

Is Alzheimer disease a disease?

Amos D. Korczyn¹✉ & Lea T. Grinberg^{2,3,4} 

Abstract

Dementia, a prevalent condition among older individuals, has profound societal implications. Extensive research has resulted in no cure for what is perceived as the most common dementing illness: Alzheimer disease (AD). AD is defined by specific brain abnormalities – amyloid- β plaques and tau protein neurofibrillary tangles – that are proposed to actively influence the neurodegenerative process. However, conclusive evidence of amyloid- β toxicity is lacking, the mechanisms leading to the accumulation of plaques and tangles are unknown, and removing amyloid- β has not halted neurodegeneration. So, the question remains, are we making progress towards a solution? The complexity of AD is underscored by numerous genetic and environmental risk factors, and diverse clinical presentations, suggesting that AD is more akin to a syndrome than to a traditional disease, with its pathological manifestation representing a convergence of pathogenic pathways. Therefore, a solution requires a multifaceted approach over a single ‘silver bullet’. Improved recognition and classification of conditions that converge in plaques and tangle accumulation and their treatment requires the use of multiple strategies simultaneously.

Sections

Introduction

What is AD?

Is AD a disease?

What causes AD?

One disease entity or more?

What does pathology tell us?

Are anti-amyloid- β therapies still relevant?

Findings from genetics

What does epidemiology tell us?

Conclusions and future directions

¹Departments of Neurology, Physiology and Pharmacology, Tel Aviv University, Tel Aviv, Israel. ²Departments of Neurology and Pathology, UCSF, San Francisco, CA, USA. ³Global Brain Health Institute, UCSF, San Francisco, CA, USA. ⁴Department of Pathology, University of Sao Paulo Medical School, Sao Paulo, Brazil. ✉e-mail: Amoskor@tauex.tau.ac.il

Introduction

Cognitive decline is a prevailing ailment among the older population and is a major cause of death. According to the World Health Organization, >55 million people worldwide are estimated to be affected by severe cognitive impairment, commonly known as dementia¹. This condition substantially affects the lives of patients and their families, and places a burden on the health-care system, society and the global economy. As the global population continues to age and individuals with dementia live longer, the impact is expected to escalate. Although numerous factors can contribute to dementia, Alzheimer disease (AD) is widely believed to be the most common cause. Consequently, numerous clinicians, scientists and researchers in academic, institutional and industry settings across the globe have dedicated substantial efforts to finding a cure for AD. Regrettably, despite these extensive endeavours, a solution remains elusive, prompting us to explore the underlying reasons for this lack of progress. One basic question that we explore here is the concept of AD itself and whether it can rightly be considered a disease, caused by a single aetiology and underlying mechanism.

What is AD?

The mere definition of AD already suggests the crux of the problem. For decades, a common definition has been: a progressive cognitive decline associated with specific neuropathological changes, that is, amyloid- β plaques usually accompanied by intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. This definition is unusual, perhaps unique, in medicine, as it includes both the clinical syndrome and the associated pathology without addressing the process leading to these changes. An analogy is that several distinct disorders are included under the term 'pneumonia'. They all share clinical features (for example, fever and respiratory distress), biomarkers (low O₂ levels and leukocytosis) and they have similar pathology. Therefore, the term pneumonia does not define a disease but rather a syndrome, with bacterial, viral and toxic causes, which must be identified in each patient to provide beneficial therapy. Thus, a disease is not defined by the clinical phenotype or the pathology (itself also a syndrome with several potential causes) but rather by the aetiology and mechanisms.

Until recently, the definition of AD was based on clinical manifestations progressing insidiously from mild cognitive impairment to full-blown severe dementia, usually considered to have high specificity for a pathological picture of amyloid- β plaques and tau tangles distributed stereotypically. An important feature in the traditional definition of AD is dysfunctional memory, particularly episodic memory. However, clinicopathological studies have shed light on the limitations of this traditional definition of AD, as clinical manifestations of AD pathology are relatively nonspecific. Episodic memory is impaired in many other brain disorders and might also be affected by drugs such as hypnotics and anticholinergics, as well as in physiological situations such as stress, lack of sleep or depression². Furthermore, a newly described neuropathological entity, limbic predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC), underlies a considerable number of cases of amnesic syndrome in older individuals³. Conversely, some individuals with evidence of plaques and tangles in the brain present with non-amnesic 'atypical' syndromes⁴ or no cognitive decline at all even with a high burden of plaques and tangles^{5,6}.

