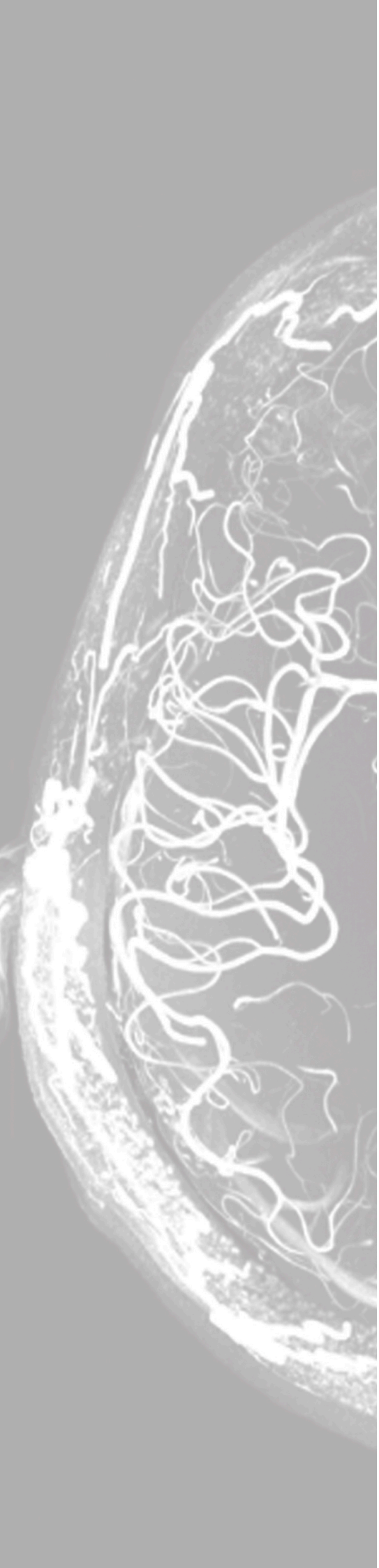

Article

Alzheimer's Disease

Global perspectives on Alzheimer's disease diagnosis and treatment: challenges and considerations in resource-limited settings

Alzheimer's disease (AD) is v most prevalent neurodegenerative disease and the leading cause of dementia worldwide, regardless of socioeconomic status.[1] *However, the burden of AD in particular, and the burden of dementia in general, greatly amplifies in countries or settings where there is a lack of general public knowledge about the disease or dementia symptoms, as well as limitations in the access to diagnosis and to adequate care management. This article discusses some challenges and considerations about the diagnosis and treatment of AD in resource-limited settings.*

Glossary:AD: Alzheimer's disease; CSF: cerebrospinal fluid; CT: computerized tomography; LMIC: low- and middle-income country; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.

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Global perspectives on Alzheimer's disease diagnosis and treatment

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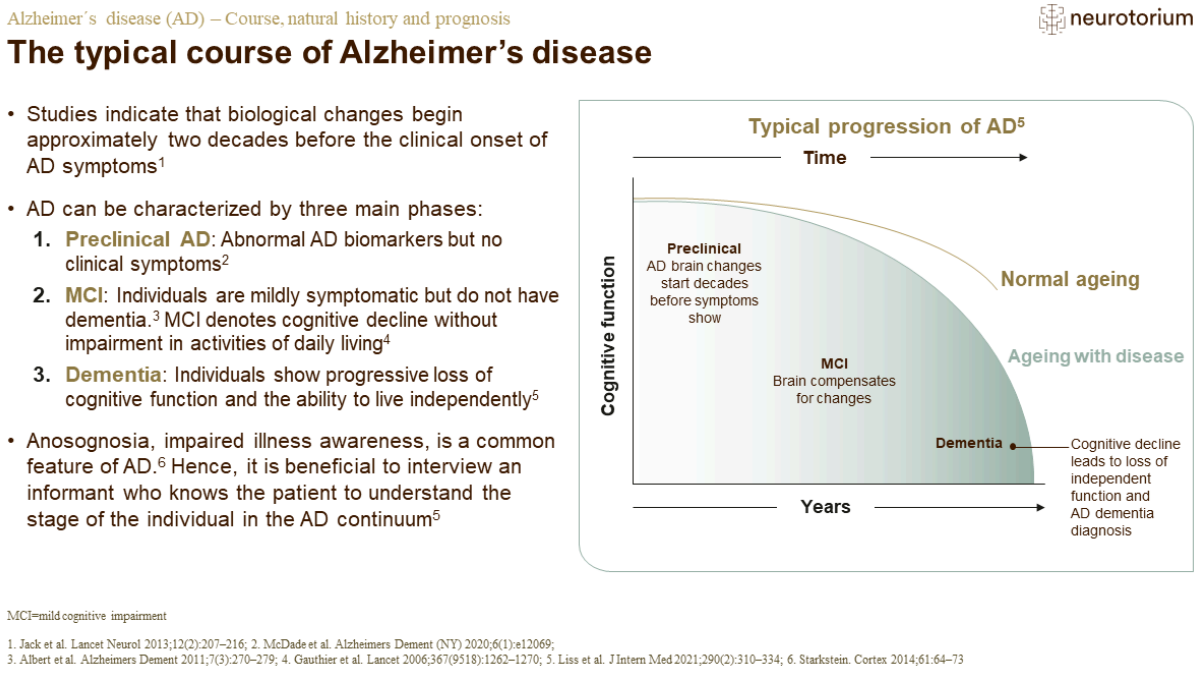
Clinical phenotypes of Alzheimer's disease

