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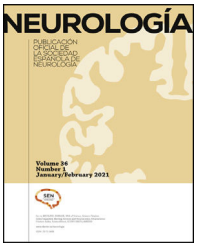

REVIEW ARTICLE

Degenerative dementias: a question of syndrome or disease?☆

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Abstract
Background: Neurologists refer to numerous ''syndromes,'' consisting of specific combinations of clinical manifestations, following a specific progression pattern, and with the support of blood analysis (without genomic-proteomic parameters) and neuroimaging findings (MRI, CT, perfusion SPECT, or ^{18}F-FDG-PET scans). Neurodegenerative ''diseases,'' on the other hand, are defined by specific combinations of clinical signs and histopathological findings; these must be confirmed by a clinical examination and a histology study or evidence of markers of a specific disorder for the diagnosis to be made. However, we currently know that most genetic and histopathological alterations can result in diverse syndromes. The genetic or histopathological aetiology of each syndrome is also heterogeneous, and we may encounter situations with pathophysiological alterations characterising more than one neurodegenerative disease. Sometimes, specific biomarkers are detected in the preclinical stage.
Development: We performed a literature review to identify patients whose histopathological or genetic disorder was discordant with that expected for the clinical syndrome observed, as well as patients presenting multiple neurodegenerative diseases, confirming the heterogeneity and overlap between syndromes and diseases. We also observed that the treatments currently prescribed to patients with neurodegenerative diseases are symptomatic.
Conclusions: Our findings show that the search for disease biomarkers should be restricted to research centres, given the lack of disease-modifying drugs or treatments improving survival. Moreover, syndromes and specific molecular or histopathological alterations should be managed independently of one another, and new ''diseases'' should be defined and adapted to current knowledge and practice.

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PALABRAS CLAVE
Biomarcadores;
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Enfermedad;
Enfermedades neurodegenerativas;
Síndrome

Demencias degenerativas: ¿un dilema de síndromes o de enfermedades?

Resumen
Introducción: En Neurología cognitiva se identifican múltiples «síndromes», consistentes en combinaciones específicas de manifestaciones clínicas, con una evolución determinada y con el apoyo de un análisis de sangre (sin parámetros de genómica-proteómica) y pruebas de neuroimagen (TAC, resonancia, SPECT de perfusión, PET con ^{18}F-fluorodesoxiglucosa). Por otra parte, las «enfermedades» neurodegenerativas demenciantes representan combinaciones clínico-histopatológicas concretas, cuya presencia debe comprobarse en la exploración del enfermo, junto con un estudio histológico o evidencia de marcadores del trastorno molecular específico. No obstante, actualmente se sabe que la manifestación sindrómica de cada alteración histopatológica o genética es variada, que el sustrato histopatológico o genético de cada síndrome también lo es y que a veces coexisten alteraciones fisiopatológicas de más de una enfermedad neurodegenerativa. Además, ocasionalmente se detectan biomarcadores específicos en la fase preclínica.
Desarrollo: Tras realizar una búsqueda bibliográfica de casos con alteración histopatológica o genética discordante con la esperada para el síndrome observado, y de casos con coexistencia de enfermedades degenerativas, resulta evidente la heterogeneidad y solapamiento entre síndromes y enfermedades neurodegenerativas. Además, en la revisión se comprueba que los tratamientos que se prescriben a pacientes con enfermedades degenerativas son sintomáticos.
Conclusiones: De la revisión se desprende que, mientras no existan tratamientos modificadores de la progresión o la supervivencia, la búsqueda de marcadores de enfermedad debe quedar reservada a Centros investigadores. Además, deberían manejarse de modo independiente los síndromes y las alteraciones moleculares e histopatológicas específicas, con definición de nuevas «enfermedades», adaptada a los conocimientos y la práctica actuales.