Thus, a recent multidisciplinary workforce proposed to define AD based on (rather qualitative) biological changes alone^{7,8}, that is, plaques

and tangles. Although this step is perceived as an advancement, this limited definition is not definitive. First, it still fails to include the multiple pathogenic processes that lead to it. Second, AD neuropathological changes, particularly amyloid- β deposition, occur frequently in older individuals with normal cognition^{5,9}, referred to as resilience to AD changes¹⁰. This lack of correlation is particularly seen in individuals >85 years of age^{11,12} and it is still unknown what the natural history of those who carry these changes is: whether they will inevitably manifest cognitive decline, and when, if ever, clinical manifestations will appear. Finally, the 'specific' pathology mentioned in the definition occurs in other pathological conditions such as Lewy body disease presenting as dementia with Lewy bodies (DLB)¹³ and LATE-NC¹⁴. For example, it has been frequently observed that DLB cases exhibit a high burden of amyloid- β plaques, yet a substantial proportion of these cases have a considerably lower tangle burden than 'pure' AD cases¹⁵. The assertion that these DLB cases, characterized by high plaque but low tangle burden, must represent comorbid DLB and AD merely based on the presence of plaques is a notable instance of circular logic.

Is AD a disease?

As stated above, defining a disease requires understanding its underlying aetiology and pathogenic processes¹⁶. Without this knowledge, we can only refer to something as a syndrome, for which various mechanisms might lead to a similar phenotype. This idea holds for both clinical and pathological entities, as different abnormal processes can result in identical pathological presentations. The mere existence of specific pathological features is insufficient to define a disease. For instance, hepatic cirrhosis can stem from various underlying causes, including alcohol abuse, viral hepatitis and autoimmune disorders, thus making cirrhosis a syndrome rather than a disease. The fact that different causes might lead to the same pathological (and clinical) phenotype represents phenotypic convergence. In AD too, the clinical phenotype (or phenotypes) represents a syndrome, not a disease with a distinct cause, given that the causes of the pathological changes are mostly unknown, and many pathways might lead to the same downstream tissue changes.

What causes AD?

The investigation into the origin of AD has a long history. Numerous hypotheses have been proposed over the years regarding its underlying processes (Box 1). However, none of these hypotheses has provided a complete answer and, in fact, most of them have been abandoned. Currently, researchers are still exploring several processes that are suspected to cause neurodegeneration, including neuroinflammation, oxidative stress, lipid and metabolic dysregulation, neurovascular unit dysfunction, and protein misfolding, seeding and spread. Among these, the roles of amyloid- β deposition and hyperphosphorylated tau are the focus of many studies. However, a definitive explanation for the primary cause of AD continues to elude us. It is increasingly evident that a single primary cause is unlikely to account for this complex and multifaceted disease. Regarding the underlying process, the case of amyloid- β serves as an informative example. Initially considered merely a biomarker of AD (even by Alois Alzheimer and Oskar Fischer themselves¹⁷), amyloid- β was later speculated to have an essential pathogenic role by Hardy and Higgins in their milestone article¹⁸ in which they proposed the 'amyloid cascade hypothesis' and presumed amyloid- β to be an active contributor to pathogenesis and, subsequently, neurodegeneration. In fact, this theory was not based on evidence provided by AD studies. Although the presence of amyloid- β deposition is necessary for AD

