Received: 14 December 2022 | Revised: 17 February 2023 | Accepted: 21 February 2023

DOI: 10.1002/alz.13041

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

PERSPECTIVE

Toward a new nosology of neurodegenerative diseases

Manuel Menéndez-González[1,2,3]

[1]Department of Medicine, Universidad de Oviedo, Oviedo, Spain

[2]Department of Neurology, Hospital Universitario Central de Asturias, Oviedo, Spain

[3]Neurology Research Group, Instituto de Investigación Sanitaria, Oviedo, Spain

Correspondence
Manuel Menéndez González, Department of Medicine, Facultad de Medicina, Calle Julián Clavería 6, 33006, Oviedo, Spain.
E-mail: menendezgmanuel@uniovi.es

Abstract

New "omic" technologies are revealing shared and distinct biological pathways within and across neurodegenerative diseases (NDDs), allowing a better understanding of endophenotypes that exceeds the boundaries of the current diagnostic criteria. Moreover, a diagnostic framework is needed that can accommodate the co-pathology and the clinical overlap and heterogeneity of NDDs. Apart from dissecting the reasons for a revolution in how we conceive NDD, this article aims to prompt a change in how we diagnose and classify NDD, drafting a general scheme for a new nosology. As identifying a cause is the key to using the term "disease" properly, we propose using a tridimensional classification based on three axes: (1) etiology or pathogenic mechanism, (2) pathology markers and molecular biomarkers, (3) anatomic–clinical; and three hierarchical levels of etiology: (1) genetic/sporadic (2) cellular pathways and processes, and function of fluidic brain systems, and (3) risk factors.

KEYWORDS
advanced therapies for central nervous system conditions, diagnostics, endophenotype, neurodegenerative diseases, neuroprotective therapies, nosology

Neurodegenerative diseases (NDDs) are a group of disorders that cause progressive loss of function and death of nerve cells in the brain and spinal cord. The disruption of neural network architecture and functional connectivity, accompanied by neuronal loss, which is limited by neurons' terminally differentiated state, lead to the disintegration of central communication pathways, culminating in a variable combination of impaired cognitive, behavioral, sensory, and/or motor function. One NDD may have several endotypes[1,2] (an endotype is a subtype of a disease condition, which is defined by a distinct pathophysiological mechanism, in contrast to phenotypes, which refer to any observable characteristic of a disease without any implication of a mechanism). The huge impact of NDDs on patients, their families, and public health systems worldwide is undeniable. Yet, little progress has been made to modify the natural courses of NDDs. To a large degree, this failure may be due to inappropriate definitions of disease—based on phenotypes more than on endophenotypes—which may lead to heterogeneous study populations in clinical trials.[2,3]

Pathologically, besides cellular loss, most NDDs exhibit molecular hallmarks that are deposits of disease-specific proteins. Because some extent of protein deposits is normal during physiological aging, precise neuropathological criteria are needed to differentiate normal brain aging from NDD.[4] In medicine, good classifications of diseases can help us better understand their symptoms and their evolution to develop better diagnostic methods and potential treatments. NDDs can be classified in various ways, including by the specific type of nerve cells affected, the part of the nervous system affected, and the underlying cause of the disease. Both in research and in clinical practice, one common way to classify NDDs is by the proteins that are deposited; in this way, NDDs can be understood as "proteinopathies." From this perspective, the central event in the pathophysiology of an NDD is a proteostasis imbalance leading to protein aggregation overwhelming the capacity of brain cells to re-establish homeostasis (e.g., via ubiquitin–proteasome and autophagy–lysosome systems), functional proteinopenia,[5] and interfering with the ability of neurons to cope

with the pathogenic proteins.[6,7] Autophagy encompasses pathways that route cytoplasmic material to lysosomes for degradation. Because these pathways are crucial for degrading aggregate-prone proteins and dysfunctional organelles such as mitochondria, they help maintain cellular homeostasis. As post-mitotic neurons cannot dilute unwanted protein and organelle accumulation by cell division, the nervous system is particularly dependent on autophagic pathways. This dependence may be a vulnerability as people age and these processes become less effective in the brain. Hence, aging is a prominent risk factor for genetic and sporadic NDDs, and the molecular mechanisms that render the aged brain particularly susceptible to sporadic NDD seem to be linked to proteostasis capacity.[8,9]