Introduction

In the latter quarter of the 19th century, Ramón y Cajal and other histologists established the basis for the development of microscopic anatomical pathology, enabling the study of the cellular substrate of healthy and diseased organic tissues. As a result, in the following decades, some neurologists and psychiatrists who also practised neuropathology described histopathological alterations in the brains of patients who developed dementia with specific clinical manifestations. After an initial publication (or communication), if other researchers reported similar cases (with the same combination of clinical and pathological signs), then a new nosological concept was introduced; the new entity was frequently assigned the name ''disease'' plus the name of the author of the first description (e.g., Pick disease, Alzheimer disease [AD], Steele-Richardson-Olszewski disease).

The laboratory and neuroimaging techniques invented and developed in the 20th century led to huge advances in our understanding of the molecular and genetic substrates of the neurodegenerative diseases that cause dementia. Furthermore, the description of patterns of cognitive impairment and other associated neurological alterations, together with neuroimaging findings, enabled the definition of specific phenotypes (e.g., corticobasal syndrome, semantic variant primary progressive aphasia, posterior cortical atrophy).

This expansion of medical knowledge resulted in the modification of diagnostic algorithms. In fact, criteria for the diagnosis of degenerative diseases that cause dementia need to be updated with ever-increasing frequency. Until several decades ago, a patient displaying progressive dementia with predominant amnestic disorder, changes in social behaviour, choreic dyskinesia, or recurrent falls and supranuclear ophthalmoparesis, and no neuroimaging evidence of hydrocephalus, tumours, or relevant vascular lesions, would be diagnosed with AD, frontotemporal degeneration (FTD; or Pick disease), Huntington disease, or progressive supranuclear palsy (PSP; or Steele-Richardson-Olszewski disease), respectively, with the assumption that the anatomopathological substrate would be that considered specific to each disease. Subsequently, diagnostic criteria included specific signs of the corresponding degenerative disease (e.g., atrophy of the medial temporal lobe in AD, or in the prefrontal and anterior temporal regions in frontotemporal dementia), which are not pathognomonic of the suspected causal entity but which do increase the probability of correct clinical diagnosis. With the arrival of functional neuroimaging in clinical settings, and the availability of some biochemical and genetic markers, some degenerative diseases (such as Huntington disease or AD) can be diagnosed in the prodromal and even in the presymptomatic phase.[1—3] More complete understanding of the chronology of syndromic patterns also resulted in new proposed criteria for aetiological diagnosis in the pre-dementia phase in the absence of molecular markers (Lewy body dementia,[4] frontotemporal dementia[5]).

The emergence of markers of the molecular substrate of degenerative diseases represents a historic step in their diagnosis. Diagnostic criteria for AD have followed this trend, with the 2018 National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria[6] requiring the detection of altered levels of β-amyloid 42 (Aβ42; measured with positron emission tomography [PET] with amyloid tracers or through determination of Aβ42 in the cerebrospinal fluid [CSF]) and phosphorylated tau protein (measured using PET with tau tracers or determination in the CSF). With a view to ensuring high specificity, the 2014 IWG-1 criteria[7] no longer consider medial temporal lobe atrophy or temporopari-

etal hypometabolism on ^{18}F-FDG PET images to be pathognomonic of AD, despite these being markers of probable neurodegeneration, and the 2018 NIA-AA criteria[6] do not allow for diagnosis based solely on the presence of the typical mutations associated with the disease. Following this line of reasoning, other neurodegenerative ''diseases'' may not be diagnosed unequivocally until markers of specific underlying molecular alterations can be established.[8–13]