Box 1

Presumed pathogenic factors in Alzheimer disease

- Oxidative stress
- Lipid peroxidation
- Aluminium toxicity
- Amyloid- β toxicity
- Tau hyperphosphorylation
- Protein misfolding, aggregation and seeding
- Inflammation
- Vascular changes
- Mitochondrial damage
- Free radical damage
- Infectious agents such as viruses and bacteria

diagnosis according to the arbitrary definition of the disorder, only minimal evidence supports a causal relationship^{19,20} and the amyloid cascade hypothesis has never been substantiated. Several failed studies, including anti-amyloid- β trials^{21–23}, have challenged the amyloid cascade hypothesis, even in autosomal dominant AD cases, in which the nature of the mutations makes the hypothesis a better fit²⁴. Another challenge to the hypothesis is the reports of resilience in autosomal dominant AD cases linked to *APOE3* or reelin mutations^{25,26}. These cases still present amyloid- β deposits, similar to other symptomatic *PSEN1* cases, but areas spared of phosphorylated tau deposits have less degeneration and clinical manifestations. It is reasonable to consider that a specific subgroup of individuals might exhibit plaques and tangles with amyloid- β changes as the initial pathogenic trigger. What is not reasonable, however, is to apply this hypothesis to the entire AD population as a generalization.

One disease entity or more?

Individuals with Down syndrome or those carrying *APP* duplication or *PSEN1* gene mutations show a more direct connection between amyloid- β deposition and the clinical manifestations. In those individuals, cognitive decline starts early, typically in their thirties or forties. However, this group of patients with autosomal dominant AD is exceptionally rare^{27,28}. Furthermore, the differences between genetic forms (autosomal dominant) of early-onset AD (EOAD) and sporadic late-onset AD (LOAD) extend beyond the age of onset (Table 1). These entities differ significantly in clinical presentations, rate of atrophy²⁹ and structure of amyloid- β filaments³⁰. In addition, although there are similarities in pathological features, they are by no means identical. The widespread disregard for individual differences among those meeting current AD criteria hinders the progress of developing effective treatments because drug development has been primarily directed towards biomarkers that are the results of phenotypic convergence. This situation is analogous to administering acetaminophen to reduce fever in pneumonia without addressing the underlying cause. Using the same term, AD, for both the genetic disease and the sporadic syndrome can be misleading, resulting in misunderstandings and misinterpretations. These distinctions must be recognized to avoid any confusion and to foster accurate understanding and interpretation in research and

clinical settings. The prevailing position that AD is one entity because all cases are positive for AD biomarkers relies on circular reasoning, as these biomarkers capture markers of phenotypic convergence.

Improved quantitative techniques, whether applied post-mortem or in vivo, are unveiling AD subtypes characterized by the regional distribution of tau tangles and, to a lesser extent, amyloid- β plaques^{31–34}. These subtypes could offer a more effective framework for investigating the diverse pathogenic mechanisms that contribute to plaque and tangle build-up. However, only a limited number of studies have integrated subtyping or patient classification based on quantitative metrics into their research design^{32,35}.

Most animal models of AD utilized in research are transgenic mice that are based on autosomal dominant forms of AD. Consequently, these models might not be directly applicable to the common, sporadic LOAD. Of note, these transgenic mice often do not exhibit AD tau inclusions (a major limitation given that tau burden has a stronger correlation with cognitive decline than amyloid- β plaque burden in humans³⁶), neither do they demonstrate the severe brain degeneration observed in terminal human disease, nor the profound cognitive decline characteristic of advanced LOAD. As a result, they do not serve as effective models for the development of therapies that specifically target LOAD. The research field has recognized these limitations through efforts to create better models^{37,38}. Nevertheless, models that better mimic the pathophysiology and clinical features of LOAD are at present elusive and the bulk of current studies still use the classical models used for years.

What does pathology tell us?

