: Foi realizado um estudo retrospetivo, unicêntrico, de doentes encaminhados pelos cuidados de saúde primários à consulta de neurologia geral por queixas cognitivas. Dados sociodemográficos e clínicos foram recolhidos dos registos dos cuidados primários e da primeira consulta de neurologia. Os diagnósticos de "doença neurodegenerativa" ou "doença não degenerativa" foram estabelecidos segundo o julgamento clínico do médico assistente, com base em *guidelines* internacionais. Doentes com demência em estadios moderados e severos foram excluídos.

Resultados: Dos 283 doentes, 169 (59,7%) tinham um quadro não degenerativo, 108 (38,2%) uma doença neurodegenerativa e 6 (2,1%) perderam o seguimento. As características associadas ao diagnóstico de doença neurodegenerativa foram: idade >76 anos (OR 1,05); estar reformado (OR 3,42); ausência de patologia psiquiátrica prévia (OR 0,54); apatia (OR 3,36); queixas cognitivas major (défice suscetível de causar danos a si ou a terceiros ou necessitar de ajuda / supervisão) (OR 2,27); ausência de tarefas de responsabilidade major (OR 0,50); presença do *head turning sign* (OR 2,00); pontuações dos testes cognitivos de cabeceira abaixo do ponto de corte (OR 7,88); atrofia focal/assimétrica no relatório do exame de imagem cerebral (OR 2,40). Após análise multivariada, a não evocação de palavras na evocação diferida e a atrofia focal/assimétrica permaneceram preditores significativos. O modelo alcançou 93,4% de precisão, 87,4% de sensibilidade e 88% de especificidade na distinção entre distúrbios degenerativos e não degenerativos, sendo que estes números devem ser interpretados à luz das limitações inerentes a este trabalho.

Alterações diagnósticas ocorreram em indivíduos mais velhos (OR 1,04), com pontuações inferiores nos testes à cabeceira (OR 4,17), sinais de parkinsonismo (OR 4,05) e apatia (OR 4,40).

Conclusão: O estudo traça o perfil de doentes em estadios iniciais de um quadro neurodegenerativo (mais velhos, queixas *major*, défices em testes cognitivos, atrofia focal/assimétrica, evocação diferida prejudicada, parkinsonismo) que podem beneficiar de estudo adicional. Recomenda-se a validação prospetiva destes critérios nos cuidados primários e em consultas de neurologia de outros centros.

Introduction

Neurodegenerative disorders and dementia affect approximately 57.4 million people worldwide.[1,2] In Portugal, it is estimated that nearly 6% of people over the age of 60 have some form of dementia (the majority of which due to Alzheimer's disease), translating into nearly 160 000 people.[3,4] It is thus unsurprising that cognitive complaints are among the top reasons for referral for a Neurology appointment. And even if a referral does occur swiftly, the waiting times for an appointment are usually longer than ideal (often several months), which in the case of a relentlessly progressive condition with a narrow treatment window can be deleterious.[3,5] The recent approval by the European Commission of disease-modifying treatments such as lecanemab and donanemab for the early stages of Alzheimer's disease (AD),[6] and the approval of blood-based biomarkers by the FDA[7] are set to transform the field. As new treatments emerge, accurately identifying patients with cognitive complaints linked to neurodegenerative conditions is increasingly vital for timely further testing, such as biomarker assessment.

The correct identification of individuals in the early stages of a neurodegenerative condition is particularly challenging. Early dementia symptoms may closely resemble those seen in non-degenerative conditions (e.g., psychiatric disorders, functional complaints, attention-deficit issues, fatigue).[8,9] Furthermore, bedside cognitive tests and structural brain imaging often have low sensitivity and specificity, especially during the initial stages of progressive cognitive decline.[10,11] And even if disease-modifying treatments are not indicated, a timely diagnosis remains important for several reasons: it enables patients to plan for their future, consider symptomatic treatment, and take steps to preserve their quality of life and autonomy for as long as possible.[12]

Thus, it is important to have appropriate clinical criteria to optimize the identification of individuals in the early stages of a neurodegenerative condition—particularly before dementia becomes established—when they are more likely to benefit from timely neurological referrals. Our study aimed to establish the clinical profile of individuals with cognitive complaints most likely to be in the early stages of a neurodegenerative disorder.

Material and Methods

Study Design and Setting

A single-centre, retrospective analysis was conducted using demographic and clinical data from adult patients referred for the first time to a Neurology outpatient clinic at the São João Local Health Unit (ULS São João) due to cognitive complaints. Data were obtained from the hospital's computerized medical records (January 2019–July 2024), including primary care and initial neurology appointment records. To assess the profile of degenerative *versus* non-degenerative conditions, only primary care and first neurology appointment records were analysed. Follow-up neurology records were used to evaluate final diagnoses and any diagnostic changes.

Inclusion and Exclusion Criteria

The inclusion criteria comprised patients aged 18 years or older who were referred to a first Neurology outpatient consultation for cognitive complaints. Patients with a prior diagnosis of dementia, as well as those presenting with clear-cut dementia at the initial visit—defined as moderate to advanced stages (Stages 4 to 7 on the Global Deterioration Scale)—were excluded.[13]

Diagnosis of Neurodegenerative and Non-Degenerative Disorder

Participants were classified as having a neurodegenerative disorder if diagnosed with early-stage dementia, mild cognitive impairment (MCI), or suspected neurodegeneration requiring follow-up and tests (e.g., imaging, neuropsychology, CSF, PET). If a degenerative diagnosis was later excluded, patients were reclassified as non-degenerative. Cognitive complaints were considered non-degenerative if due solely to attention issues, functional cognitive disorder, psychiatric conditions, medication effects, delirium, metabolic imbalance, or chronic medical decompensation.

Study Variables

All clinical and paraclinical data were collected by the same investigator and, in case of uncertainty, a senior neurologist was consulted (DF, RA). Data were collected from the records of two different neurologists.

We collected sociodemographic data including age, gender, education level, occupation, employment status, marital status and household composition. Clinical data included personal medical history, including psychiatric conditions and chronic pain, and other medical conditions such as cardiovascular risk factors (hypertension, dyslipidaemia, diabetes, smoking, excessive alcohol consumption, heart conditions, chronic obstructive pulmo-

nary disease), hearing loss, sleep disorders, and nutritional deficits. Additionally, family history of dementia, exposure to responsibility-demanding tasks, and major cognitive complaints were assessed. Tasks such as handling money and medication, being a caregiver for others, managing finances and doctor appointments were considered responsibility-demanding tasks, while missing payment deadlines, key appointments or important events, being demoted or fired at work and any action that endangered oneself or others (e.g. leaving the house without closing the door, forgetting the stove on) were considered major cognitive complaints.

