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Guardians of memory: The urgency of early dementia screening in an aging society

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SUMMARY The global aging population has led to a significant rise in the prevalence of age-related non-communicable diseases such as dementia and other cognitive disorders. In 2019, there were 57.4 million people with dementia worldwide, and this number is projected to triple by 2050. Intervening in and managing 12 potentially modifiable dementia risk factors can prevent or delay the onset and progression of about 40% of dementia cases. Neuroimaging, biomarkers, and advanced neuropsychological testing offer promising pathways for the early detection of dementia. Emphasis should be placed on educating the public about the importance of brain health and the early signs of cognitive impairment, as well as promoting dementia prevention measures. Adopting a healthy lifestyle - including a balanced diet, regular physical exercise, active social engagement, cognitive activities, and avoiding smoking and excessive alcohol consumption - can help reduce the risk of cognitive decline and prevent cognitive disorders. Government policies on dementia prevention and health care, along with early and regular dementia screening programs, can enhance the early identification and management of individuals at risk. In addition, integrating cognitive health assessments into routine medical check-ups is essential for the early screening and management of dementia.

Keywords dementia, aging, biomarker, neuroimaging, neuropsychological testing, diagnosis

The global elderly population is undergoing a notable expansion in both size and proportion. According to projections by the World Health Organization, the number of individuals age 60 and above is expected to reach 1.4 billion by 2030, and this figure is forecasted to rise to approximately 2.1 billion by 2050. Moreover, from 2020 to 2050, the number of individuals age 80 and above is predicted to double, reaching approximately 426 million (*1*). As individuals age, the incidence of age-related non-communicable diseases like dementia and other cognitive disorders rises notably. Statistics indicate that in 2019, there were 57.4 million dementia patients worldwide, with projections suggesting this figure will triple by 2050 (*2,3*). Presently, almost 60% of dementia patients reside in low- and middle-income countries, and this proportion is expected to climb to 71% by 2050 (*4*). Dementia has emerged as the seventh leading cause of death globally, accounting for approximately $1.3 trillion in societal costs (*5*). A point worth noting is that around 75% of dementia cases worldwide are not diagnosed in a timely manner (*6*). Moreover, 80% of the population expresses concerns about developing dementia in the future, with approximately one-quarter believing it to be unpreventable (*4*).

As the population ages, there has been a notable surge in dementia cases. Most people believe that a definitive diagnosis will not change clinical management; therefore, the majority of dementia patients do not undergo relevant pathological examinations. A point worth noting is that the US Food and Drug Administration (FDA) recently approved two monoclonal antibody therapies targeting amyloid for individuals with mild cognitive impairment or mild dementia (*7*). The findings suggest that removing amyloid could alleviate the decline in cognitive function in individuals with mild dementia (*8,9*). Moreover, a 2020 study revealed that intervening in and managing 12 modifiable risk factors for dementia could prevent or delay its onset and progression by around 40%, and especially in regions with a high prevalence of dementia (*10*). Hence, early identification of at-risk individuals through diagnostic techniques could potentially alter the course of dementia progression.

Research has revealed the pathology of the disease in that amyloid deposits begin accumulating at least

Table 1. Neuroimaging, fluid biomarkers, and neuropsychological screening for dementia

Biomarkers	Significance	Key findings
Neuroimaging biomarkers		
Amyloid-PET/PiB PET	Identifying amyloid pathology in the brains of patients with AD.	Appears approximately 20 years before the earliest clinical symptoms of AD (*13*).
Tau-PET	Identifying tau accumulation as a biomarker for disease staging.	Reflects the progression of AD pathology and is associated with disease severity (*14*).
FP-CIT SPECT	Brain dopamine transporter imaging is highly sensitive and specific for diagnosis.	A mature biomarker for diagnosing DLB (*15*).
PK-PET	Shows the distribution of neuroinflammation in the brain across different types of dementia.	Neuroinflammation is a part of the pathophysiology of familial FTD (*16*).
Structural MRI	Evaluating the decline in brain structural regions facilitates dementia subtyping.	Structural decline occurred 4.7 years before symptom onset (*13*).
Functional MRI	Demonstrates differences in resting-state functional connectivity and identifies specific networks and regions affected in each type of dementia.	Abnormal activity in the DMN in AD (*17*).
FDG-PET	Indicates reduced local metabolism in the brain.	Metabolic reductions can be detected as early as more than 10 years before symptom onset (*11,13*).
Fluid biomarkers (CSF, blood)		
Aβ42, Aβ42/Aβ40	Aβ deposition.	The ratio of Aβ42/Aβ40 in plasma has a high concordance with the CSF Aβ42/Aβ40 ratio and amyloid PET status (*18*).
P-tau231, P-tau181, P-tau271, P-tau205	Neurofibrillary tangle formation.	P-tau181 and P-tau271 start to increase as early as 20 years before symptom onset (*19*).
T-tau, BD-tau, NfL	Synaptic dysfunction/neural degeneration.	Increased levels of NfL in CSF serve as a biomarker of neurodegeneration and can be assessed in blood (*20*).
GFAP	Neuroinflammation.	The increase in plasma GFAP concentration in patients with AD is greater than that in CSF (*21*).
Neuropsychology		
IQCODE, p-AD8, CAMCI	Self-administered tools.	The sensitivity or specificity in evaluating mild cognitive impairment is over 80% (*22*).
MMSE, MoCA, HDS-R, DemTect, MES, MEFO, CANTAB-PAL	Interview tools.	