The origin of proteostasis imbalance may be genetic and/or the result of acquired causes. Today, the etiologies for most genetic NDDs are generally known, yet we do not have a precise understanding of the etiologies of sporadic NDDs. In sporadic NDDs, both risk and protective factors have been identified (i.e., genetic polymorphisms; lifestyle including exercise, sleep, and diet; and microbiome),[10,11] but the precise links between these factors and the pathogenic mechanisms leading to proteostasis imbalance are yet to be deciphered. There might be an interaction between trigger factors, such as microbial infections[12,13] or air pollution,[14] and risk or protective factors to impact cell function and cell viability.[15] Furthermore, the formation of aggregates of these proteins may be the consequence of different pathogenesis, including a variable combination of increased synthesis, synthesis of structurally abnormal forms, and decreased degradation, either by intracellular (autophagy, microglia) or extracellular systems.[16–19] A decrease in protein clearance to compartments outside the central nervous system (CNS) parenchyma has also been implicated, which may be linked to the impairment of the blood–brain barrier (BBB), low cerebrospinal fluid (CSF) flow, and dysfunction of the glymphatic system.[20–26]

Anatomically, the different neurodegenerative processes predominantly affect vulnerable networks, leading to a wide variety of clinical pictures. The diversity and complex organization of cellular networks in the brain have hindered the systematic characterization of age-related changes in its cellular and molecular architecture, limiting our ability to understand the mechanisms underlying its functional decline during aging and disease. However, what has become known as "omic" technologies, such as genomics, proteomics, metabolomics, and transcriptomics, aim at the collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism or organisms, and offer precise information about dysfunctional cellular and organelle processes in NDD.[16–19] Single-cell profiling facilitates comparing various diseased brain cells, such as distinct types of neurons and microglia and astrocytes, with healthy cells[27] and can provide a nuanced portrait of the diverse cellular processes perturbed in NDDs as well as their spatiotemporal relationships.[28]

While identifying regional cell-type vulnerabilities may reveal unique disease mechanisms, recent research demonstrates that neurodegeneration of any kind is a systemic disease that may even begin outside of the region vulnerable to the disease.[29] Moreover, several NDDs may share common dysfunctions in fundamental cellular pathways, such as stress, inflammation and immune response, lipid signaling and metabolism, metabolic stress and protein folding, DNA damage and cellular senescence, and interactions with brain vasculature[30] (Table 1).

Dysfunctional cellular pathways and disease mechanisms lead to disease hallmarks, which are also related to cellular aging hallmarks. Although proteinopathies share pathways with aging processes, there are distinct biological pathways for each of them.[31] Twelve cellular aging hallmarks have been described to date: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis[32] (Table 1). In turn, these hallmarks are related to the loss of hallmarks of cellular health, which include organizational features of spatial compartmentalization, maintenance of homeostasis, and adequate responses to stress. Finally, eight hallmarks of neurodegeneration have been described: pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation, and neuronal cell death[33] (Table 1).

Spatial transcriptomics measures gene transcription in cells where they are situated within the brain, and is being used to construct high-resolution cell atlases of changes in gene expression in specific regions of the brain during disease progression.[34] For instance, spatial RNA transcriptomics recently demonstrated the selective vulnerability of cell subtypes to specific neuropathological changes within one group of NDD (with different subgroups of frontotemporal dementia [FTD]),[35] while another recent study using blood RNA transcriptomics across six NDDs (amyotrophic lateral sclerosis, Alzheimer's disease [AD], Friedreich's ataxia, FTD, Huntington's disease, and Parkinson's disease) revealed similar and differential alterations in fundamental cellular processes among the six NDDs: transcription regulation, degranulation, immune response, protein synthesis, cell death or apoptosis, cytoskeletal components, ubiquitylation/proteasome, and mitochondrial complexes. In spite of these shared alterations, the eight cellular dysfunctions were more or less associated with the identifiable pathologies in the brain characteristic of each disease.[36] Thus, changes in cellular pathways and cellular processes may be shared by multiple NDDs (and even by some diseases today considered psychiatric[37]) driving distinctive anatomic–clinical features. Though more studies will be needed to better understand the processes involved, these common factors may be the initial seeds that later develop into each of the distinct CNS disorders, while the mechanisms responsible for them germinate into diverse diseases and symptomologies, attacking different regions of the brain.[38]

The characteristic clinical picture for each NDD consists of a variable combination of cognitive, motor, and neuropsychiatric symptoms at the core, with a long list of other potentially associated symptoms. These phenotypes are the "classic" forms of the disease, that is, as originally described (eponyms). Thus, traditional methods of describing and classifying NDDs are based on the original clinicopathological concept; that is, a distinct clinical profile in combination with "signature" pathological lesions. This system was used to describe the first cases of AD,[39] Pick's disease (PiD),[40] dementia with Lewy bodies

TABLE 1 On the left, the main hallmarks describe cellular health, in cellular aging and in neurodegeneration. On the right, relevant cellular pathways, cellular processes, and pathogenic mechanisms in neurodegeneration.