Other specific cognitive complaints were also collected, including memory complaints such as difficulty retaining information and repetitive speech; temporal or spatial disorientation; mood and behaviour or personality changes; executive dysfunction, including difficulty planning. Furthermore, we recorded the existence of a recognizable precipitating event before the beginning of the complaints (e.g. hospitalization, widowhood, or the death of another close relative) and whether cognitive complaints were self-reported or reported by a family member. Objective clinical examination findings assessed included the presence of primitive reflexes, focal neurological signs, and parkinsonism. Performance in bedside cognitive testing was also evaluated, and partial and total scores were analysed. Additional clinical signs analysed included the head-turning sign (patients who turn their head towards their accompanying family member to seek assistance with the questions and tasks)[14] and the attended alone sign (patients who appear alone to the appointment).[15] Reports of Imaging findings, either from computed tomography (CT), or magnetic resonance imaging (MRI) if available, were also assessed for references of brain atrophy and signs of cerebrovascular disease.

Initially, sociodemographic and clinical data were collected from patients presenting with cognitive complaints who met the inclusion criteria. Each patient was classified as having a probable neurodegenerative or non-neurodegenerative condition based on the clinician's global impression after integrating the clinical information obtained during the first Neurology appointment and the diagnostic results available at that time (all patients underwent a head CT scan and had serum levels of vitamin B12, folate, thyroid function, and HIV and syphilis serologies assessed). In this manuscript, this initial evaluation is referred to as the "first diagnosis."

Subsequently, patients' clinical trajectories were monitored through medical records from ULS São João and available primary care documentation to identify any diagnostic shift from a non-neurodegenerative to a neurodegenerative condition over a 4.5-year period. This follow-up information was used to establish the "final diagnosis." Finally, we re-analysed the data for all patients who were initially diagnosed with a probable neurodegenerative disease or who experienced a diagnostic change over time.

Regarding etiology, patients were classified as having Alzheimer's disease defined either by the clinical criteria of possible or probable Alzheimer's disease (NINCDS-ADRDA) or by clinical and biological criteria if CSF or PET biomarkers were available.[16] Patients with evidence of cerebrovascular pathology plus a neurodegenerative component were classified as neurodegenerative. Those with overt cerebrovascular pathology showing a static or stepwise course, or without Alzheimer's co-pathology, were classified as non-degenerative "vascular cognitive impairment".[17] For this study, normal pressure hydrocephalus (NPH) was classified as neurodegenerative.

Statistical Analysis

Data were analyzed using SPSS (version 30.0). Descriptive statistics are presented as frequencies (n) and percentages (%) for categorical variables, and medians (Med) with quartiles (Q1–Q3) for continuous variables. Logistic regression assessed associations between covariates and cognitive complaints in a degenerative context, as well as diagnostic transitions from non-degenerative to degenerative. For multivariate adjustment, we included variables related to symptoms, examination findings, and diagnostic tests with $p < 0.10$, carefully considering sample size and event count. ROC curves evaluated the predictive capacity of multivariate models, and the Youden index identified optimal cut-off points.

Ethics Committee Approval

This study was approved by the Ethics Committee of ULS São João/Faculty of Medicine of the University of Porto.

Results

Study Population

The study sample included 283 patients, of whom 165 (58.3%) were female, with a median age of 73.0

years (interquartile range (IQR) 65.0-79.0).

In the first neurology appointment, 202 (71.4%) were considered to have a non-degenerative condition, while 81 (28.6%) were considered to have a neurodegenerative condition. After follow-up and integration of clinical and paraclinical data, the final diagnosis was considered to be a neurodegenerative condition in 108 (38.2%) patients, while 169 (59.7%) were classified as having a non-degenerative condition, and six (2.1%) were lost to follow-up. During follow-up, a diagnostic change from a non-degenerative to a neurodegenerative condition occurred in 9.5% of the sample (27 patients), with a median time to diagnostic change of 16.0 months (IQR: 7.0–23.0 months); one patient had their diagnosis changed from a neurodegenerative to a non-degenerative condition.

Regarding cognitive complaint staging within the degenerative group, 22 individuals (20.3%) were classified as having mild cognitive impairment, and 86 (79.6%) as having mild dementia.

Regarding etiology, the most frequent diagnosis in the degenerative group was Alzheimer's disease (defined either by the clinical criteria of possible or probable Alzheimer's disease (NINCDS-ADRDA) (n=47; 40.7%),[18] or by clinical and biological criteria if CSF or PET biomarkers were available)[16] (5; 4.6%). A total of 21 patients (22.2%) with vascular and Alzheimer's co-pathology were included in the neurodegenerative group. Mild cognitive impairment (MCI) was found in 22 individuals, including six cases (5.6%) of amnestic MCI, and three cases (2.8%) of non-amnestic MCI. In 13 individuals (12.0%), the specific MCI subtype could not be determined.[19] Dementia associated with parkinsonism (Lewy body dementia or Parkinson's disease dementia) was found in 9 patients (8.3%).[20] For this study, normal pressure hydrocephalus (NPH) was classified as neurodegenerative (n=2; 1.9%). Frontotemporal dementia (n=1; 0.9%)[18] and progressive supranuclear palsy (n=1; 0.9%)[19] were each observed in one patient.

In the non-degenerative group, the most frequent etiology was anxiety and/or depression (n=47; 27.8%). The second most common cause was vascular cognitive impairment (n=25; 14.8%), followed by attention/concentration deficits (n=14; 8.3%), followed by other psychiatric disorders (n=10; 5.9%), functional cognitive disorder (n=7; 4.1%), age-related cognitive decline (n=4; 2.4%), acute confusional state (n=4; 2.4%), iatrogenic causes (n=3; 1.8%), and cognitive complaints associated with alcohol consumption (n=2; 1.2%).

In 53 patients (31.4%), the etiology of cognitive complaints was not specified.

Table 1 shows final diagnoses of degenerative and non-degenerative cognitive complaints by etiology. **Table 2** details sample characteristics and their association with a probable neurodegenerative diagnosis. **Fig. 1** displays odds ratios (OR) and *p*-values for these associations. **Table 3** presents crude ORs and p-values for factors linked to a later diagnostic change to a neurodegenerative condition. The analysis included only patients who were initially diagnosed with a non-neurodegenerative condition and had sufficient follow-up to allow diagnostic reassessment (N=170). From the original

Table 1. Etiological diagnoses of non-degenerative and degenerative cognitive complaints.