Abbreviations: AD, Alzheimer's disease; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery-Paired Associates Learning; CAMCI, Computerized Assessment of Mild Cognitive Impairment; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; DMN, default mode network; FDG, ^{18}F-Fluorodeoxyglucose; FTD, frontotemporal dementia; GFAP, glial fibrillary acidic protein; HDS-R, Revised Hasegawa's Dementia Scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; LMT, Logical Memory Test; MEFO, Memory, Fluency, and Orientation; MES, Memory and Executive Screening; MMSE, Mini–mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NfL, neurofilament light; PiB PET, Pittsburgh compound B positron emission tomography; PK-PET, ^{11}C-PK11195 positron emission tomography; FP-CIT, ^{123}I-Ioflupane.

10 to 20 years before the onset of symptoms. By the time clinical manifestations of dementia appear, the disease is already at an advanced stage (*11*). In Europe, raising awareness about Alzheimer's disease (AD), implementing early screening, and facilitating prompt diagnosis are considered essential steps to implementing future disease management strategies, improving patient quality of life, and addressing the growing burden of the condition (*12*). Researchers are currently working to explore a range of new methods for early detection and diagnosis aimed at preventing and delaying the clinical progression of dementia. Recent technological advances have revolutionized the early diagnosis of cognitive impairment (Table 1).

Neuroimaging, biomarkers, and advanced neuropsychological testing offer promising ways to detect dementia in its early stages. Significant progress has been made in developing neuroimaging methods for AD biomarkers. These advances offer great potential in identifying underlying pathophysiological changes associated with dementia, such as structural decline (*e.g.*, volume reduction and cortical thinning), functional decline (*e.g.*, fMRI activity and network connectivity), decreased connectivity (*e.g.*, diffusion anisotropy), and pathological accumulation (*e.g.*, amyloid and tau positron emission tomography (PET)) (*13,23*) (as shown in Figure 1). Molecular imaging with PET is used to identify amyloid plaque deposition and tau tangle pathology patterns, thereby aiding in the diagnosis of AD (*24*). Molecular imaging with PET can not only reveal the

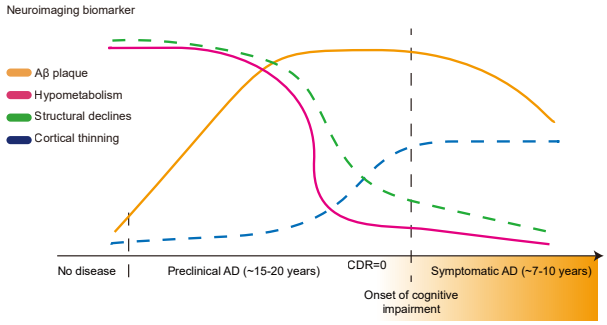

Figure 1. Neuroimaging assessment of Aβ aggregation, metabolism, and structural changes prior to the onset of Alzheimer's disease symptoms.

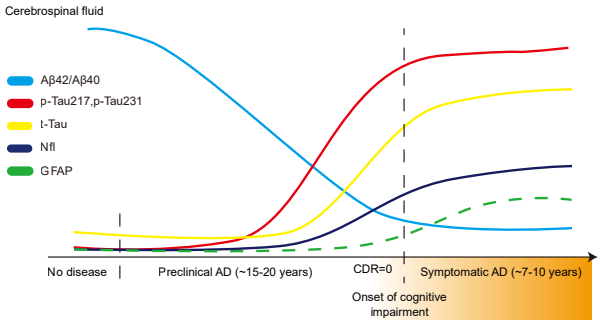

Figure 2. The pathological changes of Alzheimer's disease in cerebrospinal fluid, including amyloid deposition, tau accumulation, neuroinflammation, and neuronal degeneration.