This subject is further complicated by the fact that many patients presenting biomarkers of the molecular and/or genetic substrate of given disease eventually develop a clinical syndrome other than that expected, or show different combinations of only some parts of the syndrome. In other words, phenotypic heterogeneity has been demonstrated in association with specific proteinopathies or mutations. Likewise, patients with a specific syndrome may present diverse molecular or genetic substrates. Occasionally, patients initially present one syndrome and subsequently develop signs of one or more other syndromes, or switch between syndromes.[14,15] Moreover, some patients with a particular syndrome present neuropathological alterations characteristic of more than one disease. This historical development eventually led to the term ''Pick disease'' being replaced with ''frontotemporal degeneration,'' as many patients with classical symptoms of the disease (changes in personality and progressive dysphasia due to frontal lobe dysfunction) did not present the expected tauopathy with intraneuronal Pick bodies.[16] At least 3 phenotypes of FTD have since been described (behavioural variant frontotemporal dementia, nonfluent/agrammatic primary progressive aphasia, and semantic variant primary progressive aphasia); a clinical and neuropathological overlap has also been observed between these phenotypes and those attributed to corticobasal degeneration (CBD) and PSP. As a result, these entities were grouped together in a new construct, the ''Pick complex.''[14] The problem is compounded by the fact that CBD and PSP also display diverse phenotypes.[17,18] Furthermore, the heterogeneity and overlaps also extend to other diseases considered to be mutually independent. For this reason, criteria have had to allow for the clinical diagnosis of a ''disease'' (a nosological construct with a specific molecular substrate) to be classified as possible, probable, or definite, thereby acknowledging the fact that, without autopsy findings or unequivocal biomarkers pointing to specific underlying pathophysiological phenomena, no syndrome in and of itself is sufficient to securely diagnose a given degenerative disease as the cause.[6,7]

Given that the clinicopathological overlaps between syndromes and diseases extend to a significant part of degeneration in cognitive neurology, and the fact that we are yet to discover efficacious drugs targeting phenomena closely linked to the molecular pathologies that define these ''diseases,'' it is unclear whether we should dedicate time, effort, and resources to the diagnosis of these ''diseases'' in purely clinical settings.

Methods

Based on the hypothesis that diagnosis of a degenerative dementia disorder is non-specific in the absence of markers of the underlying molecular pathology, a literature search was performed to identify cases of discrepancies between the clinical picture observed (syndrome) and the underlying molecular alteration (specific to the disease): in other words, situations in which the aetiological diagnosis differed from that expected based on the syndrome observed. The review also included reports of cases of simultaneous presentation of at least 2 different types of neurodegenerative dementia.

Another literature search reviewed the pharmacological treatments currently prescribed to patients with neurodegenerative dementias. These drugs are intended to control specific clinical manifestations caused by the loss of activity of neuronal circuits, resulting in a progressive reduction in the subpopulation of diseased cells, which leads to an imbalance in the activity of certain neurotransmitters. In other words, symptomatic treatments are currently prescribed due to the lack of disease-modifying treatments.

Results

Table 1 shows the diseases (entities with specific molecular or histopathological features) diagnosed in patients who in life showed specific clinical syndromes. It also includes the clinical expressions observed in patients with specific genetic mutations.

Table 2 summarises cases of patients with co-presence of more than one neurodegenerative disease potentially causing dementia.

Table 3 lists the treatments currently prescribed for patients with degenerative dementia and the clinical manifestations they target.

Discussion

The literature review revealed great heterogeneity (Table 1), both in the aetiology of each syndrome (the left column of the table lists the most relevant syndromes in cognitive neurology) and in the clinical presentation of each disease (many entities in the central and right columns are repeated for various different syndromes). Therefore, while some sporadic syndromes may predominantly be caused by a specific disease, or mutations in specific genes may be more common in the aetiology of certain familial syndromes (the most frequent causes are marked with a hash sign [#]), it is clear that observing a given syndrome is not sufficient to establish the underlying disease or genetic mutation.

The fact that neurodegenerative diseases with potential to cause dementia are not mutually exclusive (Table 2) further complicates the task of establishing an aetiological diagnosis. For each patient, we must study biomarkers for a broad range of diseases potentially involved in the appearance of clinical signs. For example, detecting AD biomarkers in a patient with dementia does not rule out the possibility that the patient may simultaneously present another type of neurodegenerative dementia.