Non-degenerative diagnosis (N=169)		Degenerative diagnosis (N=108)	
Anxiety and/or depression	47 (27.8%)	Alzheimer's disease	73 (67.5%)
Vascular dementia	25 (14.8%)	AD defined by clinical criteria	47 (40.7%)
Attention/concentration deficits	14 (8.3%)	AD defined by clinical criteria plus biomarkers	5 (4.6%)
Other psychiatric disorders	10 (5.9%)	Co-pathology AD plus vascular dementia	21 (22.2%)
Functional neurologic disorder	7 (4.1%)	MCI	22 (20.4%)
Age related cognitive decline	4 (2.4%)	MCI not otherwise specified	13 (12.0%)
Acute confusional state	4 (2.4%)	MCI amnestic	6 (5.6%)
Iatrogenic	3 (1.8%)	MCI non-amnestic	3 (2.8%)
Alcohol	2 (1.2%)	Lewy body dementia and Parkinson's disease	9 (8.3%)
		Normal pressure hydrocephalus	2 (1.9%)
		Progressive supranuclear palsy	1 (0.9%)
Not specified	53 (31.4%)	Frontotemporal dementia	1 (0.9%)

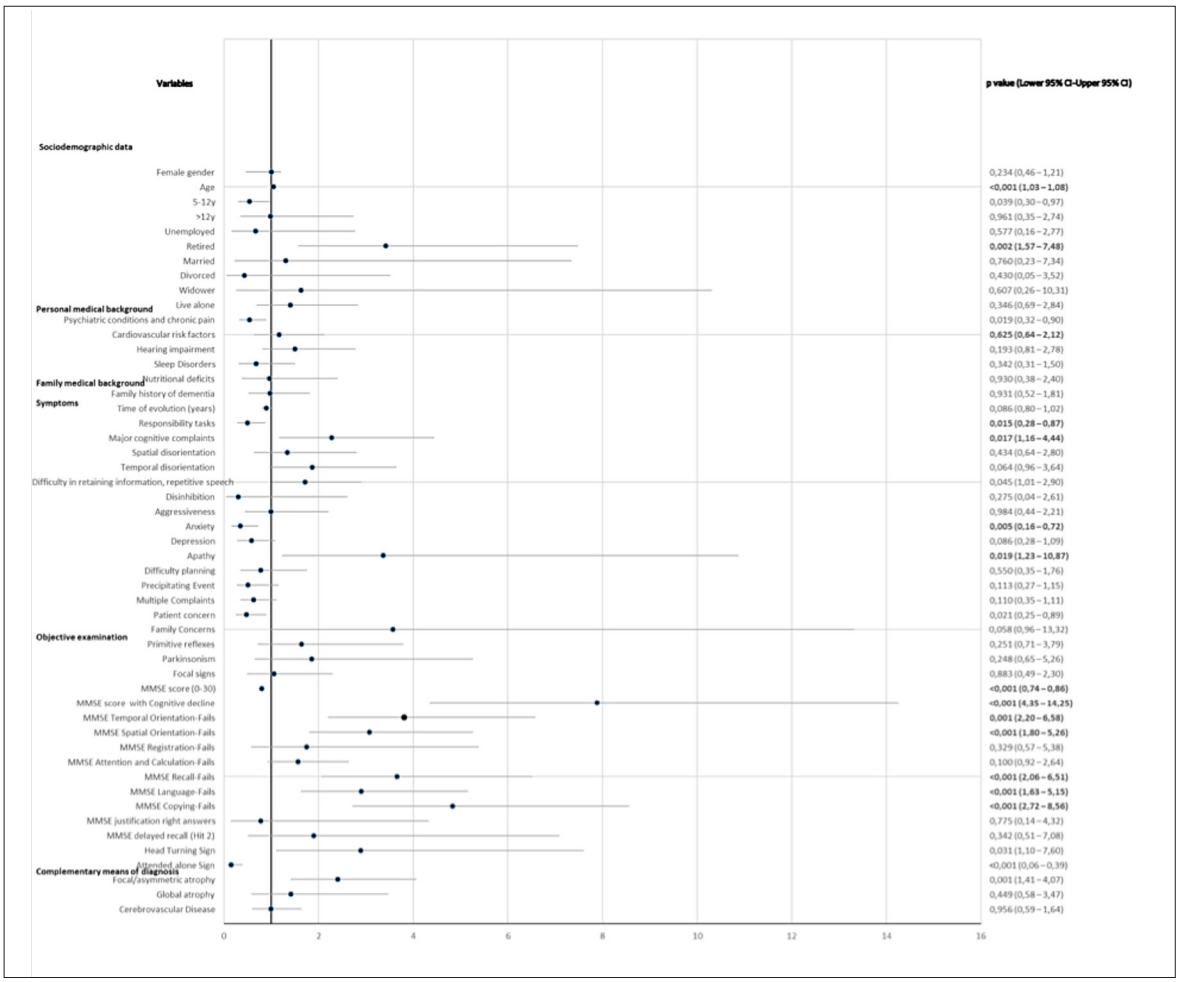

Figure 1. Schematic representation of the association between the various variables and the diagnosis of neurodegenerative disease.

For the purpose of representativeness and improved readability of Fig. 1, the values for the variables delayed recall (Hit 0) (p<0.001 (CI 6.92-629.61)) and delayed recall (Hit 1) (p=0.096 (CI 0.77-26.45)) were omitted from it.

group of 202 patients with an initial non-neurodegenerative diagnosis, 27 patients who subsequently converted to a neurodegenerative diagnosis were excluded from this comparison, as were six patients lost to follow-up; additionally, one patient whose diagnosis changed from neurodegenerative to non-neurodegenerative was included, resulting in a final sample of 170 patients.

Sociodemographic Data

In the non-degenerative group, 39.1% were male and 60.9% female; in the degenerative group, 46.3% were male and 53.7% female. There was no statistically significant difference between females and males (OR=0.74, p=0.234). The median age was 71years (IQR: 61.0–77.0) in the non-degenerative group and 76.0 years (IQR: 71.0–80.0) in the degenerative group, with older age being significantly associated with a degenerative diagnosis (OR=1.05, p<0.001).

In terms of education levels, the group who completed 5 to 12 years of school had lower chances of a neurodegenerative disorder (OR 0.54, p=0.039). Regarding professional status, retired individuals had a significantly higher odds of receiving a degenerative diagnosis (OR=3.42, p=0.002). No association was found between living alone and a degenerative diagnosis (OR=1.40, p=0.346).