Hallmarks of cellular health, cellular aging, and neurodegeneration	Neurodegeneration pathways, processes, and pathogenic mechanisms
Cellular health hallmarks	**Cellular pathways in neurodegeneration**
• Organizational features of spatial compartmentalization • Maintenance of homeostasis • Adequate responses to stress	• Immune response • Lipid signaling and metabolism • Metabolic stress and protein folding • DNA damage and cellular senescence • Interactions with brain vasculature
Cellular aging hallmarks	**Cellular processes in neurodegeneration**
• Genomic instability • Telomere attrition • Epigenetic alterations • Loss of proteostasis • Disabled macroautophagy • Deregulated nutrient-sensing • Mitochondrial dysfunction • Cellular senescence • Stem cell exhaustion • Altered intercellular communication • Chronic inflammation • Dysbiosis	• Transcription regulation • Degranulation • Immune response • Protein synthesis • Apoptosis • Cytoskeletal components • Ubiquitylation/proteasome • Mitochondrial complexes
Neurodegeneration hallmarks	**Pathogenic mechanisms in neurodegeneration**
• Pathological protein aggregation • Synaptic and neuronal network dysfunction • Aberrant proteostasis • Cytoskeletal abnormalities • Altered energy homeostasis • DNA and RNA defects • Inflammation • Neuronal cell death	• Immune and stress response • Lipids, fatty acids, and cholesterol metabolism • Endosome and cellular/neuronal death • Mitochondrial respiration and secretion • Cerebrospinal fluid/glymphatic fluid systems

(DLB),[41] and Creutzfeldt-Jakob disease (CJD).[42,43] Later, these original descriptions were refined and modified by molecular studies that resulted in the discovery of protein-specific antibodies and enabled the molecular signature of CNS lesions to be established and, hence, NDDs to be conceived as proteinopathies.[44] Ultimately, "consensus criteria" have been established for the majority of disorders, that is, AD,[45–48] FTD,[49–51] DLB,[52] multiple system atrophy (MSA),[53,54] and progressive supranuclear palsy (PSP),[53] representing the coordinated views of experts in the field regarding the most important clinical and pathological features useful in diagnosis. Most consensus diagnostic criteria propose core clinical findings that may be supported by neuroimaging, molecular, or neurophysiology biomarkers, making it possible to escalate from "possible" to "probable" diagnosis, depending on the amount of evidence gathered. Only those few cases with neuropathological studies, or where pathogenic genetic variants are found, are considered "confirmed" diagnoses. For instance, CSF amyloid beta (Aβ)42, total tau, phosphorylated tau (p-tau) concentrations or, alternatively, cerebral amyloid-positron emission tomography (PET) and tau-PET retention, essentially confirm or exclude an AD pathology; dopamine transporter single-photon emission computed tomography detects specific dopaminergic denervation; electrophysiological tests identify lower motor neuron degeneration, altered patterns of cerebral atrophy or hypometabolism on conventional magnetic resonance imaging and fluorodeoxyglucose-PET, respectively, all reflect phenotypes but not pathophysiologies. Protein misfolding amplification assays may accurately detect α-synuclein prion-like seeds in synucleinopathies and serum progranulin some genetic forms of FTD; and ultrasensitive techniques measuring blood Aβ, p-tau, and neurofilament light chain concentrations are becoming substitutes for CSF biomarkers.[55] In line with these criteria, the diagnostic workup is led by patient complaints—symptoms—and clinicians' minds are accordingly structured along anatomic–clinical coordinates.