Neuropathological analysis of the brains of individuals with dementia consistently reveals AD neuropathological changes, namely, plaques and tangles. Amyloid- β plaques initially manifest in the neocortex and subsequently extend to the allocortex, basal ganglia and brainstem³⁹. Conversely, tangles first appear in the brainstem and hypothalamic nuclei, progress to the allocortex and ultimately spread to the neocortex^{40,41}. Clinical correlations, including those predating memory-related symptoms, such as sleep dysfunction, are strongly associated with tangle burden and distribution^{32,42}. Patients with a high amyloid- β burden but lacking tangles exhibit few to no symptoms⁶. Despite the absence of evidence supporting amyloid- β pathology as the primary cause in sporadic AD cases, amyloid- β pathology might not merely be an incidental bystander. Tangle pathology seldom extends beyond the paralimbic cortices in the absence of amyloid- β pathology⁴³. An unresolved question in the field revolves around understanding the interaction between plaques and tangles and the contributions of these elements to synaptic and neuronal loss, leading to subsequent clinical decline. Furthermore, plaques and tangles are almost invariably found alongside other changes such as small vessel disease, white matter changes, and the presence of TDP-43 and α -synuclein deposits, among others^{44,45}. Consequently, multiple neuropathological changes probably contribute to dementia in older individuals⁴⁶. Attempting to attribute the extent of neurodegeneration to each component is a challenging task, and focusing solely on one of these factors might lead to an incomplete understanding as these different components probably interact with each other in complex ways, highlighting the intricate nature of neurodegenerative processes. Given that biomarkers for detecting TDP-43, α -synuclein and non-AD pathological tau are still undergoing development, caution must be exercised when assigning significance to the relationship between cognitive decline and AD neuropathological changes.

Are anti-amyloid- β therapies still relevant?

Inspired by the amyloid cascade hypothesis¹⁸, and assuming that amyloid- β is neurotoxic, both biochemical and immunological anti-amyloid- β therapies have been used in attempts to treat LOAD. As expected, these methods have successfully eliminated amyloid- β from the brain. However, none of these has been able to halt the progression of cognitive decline. Rather than accepting that amyloid- β is a wrong target, researchers then suggested that amyloid- β might only be toxic in the initial stages^{47,48}. Consequently, the focus of research shifted towards early interventions, prompting the development of numerous additional anti-amyloid- β therapies, often supported and sponsored by industry giants. Of note, the FDA has approved two drugs, lecanemab and aducanumab^{21,22}, for use in the initial stages of LOAD. A third drug, donanemab, might soon follow²³. However, instead of halting disease progression, these trials have demonstrated a weak clinical slowing effect, with an estimated progression delay of 5–6 months^{21–23}. These findings indicate that disease progression cannot be primarily ascribed to amyloid- β toxicity alone, underscoring the existence of other, potentially more significant mechanisms contributing to neurodegeneration. Once these hitherto unknown processes are identified, the answers to the pressing question of when and where have these processes started will arise.

Findings from genetics

Unlike the genetic forms of EOAD, most LOAD occurs typically as a sporadic disease with a polygenetic risk modulation. For instance, carrying the *APOE4* haplotype has been known to be a significant risk factor for LOAD for the past 30 years⁴⁹, suggesting that directing interventions towards *APOE4* could potentially serve as a treatment strategy for individuals within this group. Unfortunately, attempts to develop an anti-AD therapy based on this finding have so far failed⁵⁰. The mechanism by which *APOE4* contributes to AD pathology remains incompletely understood, and the impact of *APOE4* extends beyond LOAD to affect other neurodegenerative diseases independently of amyloid- β pathology^{51–54}. Even a seemingly robust genetic risk factor such as *APOE4* can be influenced by a potential combination of other genes, as evidenced by its varying risk profile in different ethnic groups^{55–58}. Furthermore, *APOE4* does not seem to influence the risk of the younger group of EOAD⁵⁹. Other genes identified within families also elevate the risk of AD pathology, but these genetic variants are uncommon in the general population^{60,61}. The relevant question, which is still unanswered, is what activates these genes?