The neuropathology substrate of AD is the brain accumulation of amyloid plaques and neurofibrillary tangles containing phosphorylated tau protein. These pathological changes lead to neuronal dysfunction and death, and begin 10 to 20 years before the clinical diagnosis.[2] The course of the disease includes a preclinical stage, followed by the stages of subjective cognitive decline, mild cognitive impairment (MCI), and, ultimately, dementia.[3]



Slide 1: What factors are at play in Alzheimer's disease?

Access Slide Deck: Alzheimer's disease – Neurobiology and Aetiology

The 'preclinical' stage precedes mild cognitive impairment (MCI) and includes individuals who have evidence of early AD pathological changes, but do not meet clinical criteria for MCI or dementia.[7]

Three stages of preclinical AD were first defined in 2011.[7] In Stage 1, individuals are not cognitively impaired but present with amyloidß- (Aß) pathology.[7] Stage 2 is characterized by the presence of Ab pathology and neurodegeneration, without cognitive impairment, and Stage 3 is also characterized by the presence of Aß pathology and neurodegeneration, but with subtle cognitive impairment.[7]

MCI stage describes the presence of noticeable cognitive decline which is relative to age and does not interfere with daily activities.[4] The heterogeneity of MCI presents a challenge to the timely diagnosis of MCI due to AD.[4] Cognitive impairments of different aetiologies may be more correctable than MCI due to AD (e.g polypharmacy, sleep disorders, major depressive disorder), will require different treatments, and will be associated with differing prognoses.[8] Therefore, characterizing the nature of and accurately diagnosing the aetiology of observed impairment is important.[4]

The dementia stage is the stage most associated with AD and is characterized by substantial cognitive impairment which affects more than one cognitive domain.[9] Dementia due to AD can take approximately two decades to develop.[9] Once present, individuals may live with dementia for several years.[10] Emerging evidence from both genetic at-risk and ageing cohorts suggests that there may be a time lag of a decade or more between the beginning of the pathological cascade of AD and the onset of clinically evident impairment.[7] It has been proposed that AD begins with a long asymptomatic period, during which the pathophysiological disease progresses.[7] Individuals with biomarker evidence of early AD-pathophysiological processes are then at increased risk for developing cognitive and behavioural impairment and progression to clinically manifest AD dementia.[7]