As a result, NDDs have continued to be regarded as distinct "entities," neuropathologically defined by signature pathological lesions, and characterized by specific molecular and morphological changes.[56] They are classified either clinically, based on the main symptoms, or molecularly, based on the underlying molecular hallmarks.[57] However, clinical variants have been described in all NDDs and they are progressive by nature. After a long asymptomatic period, the onset of the clinical picture evolves over time along different stages in myriad possible phenotypes. Thus, clinical heterogeneity and clinical overlap among NDDs are common.[1,58,59] Similarly, proteinopathies are not mutually exclusive and co-pathologies are frequently found.[60–62]

In view of this situation, a new framework that can accommodate the overlap, heterogeneity, and co-pathology in NDDs is needed, one in which etiologies are set at the center of a new NDD nosology.[56,63]

TABLE 2 Diagnostic axes and levels of etiology and pathogenic mechanism for the new nosology of neurodegenerative diseases.

Diagnostic axes		Levels of etiology or pathogenic branching nodes	
Axis 1	Etiology or pathogenic mechanism	Level 1	Genetic/sporadic
Axis 2	Pathology markers and molecular biomarkers	Level 2	Cellular pathways and processes, and fluidic systems function
Axis 3	Anatomic–clinical	Level 3	Risk factors

Indeed, many of the NDDs we refer to as "diseases," are actually "syndromes."[64,65] Conceptually, the basic difference between these two terms relates to whether a precise etiology has been identified. A disease can be defined as a health condition with a clearly defined cause.[66,67] A syndrome (from the Greek word meaning "run together"), however, refers to a group of symptoms that may be due to different causes or even without an identifiable cause. Therefore, identifying a cause is the key to properly using the term "disease."

This article aims to advocate for a change in the way we conceive NDDs, to draft a general scheme for a new taxonomy, and to encourage us to pursue this change. Taking the definition of "disease" as a starting point, we should shift from a conception based on clinical pictures (eponyms referring to phenotypes) or molecular hallmarks (proteinopathies) to a conception based on pathogenic mechanisms. Naming diseases properly is very important for research and clinical practice, but the process of naming can obscure the underlying biology and lead to artificial separations.[68] Thus, the new classification should be more operative, driven by the causes of the diseases. We propose a tridimensional classification scheme (Table 2). The three axes of such a system are (1) etiology or pathogenic mechanism, (2) pathology markers and molecular biomarkers, (3) anatomic–clinical. While the common current clinical diagnostic process is in inverse order, in our proposed process etiology and pathogenic mechanisms are starting points (main axis) for classifying diseases, while pathology and molecular hallmarks form the second important diagnostic criteria, and the clinical picture is the third. In addition, this scheme would integrate three hierarchical levels of etiologies or pathogenic branching nodes (i.e., associated with axis 1). The first etiology branching node would be a differentiation between genetic (familial, due to deterministic genetic variants) and non-genetic (sporadic) causes. The second branching node would be between dysfunctional cellular pathways and processes and dysfunctional brain fluidic systems (encompassing the BBB, the interstitial fluid, the CSF, and the glymphatic system). The third branching node would be between risk factors inducing these changes (typically a combination of factors for sporadic diseases, including non-deterministic genetic variants).

Albeit that the framework in this proposal needs much more detail and specific criteria for the different conditions, the general scheme should be valid for any NDD. For instance, we would refer to genetic diseases—most probably leading to specific proteinopathies—by the name of the mutation, or to sporadic diseases—most probably leading to mixed proteinopathies—by the name of the pathogenic mechanism that we have identified: we would speak of microglia dysfunction, dysfunction in the glymphatic and CSF dynamics, specific or unspecific autophagy dysfunction, and so on. When possible, we should dig into the underlying contributors of sporadic NDD, such as genetic risk factors or lifestyle risk factors. To make reliable diagnoses based on etiology and pathogenic mechanisms, we will need tools to measure protein synthesis (amount and structure) and clearance, as well as advanced and comprehensive molecular genetics, proteomics and transcriptomics and clinical methods to measure cell autophagy, microglia activity, glymphatic system function, CSF dynamics, and BBB integrity. While genetics and current biofluid and neuroimaging biomarkers may inform on the three axes, they represent only a fraction of the intricate biology underlying diseases (Figure 1). A new class of biomarkers, informing etiologies, pathogenic mechanisms, and the full spectrum of hallmarks of neurodegeneration, is highly needed. Thanks to genome-wide genetics and other "omic" techniques, and to advanced neuroimaging methods, such markers are under development[25,26,69] and hopefully will become a reality both for symptomatic and asymptomatic subjects in the next decades. In addition, data-driven strategies using quantitative rather than categorical variables, as well as tools such as cell atlases and digital neuroanatomy atlases, will allow much more reliable quantification of contributions from pathophysiological mechanisms and their spatial–temporal evolution as well as the development of precision diagnostics.[70,71] The extensive collection of data that will be gathered from each patient will probably require advanced methods (such as artificial intelligence) for integrative and comprehensive analyses to reach useful applications in the clinical setting. This should not be regarded as obviating the need for traditional clinical management including semiology and neuropsychological assessment[72] as more knowledge on semiology, neuropsychology, and neuroanatomy would indeed be needed for proper integration of the different axes and etiologies.