Personal medical background

Psychiatric conditions and chronic pain were less common in the degenerative group (29.6%) compared to the non-degenerative group (43.8%), (OR=0.54, p=0.019).

Table 2. Crude odds ratios for associations with final diagnosis.

	Final diagnosis: Non-degenerative (n=169)	Final diagnosis: Degenerative (n=108)	OR	*p*-value
Sociodemographic data				
Gender				
Male	66 (39.1%)	50 (46.3%)	REF	REF
Female	103 (60.9%)	58 (53.7%)	0.74	0.234
Age	71.0 (61.0-77.0)	76.0 (71.0-80.0)	**1.05**	**<0.001*** **
Education				
0-4y	94 (61.0%)	75 (72.1%)	REF	REF
5-12y	51 (33.1%)	22 (21.2%)	**0.54**	**0,039***
>12y	9 (5.8%)	7 (6.7%)	0,98	0,961
Unknown	15 (8.9%)	4 (3.7%)		
Professional status				
Employed	36 (21.3%)	9 (8.3%)	REF	REF
Unemployed	18 (10.7%)	3 (2.8%)	0.67	0.577
Retired	112 (66.3%)	96 (88.9%)	**3.42**	**0.002****
Unknown	3 (1.8%)	0 (0.0%)		
Marital status				
Single	4 (2.4%)	2 (1.9%)	REF	REF
Married	104 (61.5%)	68 (63.0%)	1.31	0.76
Divorced	14 (8.3%)	3 (2.8%)	0.43	0.43
Widower	16 (9.5%)	13 (12.0%)	1.63	0.61
Unknown	31 (18.3%)	22 (20.4%)		
Live alone	20 (11.8%)	17 (15.7%)	1.40	0.346
Unknown	17 (10.1%)	11 (10.2%)		
Personal medical background				
Psychiatric conditions and chronic pain	74 (43.8%)	32 (29.6%)	**0.54**	**0.019***
Cardiovascular risk factors	132 (78.1%)	87 (80.6%)	1,16	0.625
Hearing impairment	27 (16.0%)	24 (22.2%)	1.50	0.193
Sleep Disorders	22 (13.0%)	10 (9.3%)	0.68	0.342
Nutritional deficits	13 (7.7%)	8 (7.4%)	0.96	0.930
Family medical background				
Family history of dementia	32 (18.9%)	20 (18.5%)	0.97	0.931
Symptoms				
Time of evolution (years)	1.0 (0.58-3.00)	1.0 (0.83-2.0)	**0.90**	**0.086‡**
Responsibility tasks	99 (58.6%)	49 (45.4%)	**0.50**	**0.015***
Unknown	32 (18,9%)	21 (19.4%)		
Major cognitive complaints	18 (10.7%)	23 (21.3%)	**2.27**	**0.017***
Spatial disorientation	18 (10.7%)	15 (13.9%)	1.34	0.434
Unknown	11 (6.5%)	6 (5.6%)		
Temporal disorientation	20 (11.8%)	22 (20.4%)	**1.87**	**0.064‡**
Unknown	11 (6.5%)	5 (4.6%)		
Difficulty in retaining information, repetitive speech	44 (27.8%)	41 (39.8%)	**1.71**	**0.045***
Unknown	11 (6.5%)	5 (4.6%)		
Disinhibition	5 (3.0%)	1 (0.9%)	0.30	0.275
Unknown	11 (6.5%)	5 (4.6%)		
Aggressiveness	17 (10.1%)	11 (10.2%)	0.99	0.984
Unknown	11 (6.5%)	5 (4.6%)		
Anxiety	38 (22.5%)	10 (9.3%)	**0.34**	**0.005****
Unknown	11 (6.5%)	5 (4.6%)		
Depression	35 (20.7%)	14 (13.0%)	**0.58**	**0.086‡**
Unknown	11 (6.5%)	5 (4.6%)		
Apathy	5 (3.0%)	11 (10.2%)	**3.36**	**0.019***
Unknown	11 (6.5%)	5 (4.6%)		
Difficulty planning	19 (11.2%)	10 (9.3%)	0.78	0.550
Unknown	12 (7.1%)	5 (4.6%)		
Precipitating event	31 (18.3%)	12 (11.1%)	0.51	0.113
Unknown	2 (1.2%)	2 (1.9%)		
Multiple complaints	50 (29.6%)	22 (20.4%)	0.63	0.110
Unknown	1 (0.6%)	3 (2.8%)		
Patient concern	120 (71.0%)	52 (48.1%)	**0.47**	**0.021***
Unknown	23 (13.6%)	32 (29.6%)		
Family concerns	74 (43.8 %)	72 (66.7%)	**3.57**	**0.058‡**
Unknown	84 (49.7%)	33 (30.6%)		

Table 2. Crude odds ratios for associations with final diagnosis. (continuation)

	Final diagnosis: Non-degenerative (n=169)	Final diagnosis: Degenerative (n=108)	OR	*p*-value
Objective examination				
Primitive reflexes	12 (7.1%)	12 (11.1%)	1.64	0.251
Parkinsonism	7 (4.1%)	8 (7.4%)	1.85	0.248
Focal signs	18 (10.7%)	12 (11.1%)	1.06	0.883
Unknown	0 (0.0%)	1 (0.9%)		
Bedside cognitive testing scores score (0-30)	28.0 (26.0-29.0)	23.5 (21.0-26.0)	**0.80**	**<0.001*** **
Bedside cognitive testing score classification with cognitive decline	21 (12.4%)	57 (52.8%)	**7.88**	**<0.001*** **
Temporal orientation-fails	53 (31.4%)	68 (63.0%)	**3.81**	**0.001*** **
Unknown	27 (16.0%)	10 (9.3%)		
Spatial orientation-fails	45 (26.6%)	57 (52.8%)	**3.07**	**<0.001*** **
Unknown	27 (16.0%)	11 (10.2%)		
Registration-fails	6 (3.6%)	7 (6.5%)	1.75	0.329
Unknown	31 (18.3%)	13 (12.0%)		
Attention and calculation-fails	50 (29.6%)	46 (42.6%)	1.56	0.100
Unknown	31 (18.3%)	10 (9.3%)		
Recall-fails	65 (38.5%)	74 (68.5%)	**3.66**	**<0.001*** **
Unknown	30 (17.8%)	11 (10.2%)		
Language-fails	28 (16.6%)	42 (38.9%)	**2.90**	**<0.001*** **
Unknown	31 (18.3%)	9 (8.3%)		
Copying-fails	30 (17.8%)	54 (50.0%)	**4.83**	**<0.001*** **
Unknown	29 (17.2%)	13 (12.0%)		
Justification right answers	4 (2.4%)	2 (1.9%)	0.78	0.775
Delayed recall				
Hit 0	1 (0.6%)	11 (10.2%)	**66.00**	**<0.001*** **
Hit 1	4 (2.4%)	3 (2.8%)	**4.50**	**0.096‡**
Hit 2	19 (11.2%)	6 (5.6%)	**1.90**	**0.342**
Hit 3	30 (17.8%)	5 (4.6%)	REF	REF
Unknown	115 (68.0%)	83 (76.9%)		
Head turning sign	7 (4.1%)	12 (11.1%)	**2.89**	**0.031***
Attended alone sign	42 (24.9%)	5 (4.6%)	**0.15**	**<0.001*** **
Complementary means of diagnosis				
Focal/asymmetrical atrophy	42 (24.9%)	48 (44.4%)	**2.40**	**0.001*** **
Unknown	18 (10.7%)	8 (7.4%)		
Global atrophy	11 (6.5%)	10 (9.3%)	1.41	0.449
Unknown	18 (10.7%)	8 (7.4%)		
Cerebrovascular disease	70 (41.4%)	46 (42.6%)	0.99	0.956
Unknown	18 (10.7%)	8 (7.4%)		