In accordance with the recommendations of the expert panel established by the NIA-AA, which in 2018 published its diagnostic criteria for AD,[6] diagnosis of a degenerative ''disease'' may only be established if presence of the characteristic histopathological lesions can be confirmed in the brain (generally in an autopsy study) or if biomarkers unequivocally indicate the presence of the proteinopathy (or combination of proteinopathies, or occasionally another type of molecular pathology) needed to identify the disease. These markers have been studied more for AD than for other neurodegenerative diseases, and require CSF analysis or brain PET scans with very specific tracers. These tests are currently somewhat invasive (lumbar puncture) or costly, and are not included in routine diagnostic work-up for dementia. Furthermore, demonstrating the presence or absence of markers of AD in a patient does not confirm or rule out the presence of other potentially co-present neuropathological processes (Table 2).

It is important to recognise the value of the currently available markers (in our setting), such as marked atrophy (observed with CT or MRI studies) and hypometabolism (^{18}F-FDG PET) in specific brain regions; while not highly specific, these markers assist in detecting neurodegenerative processes. In research contexts, they are valuable in establishing a specific phenotype in patients whose clinical manifestations are minimal or are characteristic of more than one disease, whereas in clinical settings they show (or help to rule out) the presence of a neurodegenerative process in some cases in which the clinical expression, progression, or comorbidities may give rise to doubt. In fact, structural neuroimaging, like comprehensive blood analysis (not including special markers), should be performed in all patients with cognitive alterations presenting progression or with no clear cause, as some potentially

Table 1 Degenerative diseases and genetic alterations reported as the cause of various clinical syndromes.