One of the main therapeutic strategies during the last decades has focused on targeting the proteins building the molecular hallmarks of NDDs. As discussed here, the accumulation of proteins is not fully disease-specific, but a common endpoint for several pathogenic mechanisms. Nonetheless, clearing accumulated proteins may be a suitable therapeutic strategy, as recently shown in clinical trials on the anti-amyloid monoclonal antibody lecanemab for AD.[73] A new nosology would have a profound impact on the design of clinical trials in many ways, particularly on the definition of more homogeneous populations and more precise biomarkers as surrogate outcomes. Moreover, identifying specific pathogenic mechanisms may be key to discovering therapeutic targets and paving the way for new therapeutics specific to each disease. Hence, coupling a new nosology with new therapies targeting etiologic and pathogenic mechanisms—genes, protein translation, autophagy, microglia, glymphatic function, CSF dynamics, and so

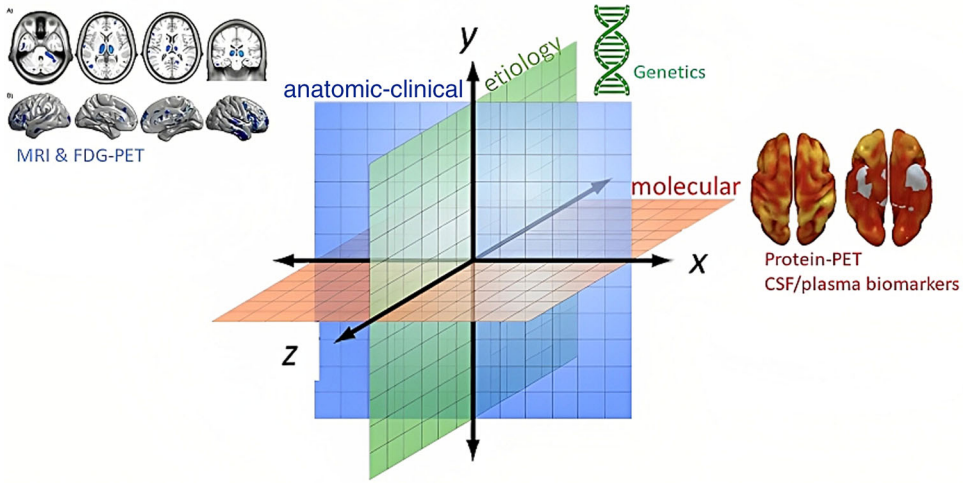

FIGURE 1 Neurodegenerative diseases can be studied and classified in a tridimensional scheme with three axes: anatomic–clinical, molecular, and etiologic. CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

on—will open the door to precision, personalized treatments as well as preventive medicine for NDDs, that is, identifying the right patients for the right drugs.[33,74]

Changing the nosology of NDD is a challenge that will require efforts from several stakeholders, including academia, scientific societies, clinicians, researchers, the medical and pharmaceutical industries, and even the public. Because "official" diagnostic criteria are dictated by scientific societies, several scientific societies would have to collaborate to achieve a global consensus that joins perspectives beyond the scope of individual societies. Working groups should define diagnostic criteria for specific NDDs and define how to operatively integrate etiology levels in axis 1. Also, familiarizing clinicians with a new nosology and related terminology, as well as standardizing the use of biomarkers, neuroanatomy, and genetic variants will require the effort of both clinicians and researchers. Academia will be the key to transmitting this diagnostic framework to new generations of doctors and researchers, and the public will also need to learn the new nomenclature, even though we all might yearn for simple names like "Alzheimer," "Parkinson," "Lewy," and "Pick."

In conclusion, the clinical–pathological diagnostic approach alone has shown serious shortcomings and there is a growing awareness of the need to change the way we think about NDDs. In parallel, research in the omics era is offering a new, more precise understanding of NDD endophenotypes that exceeds the boundaries of the current diagnostic criteria. We propose a new nosology of NDD in which etiology and pathogenesis are at the core. This will open the door to true preventive, personalized, precision medicine.