Other genetic markers, found on genome-wide association studies, include inflammatory markers and genes associated with lipid metabolism⁶². None of these is presumed to be the main cause of LOAD. Even the polygenic risk score, at its best, can only modestly predict the

Table 1 | Similarities and differences between sporadic and familial Alzheimer disease

Feature	ADAD	EOAD	LOAD
Age at onset (years)	<50	<65	≥65
Sex distribution ⁷⁵	Female=male	Female=male	Female>male
Episodic memory loss	Early ^a	Early ^a	Early ^a
Atypical signs and signals ^{4,76}	Common	Higher frequency of dysexecutive symptoms and atypical presentation than LOAD	Uncommon
Genetic contributions	Autosomal dominant	Probably polygenic	Probably polygenic
Frequency of <i>APOE4</i> carriers (%) ^{28,77–80}	Up to 30	~60 (except for low frequency in atypical cases)	~60
Neuropathological hallmarks	Plaques and tangles	Plaques and tangles	Plaques and tangles
Structure of amyloid- β filaments ³⁰	Type II	Unreported	Type I
Pattern of amyloid- β spread ^{81,82}	Neocortex first; 10–20% with striatal origin	Neocortex first	Neocortex first
Presence of plaque variations in addition to the common neuritic and diffuse plaques ^{83,84}	Cotton-wood type	Subset of cases with coarse plaques	Rare cases with coarse plaques
Initial tau accumulation ^b (refs. 85,86)	Unknown	Subcortical nuclei belonging to the neuromodulatory subcortical system ^c	Subcortical nuclei belonging to the neuromodulatory subcortical system ^c
First regional evidence of PET signal ^d (refs. 87,88)	Precuneus	Mesial temporal region	Mesial temporal region
Tau burden ^{31,89,90}	Higher in the striatum than in sporadic cases	Higher in cortical areas than in LOAD	Higher in limbic areas than in ADAD and EOAD
Rate of brain atrophy ⁸¹	Fast	Fast	Slow
Highest magnitude of brain atrophy ^{91–93}	Neocortical and medial temporal	Neocortical>medial temporal	Medial temporal>neocortical
CSF assays of amyloid- β_{42} ; amyloid- β_{40} ; tau; phosphorylated tau ₁₈₁ (ref. 81)	Reduced; reduced; increased; increased	Reduced; reduced; increased; increased	Reduced; reduced; increased; increased

ADAD, autosomal dominant Alzheimer disease; CSF, cerebrospinal fluid; EOAD, sporadic early-onset (<65 years of age) AD; LOAD, sporadic late-onset AD. ^aA subset of ADAD manifests spastic paraparesis and behavioural presentations preceding memory decline. About 5% of sporadic cases manifest AD pathology with a non-amnesic presentation, the so-called atypical AD cases.

^bAccording to post-mortem studies. ^cFor more details about the neuromodulatory subcortical system, see refs. 85,86. ^dPET has a low resolution to capture most subcortical structures.

likelihood of individuals developing the disease⁶³. In simple terms, if each gene has a role in some patients but not in others, it reinforces our argument that AD pathology represents a convergence of various pathogenic processes.

What does epidemiology tell us?

Sporadic and familial AD have many similarities in the pathological picture, including the deposition of amyloid- β plaques and tau tangles. Epidemiological studies have revealed numerous distinct underlying risk factors for dementia, supposedly associated with LOAD (Box 2). However, these risk factors, including *APOE4*, have a different profile on EOAD⁶⁴. For LOAD, despite the numerous identified risk factors, experimental studies have failed to provide evidence of causality⁶⁵, raising intriguing questions about how conditions such as hypertension, obesity, loneliness or smoking might contribute to the accumulation of amyloid- β or tau. It is more plausible that these factors have a role in compromising brain buffering mechanisms⁶⁶, thus making it challenging to counteract the damage supposedly caused by the build-up of plaques and tangles, leading to cognitive decline. Even in the case of poor sleep – traditionally considered a risk factor for AD owing to its association with amyloid- β accumulation resulting from impaired removal mechanisms – evidence suggests that early changes in AD tau pathology occur in neurons responsible for regulating the sleep cycle, suggesting that AD pathology is in fact a triggering factor for poor sleep early on⁶⁷. In any case, it is highly improbable that all of these diverse processes identified through epidemiological studies converge into the same mechanisms leading to amyloid- β accumulation. As all of these different factors converge in individuals, LOAD needs to be considered a multifactorial disorder⁶⁸. Importantly, the list of these factors might vary among different individuals. As a result, various interventions might be necessary to halt the degenerative processes, even if they eventually lead to a similar outcome (that is, amyloid- β and tau deposition, inflammation, and hippocampal degeneration or dementia). In clinical practice, this line of reasoning is implicitly followed by clinicians when addressing abnormalities such as hypertension, hearing loss or dyslipidaemia in individuals with mild cognitive impairment.