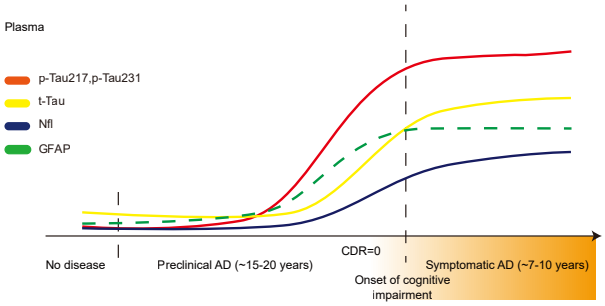

Figure 3. The occurrence of plasma tau accumulation, synaptic dysfunction, and neuronal degeneration before the onset of dementia symptoms.

pathological features of AD that begin decades before the onset of symptoms and assess the loss of dopaminergic terminals in Parkinson's disease, but it can also, with the development of new tracers for neuroinflammation and synaptic density, further elucidate the pathobiological changes characteristic of dementia (*14*). The further development of neuroimaging techniques requires more longitudinal studies with larger sample sizes, combined with advanced imaging modeling methods (such as artificial intelligence (AI)), to establish their clinical utility.

Using one or more AT(N) biomarkers has proven to be advantageous in diagnosing early dementia (*25*). Fluid biomarkers are less invasive and have a sensitivity similar to that of PET imaging in diagnosing dementia. By detecting forms of Aβ, tau, neuroinflammatory proteins, as well as markers of neuronal dysfunction and degeneration in cerebrospinal fluid (CSF) and plasma, AD can be distinguished and diagnosed from other neurodegenerative diseases, and these fluid biomarkers have significant value in predicting future cognitive deterioration (*26*). The soluble properties and post-translational modifications of tau in CSF and plasma are emerging as sensitive and reliable biomarkers for detecting tau pathology in AD. Research has shown that pThr181, pThr217, and pThr231 tau can accurately differentiate between amyloid PET-positive and amyloid PET-negative individuals (*27*). These changes help reflect the alterations in neuronal tau metabolism in the preclinical stages of AD when Aβ has aggregated (*28*).

Glial fibrillary acidic protein (GFAP) expressed by astrocytes in plasma is currently the only AD-related biomarker that outperforms its corresponding CSF measurement (*21*) . Another biomarker is neurofilament light (NFL), which is a component of the axonal cytoskeleton. NFL is released during axonal injury, leading to increased concentrations in CSF and blood. It has been found to be elevated in the CSF and plasma of individuals with mild cognitive impairment (MCI) and preclinical AD (*20*). Elevated levels of structural proteins appear to reflect synaptic loss during AD and neurodegeneration (*29*). In the CSF of patients with AD, synaptic proteins such as neuronal pentraxin 2 (NPTX2), neurogranin, and SNAP-25 are changed and may serve as biological markers for early diagnosis of AD (*30*). Therefore, monitoring fluid biomarkers helps reflect Aβ aggregation, glial activation, tau metabolic changes, synaptic dysfunction, and neurodegenerative changes in patients with preclinical dementia (*21,31*) (as shown in Figure 2,3). Using established and emerging biomarker technologies can reveal the mechanisms underlying AD and identify the earliest biological changes in the brain, marking different aspects of AD pathology for diagnostic and prognostic purposes.

Moreover, digital health technologies, including wearable devices and mobile applications, aid in the continuous monitoring of cognitive function (*32*). Digital spatial navigation can monitor early behavioral changes associated with dementia, while gait measurements facilitate early screening for dementia patients exhibiting prominent motor impairments such as dementia with Lewy bodies (DLB), vascular dementia (VaD), and Parkinson's disease dementia (PDD) (*33*). AI and machine learning algorithms are used to analyze the large datasets generated by these technologies, thus enhancing the sensitivity, accuracy, and specificity of early diagnosis (*34,35*).

Preventive measures are equally crucial in addressing cognitive impairment. At the individual level, adopting a healthy diet, engaging in regular physical exercise,

maintaining active social interactions, participating in cognitive activities, refraining from smoking, and abstaining from alcohol help mitigate the risk of cognitive decline (*36*). Public health initiatives should stress the significance of brain health and early signs of cognitive impairment and advocate for preventive measures against dementia. Notably, governments implementing healthcare policies for dementia prevention and conducting early and regular dementia screening programs aid in early identification and management of individuals at risk (*37*). Moreover, integrating cognitive health assessments into routine medical check-ups is essential for early screening and dementia management.

As we address the challenges of an aging society, what is imperative is to prioritize early diagnosis and prevention strategies for cognitive impairment. Use of new technologies for early detection and promoting preventive measures can significantly enhance individuals' quality of life and alleviate the societal and economic burdens associated with cognitive impairment. Collaborative efforts among healthcare providers, policymakers, and the medical technology industry will be vital in effectively managing cognitive impairment in our aging population.

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