AUTHOR CONTRIBUTIONS

Manuel Menéndez González is the only author of this manuscript, including tables and figures.

ACKNOWLEDGMENTS

Authors thank Professor Charles Gasparovic for his critical review of this paper. This study has been funded by Instituto de Salud Carlos III (ISCIII) through the project PI21/00467 and co-funded by the European Union.

CONFLICT OF INTEREST STATEMENT

Author disclosures are available in the supporting information. The author declares no conflicts of interest.

ORCID

Manuel Menéndez-González https://orcid.org/0000-0002-5218-0774

REFERENCES

1. Kaiser S, Zhang L, Mollenhauer B, et al. A proteogenomic view of Parkinson's disease causality and heterogeneity. *NPJ Parkinsons Dis [Internet]*. 2023;9:24. doi:10.1038/s41531-023-00461-9
2. Geifman N, Kennedy RE, Schneider LS, et al. Data-driven identification of endophenotypes of Alzheimer's disease progression: implications for clinical trials and therapeutic interventions. *Alzheimers Res Ther*. 2018;10.
3. Caldwell AB, Liu Q, Zhang C, et al. Endotype reversal as a novel strategy for screening drugs targeting familial Alzheimer's disease. *Alzheimer's Dement*. 2022;18.
4. Walker JM, Dehkordi SK, Schaffert J, et al. The spectrum of Alzheimer-type pathology in cognitively normal individuals. *J Alzheimer's Disease*. 2023;91:683-695.
5. Espay AJ, Okun MS. Abandoning the proteinopathy paradigm in Parkinson disease. *JAMA Neurol [Internet]*. 2023;80:123-124.
6. Martinez-Vicente M, Cuervo AM. Autophagy and neurodegeneration: when the cleaning crew goes on strike. *Lancet Neurol*. 2007:352-361.
7. Nixon RA. The role of autophagy in neurodegenerative disease. *Nat Med*. 2013.
8. Kluever V, Russo B, Mandad S, et al. Protein lifetimes in aged brains reveal a proteostatic adaptation linking physiological aging to neurodegeneration. *Sci Adv [Internet]*. 2023;8:eabn4437.
9. Hetz C. Adapting the proteostasis capacity to sustain brain healthspan. *Cell*. 2021.
10. Liu H, Barthélemy NR, Ovod V, et al. Acute sleep loss decreases CSF-to-blood clearance of Alzheimer's disease biomarkers. *Alzheimer's Dement [Internet]*. 2023.