Large longitudinal studies indicate a decline in the incidence of dementia over the past decades in cohorts from high-income countries, which could be associated with improved management of environmental and medical risk factors^{69,70}. Although studies on neuropathological changes confirming a direct link between reducing risk factors and diminished AD neuropathological changes are lacking, reducing risk factors is linked to improved resilience of the brain against the effect of plaques and tangles, directly reducing dementia burden⁶⁵. Robust initiatives to mitigate environmental risk factors remain particularly pertinent in low-income and middle-income countries, where two-thirds of the population with dementia reside⁷¹, and programmes aimed at reducing these risk factors are still in their early stages.

It is crucial to acknowledge that there will never be a single intervention capable of preventing dementia or altering its course in all cases. Instead, a multifaceted approach is required to effectively manage the diverse factors contributing to the condition. Such interventions have been started, to a limited extent, as in the FINGER study⁷², which targets a few of the potential causes. Although logically a useful attitude, a better one would be to individualize the treatment in a personal approach. Developing personalized polyrisk scores, including genetic and non-genetic risk scores, is crucial for assessing the optimal level of aggressiveness in risk mitigation strategies, mirroring the approach commonly used in managing cardiovascular diseases.

Box 2

Medical and environmental risk factors for Alzheimer disease

Medical

- Depression
- Diabetes mellitus
- Dyslipidaemia
- Hearing and visual loss
- Hypertension
- Obstructive sleep apnoea
- Smoking

Environmental

- Diet
- Loneliness
- Physical inactivity
- Pollution
- Poor education
- Sedentarism
- Stress

Conclusions and future directions

Dementia is a grave and expanding worldwide problem, with many different causes. However, the term ‘Alzheimer disease’ misrepresents the sporadic, late-onset form of the condition, as it deviates from the case described by Alois Alzheimer in 1907 (ref. 73), which involved a patient with a *PSEN1* gene mutation and early-onset disease⁷⁴. LOAD is a complex and multifactorial condition arising from a combination of genetic, environmental, medical and lifestyle factors. Its lack of a singular common pathogenesis prevents it from being regarded as a straightforward ‘disease’. The anti-amyloid- β trials have emphasized the constraints of this approach and suggested that amyloid- β might not have as an important a role in neurodegeneration compared with other contributing factors. Sticking to the amyloid cascade hypothesis may be an example of what John Maynard Keynes said, “The difficulty lies not so much in developing new ideas as in escaping from old ones”.

A comprehensive and multifaceted approach will be crucial in preventing and managing this complex condition effectively. In each individual, the progression of LOAD is distinctive due to a particular mixture of contributing elements. Consequently, the brain changes underlying the clinical phenotype probably involve multiple mechanisms, rather than a single cause. Focusing on a single component of this heterogeneous multifactorial process can only have a limited effect on the incidence or progression of the dementing illness. The idea that AD is heterogeneous and might manifest as a convergence of different pathogenic pathways has been on the radar of the scientific community for some time. Hypotheses regarding the pathogenic mechanisms, as outlined in Box 1, remain unrefuted, and a number of these could potentially have a role in brain alterations that give rise to LOAD in certain individuals. Resilience represents a compelling yet underexplored subject of significant importance. The notable diversity in the way symptoms emerge and progress among individuals with AD not only suggests the distinct influence of various harmful agents but also hints at the potential effect of protective elements on the clinical expression of neurodegenerative conditions. These elements encompass factors ranging from immunological to inflammatory and genetic, and pave the way for innovative preventive and therapeutic strategies.

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