Results presented as n (%), OR and *p*-values; REF, reference category; unknown, not applicable or variables were at least one of the categories ≤ 1 for degenerative diagnosis were excluded; ‡$p<0.10$; *$p<0.05$; **$p<0.01$; ***$p<0.001$.

Table 3. Crude odds ratios for associations with change of first diagnosis to degenerative.

	Changed diagnosis: No (n=170)	Changed diagnosis: Degenerative (n=27)	OR	*p*-value
Sociodemographic data				
Gender				
Male	67 (39.4%)	9 (33.3%)	REF	REF
Female	103 (60.6%)	18 (66.7%)	1.30	0.547
Age	71.0 (61.0 - 78.0)	75.0 (69.0 - 79.0)	**1.04**	**0.042***
Education				
0-4y	94 (61.0%)	15 (57.7%)	REF	REF
5-12y	51 (33.1%)	9 (34.6%)	1.11	0.825
>12y	9 (5.8%)	2 (7.7%)	1.39	0.690
Unknown	16 (9.4%)	1 (3.7%)		
Professional status				
Employed	36 (21.2%)	3 (11.1%)	REF	REF
Unemployed	18 (10.6%)	2 (7.4%)	1.33	0.764
Retired	113 (66.5%)	22 (81.5%)	2.34	0.188
Unknown	3 (1.8%)	0 (0.0%)		
Marital status				
Single	4 (2.4%)	0 (0.0%)	Excluded	Excluded
Married	105 (61.8%)	18 (66.7%)	Excluded	Excluded
Divorced	14 (8.2%)	2 (7.4%)	Excluded	Excluded

Table 3. Crude odds ratios for associations with change of first diagnosis to degenerative. (continuation)

	Changed diagnosis: No (n=170)	Changed diagnosis: Degenerative (n=27)	OR	*p*-value
Widower	16 (9.4%)	0 (0.0%)	Excluded	Excluded
Unknown	31 (18.2%)	7 (25.9%)		
Live alone	20 (11.8%)	2 (7.4%)	0.63	0.557
Unknown	17 (10.0%)	4 (14.8%)		
Personal medical background				
Psychiatric conditions and chronic pain	74 (89.2%)	9 (33.3%)	0.65	0.321
Cardiovascular risk factors	133 (78.2%)	19 (70.4%)	0.66	0.368
Hearing impairment	27 (15.9%)	8 (29.6%)	2.23	**0.088‡**
Sleep disorders	22 (12.9%)	4 (14.8%)	1.17	0.789
Nutritional deficits	13 (7.6%)	3 (11.1%)	1.51	0.543
Family medical background				
Family history of dementia	32 (18.8%)	5 (18.5%)	0.98	0.970
Symptoms				
Time of evolution (years)	2.0 (0.8 - 7.0)	1.0 (0.8 - 2.0)	0.86	0.213
Responsibility tasks	99 (58.2%)	13 (48.1%)	1.25	0.714
Unknown	33 (19.4%)	10 (37.0%)		
Major cognitive complaints	18 (10.6%)	1 (3.7%)	0.32	0.284
Spacial disorientation	18 (10.6%)	5 (18.5%)	2.06	0.198
Unknown	11 (6.5%)	3 (11.1%)		
Temporal disorientation	20 (11.8%)	5 (18.5%)	1.83	0.278
Unknown	11 (6.5%)	3 (11.1%)		
Difficulty in retaining information, repetitive speech	44 (25.9%)	8 (29.6%)	1.31	0.567
Unknown	11 (6.5%)	3 (11.1%)		
Disinhibition	5 (2.9%)	0 (0.0%)	0.00	0.999
Unknown	11 (6.5%)	3 (11.1%)		
Aggressiveness	17 (10.0%)	2 (7.4%)	0.76	0.725
Unknown	11 (6.5%)	3 (11.1%)		
Anxiety	38 (22.4%)	3 (11.1%)	0.45	0.222
Unknown	11 (6.5%)	3 (11.1%)		
Depression	35 (20.6%)	4 (14.8%)	0.71	0.553
Unknown	11 (6.5%)	3 (11.1%)		
Apathy	5 (2.9%)	3 (11.1%)	**4.40**	**0.053‡**
Unknown	11 (6.5%)	3 (11.1%)		
Difficulty planning	20 (11.8%)	2 (7.4%)	0.63	0.548
Unknown	12 (7.1%)	3 (11.1%)		
Precipitating event	31 (18.2%)	1 (3.7%)	**0.17**	**0.088‡**
Unknown	2 (1.2%)	0 (0.0%)		
Multiple complaints	50 (29.4%)	7 (25.9%)	0.83	0.698
Unknown	1 (0.6%)	0 (0.0%)		
Patient concern	120 (70.6%)	16 (59.3%)	1.16	0.828
Unknown	24 (14.1%)	8 (29.6%)		
Family concerns	74 (43.5%)	14 (51.9%)	2.08	0.499
Unknown	85 (50.0%)	12 (44.4%)		
Objective examination				
Primitive reflexes	12 (7.1%)	1 (3.7%)	0.51	0.522
Parkinsonism	7 (4.1%)	4 (14.8%)	**4.05**	**0.035***
Focal signs	18 (10.6%)	5 (18.5%)	1.92	0.240
Bedside cognitive testing score (0-30)	28.0 (26.0 - 29.0)	24.0 (23.0 - 25.5)	0.86	**0.001****
Bedside cognitive testing score classification with cognitive decline	21 (12.4%)	10 (37.0%)	**4.17**	**0.002****
Temporal orientation-fails	53 (31.2%)	15 (55.6%)	**2.29**	**0.056‡**
Unknown	28 (16.5%)	1 (3.7%)		
Spatial orientation-fails	45 (26.5%)	17 (63.0%)	**4.07**	**0.002****
Unknown	28 (16.5%)	1 (3.7%)		
Registration-fails	6 (3.5%)	1 (3.7%)	0.88	0.908
Unknown	32 (18.8%)	1 (3.7%)		
Attention and calculation- fails	50 (29.4%)	12 (44.4%)	1.41	0.422
Unknown	32 (18.8%)	0 (0.0%)		
Recall-fails	65 (38.2%)	19 (70.4%)	**2.70**	**0.029***
Unknown	31 (18.2%)	0 (0.0%)		
Language-fails	28 (16.5%)	14 (51.9%)	**4.23**	**0.001****
Unknown	32 (18.8%)	0 (0.0%)		
Copying-fails	30 (17.6%)	15 (55.6%)	**5.00**	**<0.001*****
Unknown	30 (17.6%)	1 (3.7%)		