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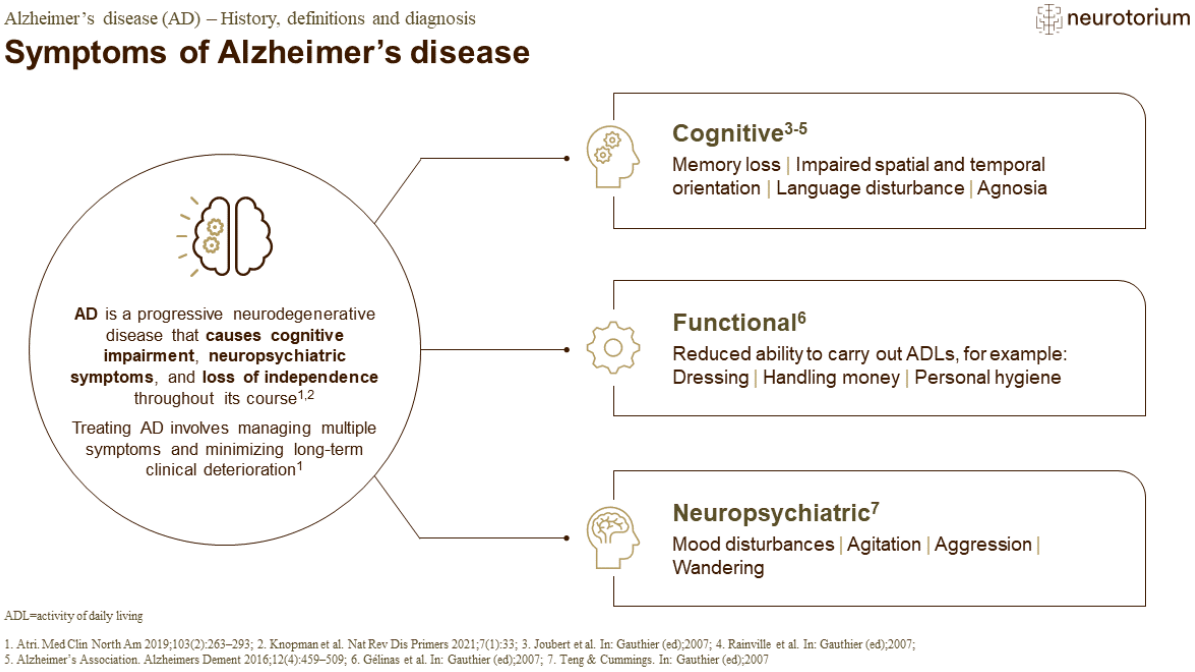
AD is clinically characterized by cognitive decline, being memory impairment the earliest and most prominent symptom in around 85% of the cases.[4,5] The remaining cases constitute

non-amnestic or atypical variants of AD, with predominance of language symptoms (primary progressive aphasia-logopenic variant), visual symptoms (posterior cortical atrophy), dysexecutive/behavioral symptoms (behavioral/dysexecutive variant), or more prominent motor symptoms (corticobasal syndrome).[6] These atypical phenotypes are more common in early-onset cases, i.e., when symptoms emerge before the age of 65 years.[7] Behavioral or neuropsychiatric symptoms are also very common over the course of the disease, from apathy (the most frequent behavioral symptom), depression and anxiety, to agitation, aggressiveness, irritability, delusion, wandering, disinhibition and hallucinations.[8]



Slide 2: Symptoms of Alzheimer's disease

Access Slide Deck: Alzheimer's disease – History, definitions and diagnosis

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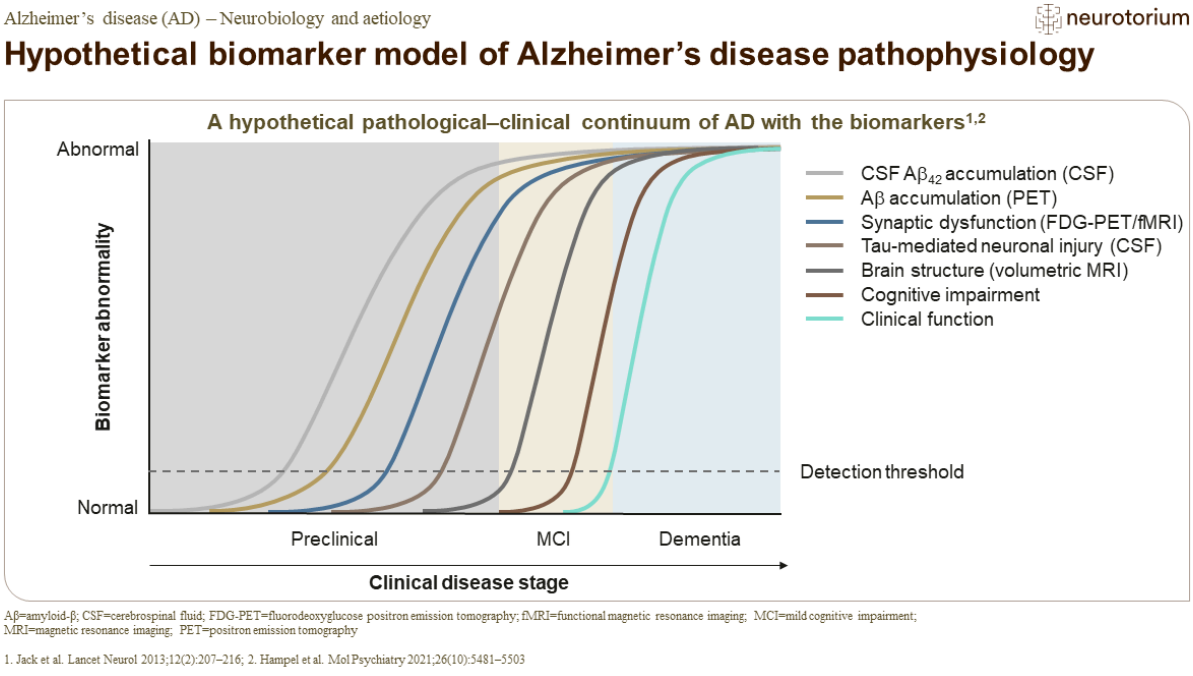
Diagnosis and therapeutic management of Alzheimer's disease