11. Fang P, Kazmi SA, Jameson KG, et al. The microbiome as a modifier of neurodegenerative disease risk. *Cell Host Microbe*. 2020.
12. Emery DC, Davies M, Cerajewska TL, et al. High resolution 16S rRNA gene Next Generation Sequencing study of brain areas associated with Alzheimer's and Parkinson's disease. *Front Aging Neurosci [Internet]*. 2022;14.
13. Levine KS, Leonard HL, Blauwendraat C, et al. Virus exposure and neurodegenerative disease risk across national biobanks. *Neuron [Internet]*. 2023. Available from.
14. Parra KL, Alexander GE, Raichlen DA, et al. Exposure to air pollution and risk of incident dementia in the UK Biobank. *Environ Res*. 2022:209.
15. de Strooper B, Karran E. The cellular phase of Alzheimer's disease. *Cell*. 2016.
16. Lona-Durazo F, Reynolds RH, Scholz SW, et al. Regional genetic correlations highlight relationships between neurodegenerative diseases and the immune system. *medRxiv [Internet]*. 2022. 2022.12.07.22283179.
17. Serrano-Pozo A, Li Z, Woodbury ME, et al. Astrocyte transcriptomic changes along the spatiotemporal progression of Alzheimer's disease. *bioRxiv*. 2022. 2022.12.03.518999.
18. Humphrey J, Venkatesh S, Hasan R, et al. Integrative transcriptomic analysis of the amyotrophic lateral sclerosis spinal cord implicates glial activation and suggests new risk genes. *Nat Neurosci*. 2022.
19. Lee J-H, Yang D-S, Goulbourne CN, et al. Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques. *Nat Neurosci [Internet]*. 2022;25:688-701.
20. Elbert DL, Patterson BW, Lucey BP, et al. Importance of CSF-based Aβ clearance with age in humans increases with declining efficacy of blood-brain barrier/proteolytic pathways. *Commun Biol*. 2022;5.
21. Mestre H, Verma N, Greene TD, et al. Periarteriolar spaces modulate cerebrospinal fluid transport into brain and demonstrate altered morphology in aging and Alzheimer's disease. *Nat Commun [Internet]*. 2022;13:3897.
22. Peng W, Achariyar TM, Li B, et al. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. *Neurobiol Dis*. 2016:93.
23. Da Mesquita S, Papadopoulos Z, Dykstra T, et al. Meningeal lymphatics affect microglia responses and anti-Aβ immunotherapy. *Nature*. 2021:593.
24. Li Y, Rusinek H, Butler T, et al. Decreased CSF clearance and increased brain amyloid in Alzheimer's disease. *Fluids Barriers CNS*. 2022:19.
25. Klostranec JM, Vucevic D, Bhatia KD, et al. Current concepts in intracranial interstitial fluid transport and the glymphatic system: part i-anatomy and physiology. *Radiology*. 2021.
26. Lee MK, Cho SJ, Bae YJ, et al. MRI-based demonstration of the normal glymphatic system in a human population: a Systematic Review. *Front Neurol*. 2022;13.
27. Luquez T, Gaur P, Kosater IM, et al. Cell type-specific changes identified by single-cell transcriptomics in Alzheimer's disease. *Genome Med*. 2022;14:136.
28. Murdock MH, Tsai L-H. Insights into Alzheimer's disease from single-cell genomic approaches. *Nat Neurosci*. 2023.
29. Fu H, Hardy J, Duff KE. Selective vulnerability in neurodegenerative diseases. *Nat Neurosci*. 2018.
30. Crawford K, Leonenko G, Baker E, et al. Golgi apparatus, endoplasmic reticulum and mitochondrial function implicated in Alzheimer's disease through polygenic risk and RNA sequencing. *Mol Psychiatry*. 2022.
31. Oatman SR, Reddy JS, Quicksall Z, et al. Genome-wide association study of brain biochemical phenotypes reveals distinct genetic architecture of Alzheimer's disease related proteins. *Mol Neurodegener [Internet]*. 2023;18.
32. López-Otín C, Blasco MA, Partridge L, et al. Hallmarks of aging: an expanding universe. *Cell [Internet]*. 2023;186:243-278.
33. Wilson III DM, Cookson MR, van den Bosch L, et al. Hallmarks of neurodegenerative diseases. *Cell [Internet]*. 2023;186:693-714.
34. Zeng H, Huang J, Zhou H, et al. Integrative in situ mapping of single-cell transcriptional states and tissue histopathology in a mouse model of Alzheimer's disease. *Nat Neurosci*. 2023.
35. Dols-Icardo O, Dolcet SS, Montal V, et al. Transcriptome wide correlations with neuropathological hallmarks in the frontal cortex of FTLD patients. *Alzheimer's Dement*. 2022;18:e059619.
36. Huseby CJ, Delvaux E, Brokaw DL, et al. Blood RNA transcripts reveal similar and differential alterations in fundamental cellular processes in Alzheimer's disease and other neurodegenerative diseases. *Alzheimer's Dement [Internet]*. 2022.
37. Wingo TS, Liu Y, Gerasimov ES, et al. Shared mechanisms across the major psychiatric and neurodegenerative diseases. *Nat Commun [Internet]*. 2022;13:4314.
38. Wisch JK, Butt OH, Gordon BA, et al. Proteomic clusters underlie heterogeneity in preclinical Alzheimer's disease progression. *Brain*. 2022:awac484.
39. Stelzmann RA, Norman Schnitzlein H, Reed Murtagh F. An english translation of alzheimer's 1907 paper, "über eine eigenartige erkankung der hirnrinde". *Clinical Anatomy*. 1995;8.
40. Pick A. Uber einen weiteren Symptomenkomplex im Rahman der Dementia senilis, bedingt durch umschriebene starkere Hirnatrophie (gemischte Apraxie). *Monat Psych Neurol*. 1906;19:97-108.
41. Lewy FH. Paralysis agitans. I. Pathologische Anatomie. In: Lewandowsky M, ed. *Handbuch der Neurologie*. Springer; 1912:920-933.
42. Creutzfeldt HG. Uber eines eigenartige herd-formige Erkrankung des Zentralnervensystems. In: Nissl F, ed. *Histologische und Histopathologische Arbeiten uber die Grosshirnrinde*. Alzheimer A; 1921:1-48. editors. Jena: Gustav Fisher.
43. Jakob A. Uber eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswerten anatomischen Befunden (spastische Pseudosklerose-Encephalomyelopathic mit disseminierten Degenerationsherden). *Dtsch Z Nervenheilk*. 1921;70:132-146.
44. Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. *Cold Spring Harb Perspect Biol*. 2017.
45. Jack CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7.
46. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7.
47. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7.
48. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7.
49. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011:134.
50. Chare L, Hodges JR, Leyton CE, et al. New criteria for frontotemporal dementia syndromes: clinical and pathological diagnostic implications. *J Neurol Neurosurg Psychiatry*. 2014:85.
51. Barker MS, Gottesman RT, Manoochehri M, et al. Proposed research criteria for prodromal behavioural variant frontotemporal dementia. *Brain*. 2022:145.