Syndrome[a]	Degenerative disease responsible	Mutated gene
Alzheimer syndrome[b]	AD,[#];[19,20] LBD,[19,20] FTD,[20] CBD,[20] CJD,[21], AGD,[19,20] PSP[20]	*PSEN1*,[#] *APP*, *PSEN2*, *C9orf72*,[22] *MAPT*,[23] *GRN*[23]
''Posterior cortical atrophy'' syndrome	AD,[#];[24] CBD,[24,25] LBD,[24] CJD[24]	*PRNP*,[26] *GRN*,[26] *HTT*,[27] *MAPT*,[26] *PSEN1*,[26] *PSEN2*,[26] *TREM2*,[26] trisomy 21 (Down syndrome)[28]
Logopenic variant PPA	AD,[#];[29] FTD[29]	*GRN*[30]
Nonfluent variant PPA	FTD,[#];[29] AD,[29] CBD,[29] PSP,[29] LBD,[29] CJD,[31] MSA[32]	*C9orf72*,[22] *CSF1R*,[33] *GRN*,[34] *MAPT*[35]
Semantic variant PPA	FTD,[#];[29] AD,[29] LBD[36]	*C9orf72*,[22,37] *GRN*[37]
Dementia with apathy or abulia	FTD,[#];[38,39] PDD,[#;40] PSP,[#];[38,41] LBD,[38] CBD,[38,42] AD[39]	*GRN*,[#];[34,43] *HTT*,[#;44] *DCTN1*,[45] *C9orf72*,[46] *MAPT*,[47] *PRNP*,[48,49] *PSEN1*,[50] *SNCA*[51]
Dementia with early or intense behavioural disinhibition and/or changes in personality	FTD,[#];[52,53] AD,[52—54] AGD,[55] CBD,[56] PSP,[57] Tourette Sd.[58]	*C9orf72*,[#];[46] *HTT*,[53,59] *MAPT*,[60] *TBK1*[43]
Progressive dysexecutive syndrome	AD,[54] PSP,[61] FTD,[52] CBD[62]	*SCA36*,[63] *SNCA*,[51] *PSEN1*[50]
Dementia with MND[c]	FTD,[#];[64,65] AD,[66] CJD[67]	*C9orf72*,[#];[46,64] *ATXN2*,[68] *FUS*,[69] *GRN*,[64] *HTT*,[70] *OPTN*,[64] *SQSTM1*,[64] *TARDBP*,[64] *TBK1*,[60] *SOD1*,[71,72] *SPG11* or *SPG4*,[73] *UBQLN2*,[64] *VCP*[64]
Dementia with early or marked psychotic symptoms	LBD,[#] FTD,[74] AD,[52,74] CJD,[74,75] HD[74]	*C9orf72*,[22,23,76] *CLN3*,[77] *GRN*,[23] *HTR2A*,[78] *NPC1* or *NPC2*,[79] *PSEN2*[80]
Dementia with marked primary parkinsonism	PDD,[#] LBD,[#] PSP,[#];[81] MSA,[82] Guam parkinsonism—dementia complex,[83] CBD,[81] AD,[84] CJD,[21,85] Guadaloupean parkinsonism[86]	*ATP13A2*,[87] *ATP7B*,[88] *C9orf72*,[81] *CHMP2B*,[81] *DCTN1*,[23,89] *FXTAS*,[90] *GBA*,[87,91] *GRN*,[81] *HTT*,[92] *JPH3*,[93] *MAPT*,[81] *LRRK2*,[94] *PRNP*,[95] *PSEN1*,[87] *SNCA*[87]
Corticobasal syndrome	CBD,[#];[25,56,96] PSP,[25,56,96] FTD,[25,96] AD,[19,25,96] CJD,[97] MSA,[32] PDD[96]	*GRN*,[#];[60,98] *MAPT*,[23,98] *C9orf72*,[22,98] *PSEN1*[99]
Steele—Richardson—Olszewski syndrome (classical PSP)	PSP,[#];[55] CBD,[55,96] FTD,[100] LBD,[35] CJD[84]	*MAPT*,[#];[23,98] *C9orf72*,[98] *GRN*,[98] *TBK1*[101]
Dementia with choreic dyskinesia (Huntington syndrome or HD phenocopy)	Primary Huntington syndrome without known mutation[102]	*HTT*,[#] *C9orf72*,[#];[22,103] *ATN1*,[103,104] *ATXN2*,[105] *ATXN8*,[103] *CP*,[106] *FTL1*,[107] *GM2A*,[108] *JPH3*,[103] *PPP2R2B*,[109] *PRNP*,[103] *RNF216*,[110] *TARDBP*,[111] *TBP*,[103] *TREM2*,[112] *VPS13A*,[103] *XPA*[113]
Dementia with cerebellar ataxia	MSA,[114] CJD,[115] mitochondrial disease,[116] PSP[117]	mtDNA,[118] *ATN1*,[104] *ATXN2*,[119] *CP*,[106] *EPM2A*,[120] *EPM2B*,[121] *HTT*,[122] *NPC1* or *NPC2*,[78] *PRNP*,[123] *TBP*[124]
Dementia with marked alteration of the autonomic nervous system	MSA,[125] LBD,[125,126] PDD,[126] FTD,[127] AD,[127] CJD[128,129]	*HTT*,[130] *DCTN1*,[23] *PRNP*[131]
Suspected CJD	CJD,[#];[21] LBD,[74] FTD[132]	*PRNP*,[133] *C9orf72*[22]

AD: Alzheimer disease; AGD: argyrophilic grain disease; CBD: corticobasal degeneration; CJD: Creutzfeldt-Jakob disease; FTD: frontotemporal degeneration (in Tables 1 and 2, the abbreviation encompasses all categories [FTD-tau, FTD-TDP; FTD-FUS, and FTD secondary to ubiquitin-proteasome system alterations] and their elements, with the exception of PSP, CBD, and AGD, which are considered separately); HD: Huntington disease; LBD: Lewy body dementia; MND: motor neuron disease (including amyotrophic lateral sclerosis, primary lateral sclerosis, and hereditary spastic paraplegia); MSA: multiple system atrophy; PDD: Parkinson's disease dementia; PPA: primary progressive aphasia; PSP: definite progressive supranuclear palsy.