Diagnosis of AD is based on clinical history (with the affected person and a close informant) and structured clinical assessment, which must include cognitive and functional evaluation, physical examination, as well as laboratory tests and structural neuroimaging (e.g., computed tomography (CT) or magnetic resonance (MRI) of the brain). These latter two procedures aim to exclude other causes of cognitive impairment, but neuroimaging (especially MRI) can depict atrophy of the medial temporal lobes that serves as a biomarker of neurodegeneration and may be a supportive feature for the diagnosis of AD.[5]

In recent years, specific biomarkers have emerged as useful diagnostic tools, allowing earlier and more precise diagnosis. AD biomarkers can be classified as amyloid-related (e.g., low levels of beta-amyloid 42 levels in the cerebrospinal fluid (CSF) or increased amyloid deposition in the brain detected by positron emission tomography (PET) images using amyloid radiotracers) or tau-related (e.g., increased levels of phosphorylated tau levels in the CSF or increased tau protein deposition in the brain in PET images using tau radiotracers).[6] Biomarkers are especially useful for the diagnosis of AD in the prodromal stage of MCI, for the differentiation with other causes of cognitive impairment (especially other neurodegenerative diseases) and in cases with atypical clinical presentations.[9]



Slide 3: Hypothetical biomarker model of Alzheimer's disease pathophysiology

The time-course of biomarker abnormalities and the point at which they become detectable can help determine the primary cause of AD progression.[3] The A/T/N biomarker classification system for AD

includes three main classes of biomarkers – Aß, tau, and neurodegeneration – and provides the ability to classify biomarker status of an individual independently of their cognitive status.[3] Aβ biomarkers include amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) concentrations of Aß.[3] Tau biomarkers include tau-PET and CSF concentrations of phosphorylated P-tau. There are multiple neurodegeneration biomarkers, including fluorodeoxyglucose (FDG)-PET, magnetic resonance imaging (MRI) atrophy, CSF concentrations of total tau and of neurofilament light chain.[3]

In the preclinical phase, the first measurable evidence of AD is an abnormal reduction in Aß1-42 levels within the CSF due to an increased sequestering of Aβ in the brain parenchyma.[4-7] Following this, Aß tracer retention is observed in PET scans, directly reflecting the build-up of amyloid.[2,7] As AD progresses, neurodegeneration and synaptic dysfunction can be observed using structural and functional neuroimaging techniques, such as FDG-PET and MRI.[2,7] In carriers of the e4 APOE allele, synaptic dysfunction may be observed before detectable Aß accumulation.[2] Following this, elevated concentrations of CSF biomarkers that are directly associated with neuronal injury/death, such as t-tau, p-tau181, visinin-like protein 1 (VILIP-1) and neurogranin, are detected.[1,2] Continuation of disease results in hippocampal and entorhinal cortex atrophy and cortical thinning that can be detected by volumetric MRI.[5,7,8] As with Aß biomarkers, these biomarkers may be detected in individuals at high risk of AD many decades before cognitive decline occurs.[7,9] The MCI phase represents the first symptomatic occurrence in AD, with patients experiencing a decline or plateau in Aß accumulation,[10,11] and continued tau accumulation and neurodegeneration.[7] The progression of AD pathology results in a display of cognitive deficits, with memory and executive function often being the most affected cognitive domains.[7] For most patients with MCI due to AD pathology, the subsequent stage is AD dementia, which is a decline in clinical function, and represents the late stages of disease.[7] At this stage, Aß and tau accumulation are at their maximum, changes in brain structure continue, and neurodegeneration becomes macroscopically evident.[7]

