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EDITORIAL

Towards a new era in Alzheimer's disease diagnosis and treatment

Rumo a uma nova era no diagnóstico e tratamento da doença de Alzheimer

Hacia una nueva era en el diagnóstico y tratamiento de la enfermedad de Alzheimer

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In terms of health and social care, dementia is the main challenge of the 21st century (1, 2). It affects about 50 million people worldwide and this number is estimated to reach 152 million by 2050 (3). Importantly, this growth is expected to happen especially in low-income and middle-income countries (such as Brazil), where more than two-thirds of individuals with dementia live (3). Besides impacting the health and quality of life of patients living with this condition, as well as their families and caregivers, it presents an important economic burden – the estimated annual global cost of dementia is US$1.3 trillion (3, 4). Therefore, dementia is recognized as a public health priority by the World Health Organization (4).

Dementia is a clinical syndrome reflecting cognitive and functional impairment that can result from a variety of pathologies that primarily or secondarily affect the brain, particularly in older individuals (5). In recent decades, much attention has been focused on Alzheimer's disease (AD), as it is responsible for 60-70% of dementia cases (4). This is an insidious and progressive neurodegenerative disease that is neuropathologically characterized by the presence of amyloid-β (Aβ) plaques and tau neurofibrillary tangles, which are believed to promote neurodegeneration and clinical deterioration (6, 7). AD is typically associated with gradual memory impairment that slowly progresses to involve other cognitive domains (visuospatial, executive, and language are the most commonly affected) (8). Remarkable development was observed in AD research in recent years, which has potentially revolutionized the clinical approach to AD, mainly in terms of diagnosis, prognostic assessment, and treatment.

The first widely used criteria for diagnosing AD was proposed in 1984, which defined this neurodegenerative condition as a clinical-pathological entity (9). According to these criteria, the definitive diagnosis required a clinical diagnosis of dementia and neuropathological detection of A plaques and tau neurofibrillary tangles. During life, only a possible

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or probable diagnosis could be made based on clinical symptomatology and exclusion of other causes of dementia. Even though this is still the dominant framework to diagnose AD in clinical settings nowadays, autopsy investigations estimated that 25–30% of patients with a clinical diagnosis of AD are misdiagnosed, and dementia symptoms occurred due to other degenerative processes (10). Accurate and timely diagnosis in clinical practice is extremely important to provide patients with diagnostic and prognostic information about their disease, as well as the most appropriate therapeutic strategy. Therefore, there is an urgent need to improve the clinical diagnostic workup of AD.

Major advances in the development of neuroimaging and fluid biomarkers allowed *in vivo* detection of AD pathophysiological processes, even in asymptomatic and prodromal stages. This drastically changed the landscape to understand AD, from a clinic-pathological entity to a biological entity defined throughout a continuum with different clinical stages. This culminated in the proposal of several sets of guidelines that shifted the diagnosis of AD from the dementia stage to the earlier prodromal (or even preclinical) stage. Two main groups were responsible for creating these diagnostic research frameworks: the International Working Group (IWG) (11-14) and the National Institute on Aging-Alzheimer's Association (NIA-AA) (15-19). Although there are differences between these different criteria (principally concerning the interpretation of biomarker abnormality in asymptomatic individuals), both strongly recommend that the diagnosis of AD must be supported by biomarker evidence of AD pathology (14, 19). Following the recommendations of the most updated guidelines, groups around the world have proposed different diagnostic consensus that are applicable to the challenges faced locally, such as in Brazil (20). The AD biomarker signature relies on the detection of Aβ pathology (low cerebrospinal fluid [CSF] $A\beta_{42}$ or $A\beta_{42/40}$ ratio and increased cortical tracer binding in Aβ positron emission tomography [PET]), tau pathology (elevated CSF phosphorylated tau [p-tau] and increased tracer retention in tau PET), and neurodegeneration (atrophy on structural magnetic resonance imaging [MRI], fluorodeoxyglucose [FDG] PET hypometabolism, and elevated CSF neurofilament light chain [NfL]) (7).