[#] Most frequent reported cause according to the literature search.

[a] In the field of cognitive neurology.

[b] Typical Alzheimer syndrome consists of progressive amnestic syndrome of hippocampal type, presenting early in the course of the disease, either in isolation or associated with other cognitive or behavioural alterations characteristic of cognitive impairment or dementia. Amnestic syndrome of hippocampal type causes significant difficulties solving tests of episodic memory that include hints for coding when information is recorded, or cues to assist with retrieval. Medical history interviews, examination, and complementary tests (at least one blood analysis and one neuroimaging study) may not identify potential causes of the symptoms, whether they are characteristic of non-Alzheimer degenerative disease and/or non-degenerative disorders.

Table 2 Cases presenting anatomical pathology findings suggesting more than one of the classical degenerative diseases that cause dementia.

	AD	FTD	PSP	CBD	PDD/LBD	MSA	HD	CJD
FTD	x[19,134]							
PSP	x[19,134]	x[19]						
CBD	x[19,134]	x[135]	x[136]					
PDD/LBD	x[19,134,137]	x[19,134]	x[134,138]	x[19,138]				
MSA	x[134]		x[139]		x[138]			
HD	x[140]	x[141]		x[142]				
CJD	x[19,134]				x[143,144]	x[145]		
AGD	x[19,146,147]	x[147]	x[146,147]	x[146,147]	x[143,146]	x[148]		x[143,149]

Abbreviations: see footnote to Table 1.

Table 3 Drugs habitually prescribed to treat cognitive symptoms.

Syndrome	Drugs indicated or with recognised efficacy	References
Alzheimer syndrome[a]	Cholinesterase inhibitors, memantine	150
Corticobasal syndrome and Steele-Richardson-Olszewski syndrome	Levodopa,[b] rotigotine,[b] baclofen,[c] clonazepam,[c,d] diazepam,[c,d] zolpidem,[c,d] levetiracetam[d]	151
Huntington syndrome or HD phenocopy	Tetrabenazine,[e] deutetrabenazine,[e] antipsychotics[e,f]	152,153
Suspected CJD	Clonazepam[d]	154
Apathy syndrome	Cholinesterase inhibitors,[g] methylphenidate, ginkgo biloba	155,156
Behavioural disinhibition (social, sexual, dietary)	SSRIs, quetiapine, gabapentin, carbamazepine, medroxyprogesterone	157
Primary psychotic symptoms in degenerative dementia	Second-generation antipsychotics, rivastigmine,[g] donepezil[g]	158—161
Primary parkinsonism in patients with cognitive-affective disorder of degenerative origin	Levodopa, non-ergot dopaminergic agonists,[h] MAO-B inhibitors	162—164
Ataxia in patients with neurodegeneration and dementia	Miglustat,[i] riluzole	165,166
Dementia with marked alteration of the autonomic nervous system	Symptomatic treatment for each dysautonomic symptom[j]	167

CJD: Creutzfeldt-Jakob disease; HD: Huntington disease; MAO-B: monoamine oxidase B; SSRI: selective serotonin reuptake inhibitors.
[a] See description for *b* in the footnote to Table 1.
[b] Improve rigidity and hypokinesia.
[c] Improve dystonia.
[d] Improve myoclonus.
[e] Improve chorea.
[f] Improve psychotic symptoms, aggressiveness, and impulsivity.
[g] In patients with Alzheimer disease, Lewy body dementia, or Parkinson's disease dementia.
[h] Greater benefit in patients presenting apathy or depression; not indicated in patients with psychotic symptoms or impulse control disorders.
[i] For patients with Niemann-Pick disease type C.
[j] Neurogenic orthostatic hypotension; neurogenic supine hypertension, dysphagia, sialorrhoea, gastroparesis, constipation, neurogenic detrusor overactivity or underactivity, erectile or ejaculatory dysfunction, anorgasmia.