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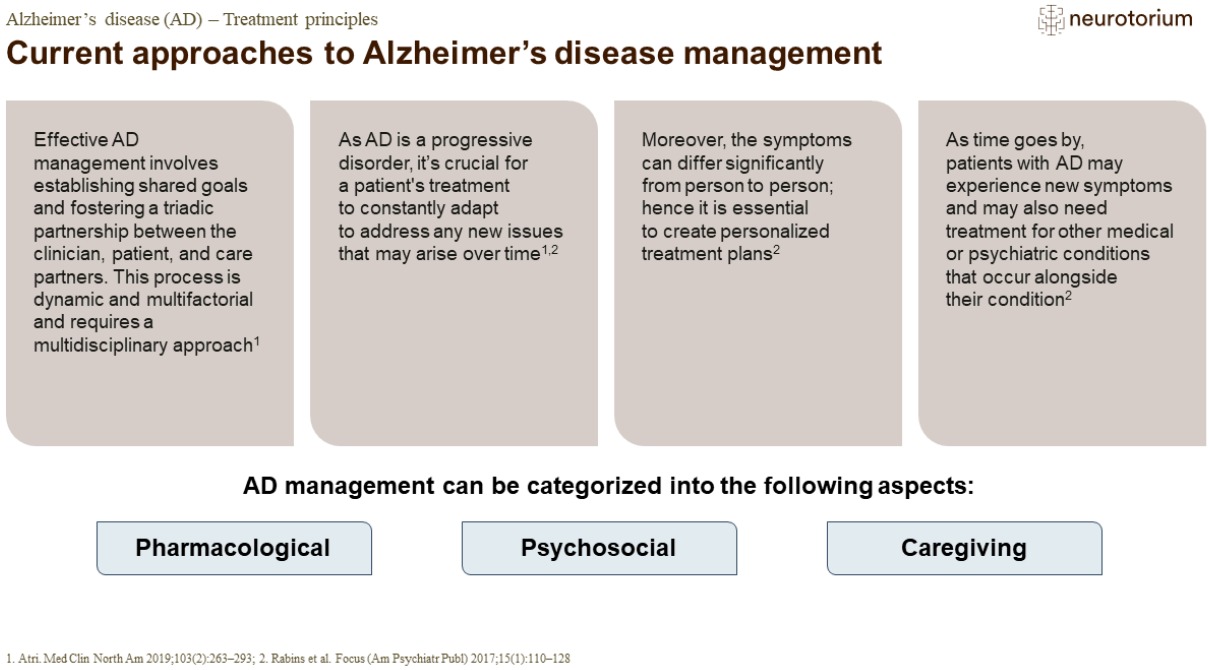
Accurate diagnosis of AD is paramount for proper therapeutic management. Treatment of AD includes pharmacological and non-pharmacological interventions. Cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and memantine have been approved for the treatment of different stages of AD dementia.[10] More recently, monoclonal antibodies (aducanumab, donanemab and lecanemab) were approved by some drug federal agencies for the treatment of MCI or mild dementia due to AD, although commercialization of aducanumab has been subsequently discontinued.[11,12]

Different non-pharmacological treatments have been proved useful for the management of cognitive and neuropsychiatric symptoms in dementia due to AD, such as cognitive stimulation therapy, multidisciplinary cognitive rehabilitation, reality orientation, and psychosocial intervention for people with dementia and their caregivers.[10]



Slide 4: Current approaches to Alzheimer's disease management

Access Slide Deck: Alzheimer's disease – Treatment principles

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Alzheimer's disease in low-resource settings: The challenges

Around 2/3 of people with dementia live in low- or middle-income countries (LMIC).[13] Different factors impede the timely and accurate diagnosis of AD in these countries, particularly in scenarios with low resources.

One of the primary challenges in resource-limited settings is the lack of awareness and understanding of AD and dementia symptoms by the general population. Stigma, misconceptions, and cultural beliefs can hinder timely diagnosis and access to care. Symptoms of cognitive decline are often considered to be part of normal aging, significantly delaying diagnosis (or leading to non-diagnosis) and intervention. Therefore, community education programs and awareness campaigns tailored to local cultures and languages are essential to increase recognition of the disease and to encourage seeking medical help.