Table 3. Crude odds ratios for associations with change of first diagnosis to degenerative. (continuation)

	Changed diagnosis: No (n=170)	Changed diagnosis: Degenerative (n=27)	OR	*p*-value
Justification right answers	4 (2.4%)	2 (7.4%)	3.32	0.179
Delayed recall				
Hit 0	1 (0.6%)	1 (3.7%)	30.00	0.051
Hit 1	4 (2.4%)	0 (0.0%)	0.00	0.999
Hit 2	19 (11.2%)	2 (7.4%)	3.16	0.361
Hit 3	30 (17.6%)	1 (3.7%)	REF	REF
Unknown	116 (68.2%)	23 (85.2%)		
Head turning sign	7 (4.1%)	2 (7.4%)	1.86	0.454
Attended alone sign	42 (24.7%)	0 (0.0%)	0.00	0.997
Complementary means of diagnosis				
Focal/asymmetrical atrophy	42 (24.7%)	11 (40.7%)	**2.22**	**0.076‡**
Unknown	18 (10.6%)	3 (11.1%)		
Global atrophy	11 (6.5%)	3 (11.1%)	1.83	0.382
Unknown	18 (10.6%)	3 (11.1%)		
Cerebrovascular disease	71 (41.8%)	12 (44.4%)	1.14	0.764
Unknown	18 (10.6%)	3 (11.1%)		

Results presented as n (%), OR and *p*-values; REF, reference category; unknown, not applicable or variables were at least one of the categories ≤ 1 for degenerative diagnosis were excluded; ‡$p<0.10$; *$p<0.05$; **$p<0.01$; ***$p<0.001$

Family medical background

No association between a degenerative diagnosis and a family history of dementia was found.

Symptoms

Engagement in responsibility-demanding tasks was less common in the degenerative group (45.4%) compared to the non-degenerative group (58.6%), with a significant association (OR=0.50, $p=0.015$). *Major* cognitive complaints were more frequently reported in the degenerative group (21.3%) compared to the non-degenerative group (10.7%), with a statistically meaningful association (OR=2.27, $p=0.017$). The degenerative group showed higher rates of information retention difficulties and repetitive speech (39.8% *vs* 27.8%; OR=1.71, $p<0.045$). Anxiety was less frequent in the degenerative group (9.3% *vs* 22.5%; OR=0.34, $p=0.005$), while apathy was more common (10.2% *vs* 3.0%; OR=3.36, $p=0.019$). Symptom self-awareness was also reduced in this group (48.1% *vs* 71.0%; OR=0.47, $p=0.021$).

Objective examination

Primitive reflexes were more common in the degenerative group (11.1%) than in the non-degenerative group (7.1%), but this association was not statistically significant (OR=1.64, $p=0.251$). The degenerative group had a lower median score in bedside cognitive testing (23.5 *vs* 28.0; OR=0.80, $p<0.001$) and higher cognitive decline prevalence (52.8% *vs* 12.4%; OR=7.88, $p<0.001$).

Patients with a neurodegenerative condition performed worse in temporal orientation (63.0% *vs* 31.4%, OR=3.81, $p=0.001$), spatial orientation (52.8% *vs* 26.6%, OR=3.07, $p<0.001$), recall (68.5% *vs* 38.5%, OR=3.66, $p<0.001$), language (38.9% *vs* 16.6%, OR=2.90, $p<0.001$), and visuospatial tasks (50.0% *vs* 17.8%, OR=4.83, $p<0.001$).

The head-turning sign was more frequent in the degenerative group (OR 2.89, $p=0.031$), while the attended alone sign was more common in the non-degenerative group (OR 0.15, $p<0.001$).

Parkinsonism was significantly more prevalent among patients whose diagnosis changed to neurodegenerative disorder during follow-up (14.8% *vs* 4.1%; OR=4.05, $p=0.035$).

Ancillary diagnostic testing

Focal/asymmetrical atrophy was more common in the degenerative group (44.4% *vs* 24.9%, OR=2.40, $p=0.001$), while reports of "global atrophy" and "cerebrovascular disease" showed no significant association.

Multivariate Analysis

After univariate analysis, key variables linked to neurodegenerative diagnosis and progression were selected based on clinical relevance and senior investigator judgment. These included age; major cognitive complaints; cognitive decline by bedside testing; temporal orientation; immediate recall; delayed recall; and focal or asymmetrical brain atrophy on imaging (**Table 4**).

In the multivariate analysis, failure to recall any of the words on the delayed recall task (aOR= 39.66, $p=0.006$)

Table 4. Multivariate analysis for final and for change to degenerative diagnosis.