52. Yamada M, Komatsu J, Nakamura K, et al. Diagnostic criteria for dementia with lewy bodies: updates and future directions. *J Mov Disord*. 2020.
53. Höglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord*. 2017:32.
54. Wenning GK, Stankovic I, Vignatelli L, et al. The movement disorder society criteria for the diagnosis of multiple system atrophy. *Mov Disord [Internet]*. 2022;37:1131-1148.
55. Young PNE, Estarellas M, Coomans E, et al. Imaging biomarkers in neurodegeneration: current and future practices. *Alzheimers Res Ther*. 2020.
56. Armstrong RA. Can neurodegenerative disease be defined by four "primary determinants": anatomy, cells, molecules, and morphology? *Folia Neuropathol*. 2016:89-104.
57. Kovacs GG. Molecular pathological classification of neurodegenerative diseases: turning towards precision medicine. *Int J Mol Sci*. 2016.
58. Armstrong RA, Lantos PL, Cairns NJ. Overlap between neurodegenerative disorders. *Neuropathology*. 2005.
59. Morris JC. The nosology of dementia. *Neurol Clin*. 2000;18.
60. Robinson JL, Richardson H, Xie SX, et al. The development and convergence of co-pathologies in Alzheimer's disease. *Brain*. 2021:144.
61. Robinson JL, Lee EB, Xie SX, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. *Brain*. 2018:141.
62. Perl DP, Olanow CW, Calne D. Alzheimer's disease and Parkinson's disease: distinct entities or extremes of a spectrum of neurodegeneration? *Ann Neurol*. 1998.
63. Armstrong RA. On the "classification" of neurodegenerative disorders: discrete entities, overlap or continuum? *Folia Neuropathol*. 2012.
64. Robles Bayón A. Degenerative dementias: a question of syndrome or disease? *Neurología (English Edition)*. 2022:37.
65. Weiner WJ. There is no parkinson disease. *Arch Neurol*. 2008.
66. Calvo F, Karras BT, Phillips R, et al. Diagnoses, syndromes, and diseases: a knowledge representation problem. AMIA. Annual Symposium proceedings /AMIA Symposium AMIA Symposium. 2003.
67. Moriyama IM. The classification of disease-A fundamental problem. *J Chronic Dis*. 1960:11.
68. Hardy J, Gwinn-Hardy K. The relationship between nosology, etiology and pathogenesis in neurodegenerative diseases. *Handb Clin Neurol*. 2008.
69. Higginbotham L, Ping L, Dammer EB, et al. Integrated proteomics reveals brain-based cerebrospinal fluid biomarkers in asymptomatic and symptomatic Alzheimer's disease. *Sci Adv*. 2020;6.
70. Rood JE, Maartens A, Hupalowska A, et al. Impact of the Human Cell Atlas on medicine. *Nat Med*. 2022.
71. Baldacci F, Mazzucchi S, della Vecchia A, et al. The path to biomarker-based diagnostic criteria for the spectrum of neurodegenerative diseases. *Expert Rev Mol Diagn*. 2020.
72. Jónsdóttir MK, Harrison J, Hannesdóttir KI. The ambivalence toward neuropsychology in dementia research, diagnosis, and drug development: myths and misconceptions. *Alzheimer's Dement [Internet]*. 2023.
73. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 0:null.
74. Morató X, Pytel V, Jofresa S, et al. Symptomatic and disease-modifying therapy pipeline for Alzheimer's disease: towards a personalized polypharmacology patient-centered approach. *Int J Mol Sci*. 2022;23. cited 2022 Dec 13.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Menéndez-González M. Toward a new nosology of neurodegenerative diseases. *Alzheimer's Dement*. 2023;19:3731–3737. https://doi.org/10.1002/alz.13041