Around 2/3 of people with dementia live in low- or middle-income countries (LMIC).13 Different factors impede the timely and accurate diagnosis of AD in these countries, particularly in scenarios with low resources

Another significant challenge is the scarcity of specialized healthcare professionals trained in Geriatrics, Neurology, or Old Age Psychiatry. Moreover, in many of LMIC countries general practitioners do not receive adequate training in dementia diagnosis and care.[14] In rural areas of some LMIC, the nearest physician might be hundreds of kilometers away, causing significant delays in diagnosis and treatment.[15]

Diagnostic tools such as neuropsychological assessment and neuroimaging (MRI, PET) are often unavailable or too expensive in these settings. Consequently, many cases go undiagnosed or misdiagnosed, exacerbating suffering of the affected people and their families, and hindering access to appropriate care and support services.[16]

Diagnostic tools such as neuropsychological assessment and neuroimaging (MRI, PET) are often unavailable or too expensive in these settings. Consequently, many cases go undiagnosed or misdiagnosed

Cultural and linguistic diversity adds another layer of complexity to AD diagnosis and management in resource-limited settings. In many regions, traditional beliefs and stigma surrounding mental illness prevail, leading to underreporting and reluctance to seek medical help.[13,17] Additionally, language barriers can impede effective communication between affected individuals, family caregivers, and healthcare providers, affecting the accuracy of diagnostic assessments and treatment adherence.[16]

Treating AD poses significant challenges, especially in resource-limited settings where access to pharmacotherapy and supportive

care is constrained. Cholinesterase inhibitors and memantine are costly for people from low socioeconomic levels and are not covered by public health programs in many countries. Consequently, many families must assume the financial burden of treatment.[13,14]

Finally, non-pharmacological interventions, such as cognitive stimulation therapy or caregiver support programs, are scarce in resource-limited settings due to funding constraints and to a shortage of trained health professionals.[16] The restricted access to comprehensive care exacerbates the burden on caregivers and diminishes the quality of life for affected people and their families, leading to caregiver depression and burnout, and compromising their physical and mental health.

Alzheimer's disease in low-resource settings: Possible solutions

The approach to tackle the challenges of AD in resource-limited settings requires a multifaceted strategy that encompasses capacity building, engagement of the community, and public health policies. Investments in training healthcare workers at the primary care level and raising public awareness about AD/dementia are essential steps toward improving diagnosis, treatment, and support.[14]

The approach to tackle the challenges of AD in resource-limited settings requires a multifaceted strategy that encompasses capacity building, engagement of the community, and public health policies

Community-based interventions, such as caregiver training programs and care services, are promising in alleviating caregiver burden in resource-limited settings. However, these initiatives require sustainable funding and collaboration between government agencies, non-profit organizations, and local communities to be effective.[18]

The approach to tackle the challenges of AD in resource-limited settings requires a multifaceted strategy that encompasses capacity building, engagement of the community, and public health policies

Technological advances may help to overcome some of the challenges associated with diagnosis and care of AD and dementia in resource-limited settings. Telehealth applications, for instance, can facilitate remote clinical monitoring and adherence to treatment even in underserved areas. Telemedicine platforms are also promising in improving access to specialized care individuals living in remote regions, such as rural areas. Online consultations by experienced clinicians can be provided, thus reducing the costs and sparing time with travels to distant regions. However, technological solutions must be adapted to the context of the specific settings, considering factors such as internet access, educational level, cultural issues and population acceptance.[18]

Furthermore, governments and non-profit national and international organizations must consider AD and dementia as a public health priority and allocate adequate resources to community education, research, prevention, diagnosis, and care. Collaborative efforts

between governments, non-government organizations, academia, as well as the private sector, are essential to develop sustainable solutions that meet the needs of vulnerable populations affected by AD in low-resource settings. In this sense, creation of national dementia plans in LMIC is essential to deal with the growing impact of AD and related disorders in these countries.[20]

Conclusion

AD and dementia pose significant challenges in resource-limited settings, where access to healthcare, diagnostic tools, and treatment options is often limited. Addressing these challenges requires a comprehensive approach that involves capacity building, community engagement, technological innovation, and public health policies. Investments in education of the general public about AD/dementia symptoms, early diagnosis, comprehensive care, and caregivers' support are necessary to alleviate the burden of affected people, their families, and healthcare systems, ultimately promoting a more inclusive and equitable approach that may provide better quality of life for these individuals.

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