Final diagnosis			
N=68, events= 19	**aOR**	***p*-value**	**95% CI**
Age	1.08	0.135	0.98 – 1.19
Major cognitive complaints	1.62	0.898	0.12 – 11.44
Bedside cognitive testing score classification with cognitive decline	1.45	0.675	0.24 – 9.12
Temporal orientation-Fails			
Fails	2.93	0.210	0.55– 15.76
Recall-Fails			
Fails	0.91	0.909	0.19 – 4.41
Delayed recall			
Hits 0	39.66	0.006	2.94-535.00
Hits 1	1.39	0.79	0.12-15.70
Hits 2	0.64	0.64	0.10 – 4.00
Hits 3	0.03	0.006**	0.02– 0.34
Focal/asymmetrical atrophy in brain imaging	10.21	0.014*	1.59 – 65.56

Change to degenerative diagnosis			
N=151, events= 24	**aOR**	***p*-value**	**95% CI**
Age	1.01	0.554	0.97 – 1.06
Low cognitive testing score compatible with cognitive decline	2.49	0.111	0.81 – 7.65
Recall-fails	1.49	0.444	0.54 – 4.18
Focal/asymmetrical atrophy in brain imaging	2.05	0.149	0.77 – 5.42
Parkinsonism	1.27	0.007**	1.89 – 55.94

Results presented as adjusted OR (aOR), *p*-values and 95% confidence intervals (95% CI); REF, reference; ‡$p<0.10$; *$p<0.05$; **$p<0.01$; ***$p<0.001$

and the presence of focal or asymmetrical atrophy on imaging studies (aOR=10.2; $p=0.014$) remained statistically significant predictors of a neurodegenerative diagnosis.

The set of explanatory variables for change to neurodegenerative diagnosis over time included: age (over 76 years); poor performance in memory tasks or overall cognitive testing; presence of focal or asymmetrical atrophy in brain imaging reports; and the presence of parkinsonism (**Table 4**). The presence of parkinsonism remained significantly associated with diagnostic change, with an aOR of 1.27 ($p=0.007$).

Finally, we evaluated two multivariate models' diagnostic performance in predicting neurodegenerative diagnosis and changes over time. A score based on each model's non-exponentiated coefficients was applied to the patients (**Table 5**).

ROC curves were constructed to assess the predictive quality of the models. The predictive capacity for a neurodegenerative diagnosis was 93.4%.

The Youden index was used to determine the optimal sensitivity and specificity balance. Hence, for identifying clinical characteristics indicative of a neurodegenerative disease as a final diagnosis, a score ≥7.56 yielded a sensitivity of 87.0% and a specificity of 88.4%.

Table 5. Coefficients of multivariate analysis for final and change to a degenerative diagnosis.

	First diagnosis		**Change of diagnosis**	
	B	**S.E.**	**B**	**S.E.**
Age	0.08	0.05	0.01	0.02
Major cognitive complaints	0.15	1.17		
Bedside cognitive testing score classification with cognitive decline	0.39	0.93	0.91	0.57
Temporal orientation-Fails	1.08	0.86		
Recall-Fails	-0.92	0.80	0.40	0.52
Delayed recall				
Hits 0	3.68	1.33		
Hits 1	0.33	1.24		
Hits 2	-0.44	0.93		
Focal/asymmetrical atrophy in neuroimaging	2.32	0.95	0.72	0.50
Parkinsonism			2.33	0.86
Mean score in data	6.98	0.29	1.88	0.06

B, unstandardized coefficient; S.E., standardized error

Discussion

Sample Characteristics Associated with Neurodegenerative Disease

It is expected that the number of people at risk for cognitive impairment and dementia will significantly increase in the coming years.[8,18] Identifying people in the early stages of a neurodegenerative disorder is important for prevention and treatment, given the recent approval of anti-amyloid treatments for the early stages of Alzheimer's disease in Europe.[6,19] Therefore, it is critical to triage as efficiently as possible the largest number of patients who may be eligible for treatments and further studies. In our study, we identify a profile of people who may be in the early stages of a neurodegenerative condition and who present themselves for a neurology appointment for the first time following referral from primary care.

In our cohort, younger patients had lower odds of having a degenerative diagnosis, which is noteworthy since age is one of the most well-established risk factor for developing dementia.[8] Regarding professional status, retirement was significantly associated with a degenerative diagnosis, which may be explained not only by the fact that this group comprises older individuals, but also by possibly a lower cognitive demand and output observed at this particular time in people's lives. Research suggests that a lack of mentally challenging activities might exacerbate the loss of cognitive function.[20] On the other hand, a deterioration in cognitive function can adversely impact the ability to manage work-related tasks and, consequently, may accelerate the decision to retire in people who may still be professionally active.[21]

Regarding personal medical history, we observed a lower frequency of psychiatric conditions in the neurodegenerative group. The association between a major depressive episode and diminished cognitive performance is well established, and depression may act as an independent risk factor for developing dementia.[22] Also, cardiovascular disease and cognitive decline share common risk factors, with hypertension as the main modifiable one, even though our study did not find an association.[23]

On the other hand, although we would expect to observe an association between the existence of a family history of dementia and a degenerative diagnosis, since family history is a known dementia risk factor, its absence in our cohort is unexpected, and may reflect insufficient clinical notes.[24] In addition, it is expected that a family history of dementia is associated with increased concern and vigilance for cognitive symptoms in other family members, which may lead to hypervigilance and overvaluation of minor symptoms that may not indicate a neurodegenerative diagnosis.[25,26] *Major* complaints, such as missing payment deadlines, key appointments or important events, being demoted or fired at work, or any action that endangers oneself or others, were associated with a degenerative diagnosis

Also, an intact capacity of performing responsibility-demanding tasks and successfully managing instrumental activities of daily living, including driving, working, handling money and medication, being a caregiver for others, managing finances and important events such as doctor appointments was significantly less common in the degenerative group.

Family members who report that the patient is struggling with episodic memory, such as difficulty in retaining information, repetitive behaviour and speech, were also more frequent in the degenerative group.[27]

Similarly, apathy was related to a diagnosis of a neurodegenerative disease in our cohort, as apathy is one of the most prevalent and enduring symptoms of dementia.[28]

As expected, symptom awareness was lower in the degenerative group, as these patients often lack insight, while family concern was higher. In non-degenerative cases, hypervigilance leads to more patient awareness.[29]

The head-turning sign, is a specific sign of cognitive impairment, with a high positive predictive value, and was significantly more common in the degenerative group. Conversely, the attended alone sign was much less common, serving as a robust marker of both the absence of dementia and of cognitively healthy individuals with cognitive complaints.[30,31] Also, parkinsonism was a feature frequently present in patients who were originally diagnosed as non-degenerative, but later were reclassified as a neurodegenerative condition. While these features may be difficult to assess in primary care, it is a red flag that warrants careful follow-up in patients presenting with cognitive complaints.