reversible causes may not be suspected after medical history-taking and clinical examination, and cannot be ruled out without these complementary tests. In other words, determination of disease-specific biomarkers may be performed in addition to structural neuroimaging, but should not replace these studies. The authors of a series of international recommendations on the use of CSF biomarkers of AD describe their value for the diagnosis of AD, especially during the prodromal phase of dementia or in patients with uncertain clinical diagnosis.[168] In turn, they also acknowledge that CSF biomarkers have not been demonstrated to be superior to imaging biomarkers and that their use does not improve patient well-being or reduce overall expenditure related to these patients. Another recent article, reviewing the usefulness of AD biomarkers, highlighted their value for research into new drugs, noting the current lack of treatments that effectively modify the pathophysiological alterations caused by the disease.[169]

The treatments currently prescribed to treat cognitive or behavioural disorders secondary to neurodegeneration aim to relieve symptoms. Treatments intended to interfere in aetiological and pathogenic processes, in order to modify the course of neurodegenerative diseases, are currently being researched. The drugs recommended in the clinical setting alter the activity of the brain's functional circuitry. Some increase or decrease the production or reuptake of specific neurotransmitters or activate or inhibit the corresponding receptors. Through a range of mechanisms, these changes increase or reduce activity in neuronal circuits with stimulatory or inhibitory action that, due to their topographical location in the brain, affect the control or modulation of specific functions (Table 3, left column). Of all the active ingredients listed in Table 3, only miglustat aims to increase survival times (in patients with Niemann-Pick disease type C), in addition to its symptomatic effect.[165] Among treatments for degenerative dementia, cholinesterase inhibitors are specifically prescribed to patients with suspected AD or Lewy body dementia, as they partially counteract the acetylcholine deficiency in the brain; memantine is indicated for patients with suspected AD to reduce the abnormal accumulation of glutamate in affected brain regions (a paraphenomenon of the degenerative process). Nonetheless, they have not been shown to modify the course of the disease (e.g., they do not slow the progression from mild cognitive impairment to dementia[170]), and only improve the cognitive and behavioural symptoms of ''Alzheimer syndrome''; more than half of patients do not present any significant improvement, either due to inefficacy or intolerance.[150] It is unclear whether treatment inefficacy in these patients may be because the underlying disease differs from the working diagnosis based on the clinical syndrome (Table 1), or explained by the co-presence of another degenerative disease (Table 2) or the presence of a non-degenerative comorbidity. It has been suggested in some settings that trials of new drugs should take into account the possible co-presence of different degenerative diseases.[137]

In line with the main hypotheses, it seems reasonable to consider that in everyday clinical practice, searching for biomarkers to establish the specific neurodegenerative disease (nosological entity associated with a specific molecular pathophysiological process) is

not relevant. Rather, we should identify the functional modules that are altered in the patient, which are responsible for the clinical manifestations, in order to identify the most effective of the available symptomatic treatments. According to the 2018 American Academy of Neurology (AAN) clinical practice guidelines,[170] starting at the stage of mild cognitive impairment, we should aim to identify causes to which corrective measures can be applied (changing harmful medications, reducing sleep apnoea, treating depression or other comorbidities [vascular disease, cancer, infections, inflammation, metabolic/toxic disorders, etc.]).[170] In terms of establishing a prognosis, we need to determine whether aetiology is neurodegenerative. If the cognitive disorder progresses and no non-degenerative cause is detected (or after effective treatment of potential causes), and especially in the presence of some non-specific paraclinical marker of neurodegeneration (e.g., excessive or rapidly progressive atrophy of specific brain areas on neuroimaging studies, or marked hypometabolism in specific regions, as observed in ^{18}F-FDG PET scans), then the patient is considered to be developing a degenerative disease. In these cases, the AAN guidelines emphasise the benefit of informing patients and family members about the lack of approved drugs that may halt or slow the progression of dementia and the possibility of directing interested patients to centres conducting therapeutic trials. It should be noted that the current, theoretically disease-specific, drugs (cholinesterase inhibitors and memantine) were tested and approved at a time when the diagnosis of ''Alzheimer disease'' would correspond to what the most recent diagnostic criteria (the 2018 NIAA-AA criteria[6]) classify as ''Alzheimer syndrome.'' When presence of a degenerative dementia disorder is established, patients are also offered counselling regarding the progressive loss of functional and decision-making capacity. For example, patients should be advised of the progressive increase in the risks associated with driving or continuing to assume certain professional or family responsibilities, as well as the possibility of certain personal or financial decisions (such as drafting a will or advance directives, granting power of attorney to a trusted individual, etc.). The counselling offered may differ according to the patient's specific clinical syndrome, not as a function of the histopathological substrate according to which the underlying disease is defined.