PET and CSF biomarkers have been shown to be highly reliable and accurate in measuring AD pathophysiological processes; however, they are invasive or costly, limiting their application in clinical practice (10, 21). Recently, blood-based biomarkers have been showing very promising results in measuring AD-related pathologies in the living human brain. Specifically, studies indicate that plasma $A\beta_{42/40}$ ratio (22-25), p-tau (26-29), NfL (30-32), and glial fibrillar acid protein (GFAP) (33-35) are the main candidates to support the diagnosis and prognosis of AD, as well as to track the effects of disease-modifying therapies. The development of these biomarkers represents a major step forward in AD medical research as they are easily accessible, accurate, and cost-effective, having the potential for widespread use, especially in primary care (10). However, several factors still limit the implementation of blood-based biomarkers in clinical settings. For instance, most of the data available so far come from retrospective studies that were conducted in very well-characterized research-based populations of mostly highly educated white volunteers and that used blood samples collected previously and analyzed in large batches. Additionally, the lack of standardization in assay methods and generation of validated cutpoints, as well as the high variability in longitudinal measures represent important challenges that need to be overcome (21, 36, 37). Together with the development of analytical guidelines, standardization of inter-laboratory methods, and validation of cutpoints, future prospective longitudinal studies conducted over long periods of time in real-world settings including diverse populations (*e.g.*, Black, Asian, and LatinX) are required to guide the clinical implementation of blood-based biomarkers for AD.

Regarding neuropathology, a major milestone

in AD-related research in the last decades was the recognition that late-life dementia commonly presents multiple etiologies (38). At first, it was believed that patients with neurodegenerative diseases usually had a single pathological process in the brain causing the symptoms. However, multiple neuropathological investigations recently demonstrated that dementia symptoms are associated with the presence of mixed pathologies (39-43). In fact, it was observed that old people living with dementia are more likely to present multiple pathologies (mostly Aβ, tau tangles, Lewy bodies, TAR DNA-binding protein 43, hippocampal sclerosis, and vascular pathologies) rather than single disease processes (44, 45). Together, this evidence suggests that the possible (or even likely) presence of multiple brain pathologies beyond Aβ and tau needs to be taken into account when assessing an older individual with AD. Specifically, identifying the underlying brain pathology promoting clinical deterioration is extremely important for an accurate diagnostic and prognostic assessment of patients. Furthermore, in the context of emerging disease-modifying therapies targeting biological processes, the detection of the primary cause of dementia symptoms in each case will also be crucial to select the most appropriate individuals to receive a specific treatment (*e.g.*, anti-Aβ therapy).

Until recently, approved pharmacological treatments for AD were only symptomatic agents aiming to improve cognitive performance without halting the pathophysiological progression of the disease (46). In 1993, tacrine was the first approved acetylcholinesterase inhibitor for AD treatment; however, it was discontinued due to hepatotoxic side effects (47, 48). The development and approval of further acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and, subsequently, an NMDA receptor antagonist (memantine) then followed, all of which continue to be widely used nowadays (47). Since memantine's approval in 2003, no medication was approved by the US Food and Drug Administration (FDA) for the treatment of AD for 18 years (46). After setbacks over almost two decades, the first disease-modifying treatments for AD (aducanumab in 2021, and lecanemab in 2023) have gained approval from the FDA (49, 50). This represented a crucial step further in the ongoing fight to modify the clinical and pathophysiological progression of AD by directly targeting brain Aβ. However, important factors may limit the widespread prescription of these recently approved drugs for early-stage AD, such as the elevated treatment costs (*e.g.*, the annual treatment with lecanemab is estimated to cost $26,500 per year) (51), uncertainty in relation to the clinical meaningfulness of the interventions (in 18-month phase 3 clinical trials, aducanumab showed a clear biomarker but not clinical response, while lecanemab slowed clinical decline by 27%) (52, 53), and frequent adverse events (mainly amyloid-related imaging abnormalities [ARIA] with edema/effusion [ARIA-E] and with hemorrhage/hemosiderin deposition [ARIA-H]) (51, 54). Even though therapies targeting Aβ are in the spotlight, several interventional clinical trials are currently ongoing testing other disease-modifying drug candidates in symptomatic and asymptomatic individuals. The targets beyond A include tau, inflammation/immunity, synaptic plasticity and neuroprotection, oxidative stress, vasculature, metabolism and bioenergetics, epigenetic regulators, apolipoprotein E (ApoE), and others (55). Because AD is a heterogeneous disease, it has already been suggested that the combination of therapies – rather than single-target treatments – could potentiate treatment outcomes (56-58). As it has already resulted in improved outcomes for other complex diseases (*e.g.*, cancer, acquired immunodeficiency syndrome, and cardiovascular disease), this seems a promising strategy (59). Nevertheless, this hypothesis should be tested in future trials. Taken together, these observations suggest that we are rapidly moving forward to the development of effective therapeutic strategies for AD.

To conclude, outstanding progress has recently been made in AD-related research. The clinical view of AD is evolving as a consequence of the

development of novel accurate and reliable biomarkers, the proposal of new diagnostic criteria, and the approval of the first disease-modifying drugs. Although there are still major gaps that need to be addressed, we are entering a new era of tackling Alzheimer's.

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