The presence of parkinsonism (established clinically by the attending physician, in agreement with MDS-UPDRS diagnostic criteria, specifically bradykinesia plus rest tremor or rigidity)[32] was significantly more common in the group where a change in diagnosis occurred from non-degenerative to degenerative. Parkinsonism typi-

cally emerges in association with cognitive complaints in diseases such as Parkinson's disease-associated dementia, dementia with Lewy bodies, and normal pressure hydrocephalus, which are challenging diagnoses in the early stages but may become clearer as the disease progresses.[33-35] This finding highlights the importance of thorough neurological examination, as the presence of even subtle parkinsonian features should prompt clinicians to consider neurodegenerative etiologies and maintain closer follow-up.

As expected, being classified as having cognitive decline according to bedside cognitive testing was significantly more common in the degenerative group, even though this only correctly classified 58% of degenerative cases. In fact, the presence of false negatives constitutes a limitation of bedside cognitive testing, as it may be insufficiently sensitive for subtle cognitive changes in mild cognitive impairment patients, and for dementias without an important decline in the memory domain.[36,37] Temporal and spatial orientation, language, and copying and drawing were the main domains where poorer performance was found in the neurodegenerative group. This highlights that, even if the final result of the bedside cognitive test score is within the normal range, patients who struggle with these specific domains, might warrant further attention due to the possibility of an underlying degenerative process. In the delayed recall task, we found that people who were unable to recall any of the words (i.e., a score of 0) had a significantly higher likelihood of receiving a neurodegenerative diagnosis. Patients who did not retrieve any of the three words presented to them in the middle of the test being administered had a significantly higher risk of being diagnosed with a neurodegenerative disorder, even though the very high OR and very wide confidence interval make this specific statistic unreliable. However, in clinical practice, if a patient struggles with remembering any of the words, he/she was asked to memorize during bedside cognitive testing, we usually consider it a red flag, which may warrant further testing.

Although performance on the three-word recall task, a brief assessment of verbal memory, declines with age, most individuals experiencing normal aging can typically recall 2 or 3 words. This contrasts sharply with individuals with dementia, who are often able to recall 0 or 1 word, a pattern reflected in our findings.[38]

Ancillary diagnostic tests revealed that reports of focal or asymmetrical atrophy were more commonly seen in the degenerative group. This was an anticipated finding, as both clinical manifestations and focal atrophy correlate to the pattern of dysfunctional protein accumulation involved in the pathophysiology of dementias. In AD, for example, the initial changes occur in the medial temporal lobe structures, including the entorhinal, perirhinal cortex, and hippocampus, and then spread throughout the brain, affecting other regions in more advanced stages of the disease.[39,40] In clinical practice, the written report of the brain imaging may be the only result available, and the actual images may not be readily available for review. We consider this a particularly important finding of our study: when a neuroradiologist mentions focal or asymmetrical atrophy (as opposed to unspecified vascular changes or global atrophy), this may be suggestive of an underlying neurodegenerative dementia.

Our proposed diagnostic model demonstrated strong predictive performance for degenerative disease, with a sensitivity of 87.4% and a specificity of 88.0%. Regarding diagnostic change, lower sensitivity and specificity values were observed, reflecting the smaller number of events and reduced diagnostic accuracy. The accuracy of our diagnostic model should, however, be interpreted as an optimistic estimate of its true performance, as training and testing were conducted in the same dataset. Future studies incorporating external validation or additional internal validation techniques (e.g., cross-validation or bootstrapping) will be essential to confirm the robustness and generalizability of these findings.

Based on these findings, we recommend that clinicians remain alert to the variables included in our model when evaluating patients with cognitive complaints, as these seem to have the strongest associations with a neurodegenerative disease diagnosis.

Limitations:

As a retrospective, single-centre study based on records from two physicians and a relatively small sample, the design may introduce selection, information, and self-confirmation biases. Therefore, the sample may not fully represent the broader population with cognitive complaints. Additionally, external validity may be limited, as results could reflect the specific practices of these physicians.

Another important limitation is that we only examinated cases initially classified as non-degenerative that

were later reclassified as degenerative, without investigating the reverse scenario. Although less frequent, the exclusion of this scenario means our study may fail to fully capture the extent of diagnostic errors and may not address all the clinical challenges and uncertainties clinicians face when evaluating cognitive complaints.

The diagnosis of neurodegenerative and non-degenerative conditions was primarily based on clinical judgment and established guidelines. However, the 4.5-year follow-up provides a reasonable timeframe to capture misdiagnoses, assuming patients with undetected neurodegenerative disorders would likely have returned to tertiary care if they had progressed. The reverse is also possible—non-degenerative cases mislabelled as neurodegenerative—which are often more challenging situations. This lack of more objective criteria may limit the study's conclusions.

Additionally, Alzheimer's disease was the predominant cause of dementia in our cohort. While not all patients with a possible or probable Alzheimer's diagnosis had biomarkers, these are not essential for the primary aim of this study—characterizing the profile of cognitive complaints in early-stage neurodegenerative disorders, which, based on epidemiology, are most often Alzheimer's disease.[16]

Conclusion

Our study identified several key characteristics that should alert clinicians to the possibility of a neurodegenerative diagnosis: advanced age (>76 years); being retired; low bedside cognitive testing scores; presence of parkinsonism; a positive head turning sign; difficulties in temporal and/or spatial orientation, language and/or visuospatial tasks; or asymmetrical atrophy in neuroimaging. Our diagnostic model suggests 88% sensitivity and specificity. Specifically, we propose that patients fitting this profile should be swiftly referred to a neurology outpatient clinic or, when blood-based biomarkers become available, prioritized for biomarker plasma testing. This will be increasingly relevant when disease-modifying treatments for the early stages of Alzheimer's disease finally become available. Finally, future validation and prospective application of these criteria in general neurology and primary care settings would be important next steps. ■

Contributorship Statement / Declaração de Contribuição

AR: Conceived and designed the study; contributed significantly to early and later drafts and performed critical revisions.

SM: Wrote the first draft; handled material preparation, data collection, and analysis

CC: Handled material preparation, data collection, analysis, and review.

All authors approved the final manuscript to be published.

AR: Concebeu e desenhou o estudo; contribuiu significativamente para as versões preliminares e posteriores e realizou revisões críticas.

SM: Redigiu a primeira versão; tratou da preparação do material, recolha de dados e análise.

CC: Tratou da preparação do material, recolha de dados, análise e revisão.

Todos os autores aprovaram o manuscrito final a ser publicado.

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Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

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