Based on the previous observations, it may be reasonable for national health systems to include referral services providing comprehensive testing for disease markers for all patients who agree to undergo this test, and to conduct thorough analysis of the pattern of neuropsychological, neurological, and systemic alterations, in order to further advance in the identification of phenotypes and in the search for highly efficacious treatments. We should determine the highest possible number of markers of mutations and proteinopathies, both in patients and in healthy controls, with a view to optimising the characterisation of phenotypes. This would enable us to reduce the risk of misdiagnosis, with the patient potentially presenting a different disease in a preclinical phase, or a combination of neurodegenerative diseases. In the absence of treatments with the capacity to substantially modify specific neuropathological molecular phenomena, delaying or significantly slowing the course of neurodegenerative diseases, it does not seem reasonable to dedicate time and resources to the routine performance of certain complementary tests (to search for specific markers of these diseases) in purely clinical settings.

We should also consider whether there is a need to update the terminology used in cognitive neurology. Some of the concepts of disease currently used in medicine correspond to specific, mutually exclusive clinicopathological constructs. We now know that each ''syndrome'' may have a range of genetic and neuropathological substrates, and each mutation and histopathological alteration can give rise to diverse clinical phenotypes; therefore, many of the clinicopathological combinations observed do not fit the accepted definitions of ''diseases'' described in the medical literature. There seems to be a need for change, with a separation of syndromes and specific molecular alterations (genetic and other types). For example, rather than being considered a clinicopathological concept, AD is now defined according to the presence of markers of a pathophysiological alteration[6]; this shift may also occur for other neurodegenerative dementias in the coming years. This development would lead to communication problems, with each disease known by a given name having different meanings according to the diagnostic criteria applied. In addition, there is a need for precise definitions of syndromes diagnosed prior to identification of the pathophysiological substrate, when this is known to be variable.

Before asserting that a symptomatic treatment is efficacious ''for AD,'' we must verify its efficacy in patients with Alzheimer syndrome, frontal lobe syndrome, posterior cortical atrophy, or logopenic primary progressive aphasia who also present biomarkers of AD. In the case of symptomatic treatments for progressive nonfluent aphasia, we must also verify their effectiveness in patients with markers of FTD, AD, CBD, PSP, Lewy body dementia, Creutzfeldt-Jakob disease, and multiple system atrophy (Table 3). Research into treatments targeting the proteinopathies involved in degenerative diseases (or other treatments intended to modify the course of the disease) should assess their level of efficacy in patients in presymptomatic, prodromal, and more advanced phases; in the latter group, we need to know whether or not these treatments are effective independently of the patient's clinical syndrome.

In conclusion, medical advances will enable the detection of biomarkers of neurodegenerative dementias at any time from the presymptomatic stage; patients with specific biomarkers can develop a range of syndromes; the aetiology of each syndrome is heterogeneous; and syndromes should be assessed over a time interval from the prodromal stage to very advanced dementia. This results in a need for new concepts and a new terminology to avoid confusion, constantly adapting to the present situation. The use of these new concepts in clinical, research, and teaching activities should be helpful and enlightening, unlike the present situation.

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Conflicts of interest

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