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Preventing cognitive decline in preclinical Alzheimer's disease

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Alzheimer's disease (AD) is a chronic neurodegenerative disease leading to cognitive decline, dementia, and ultimately death. Despite extensive R&D efforts, there are no diseases modifying treatments for AD available. The stage in which patients receive a clinical diagnosis of probable AD may be too late for disease modifying pharmacotherapy. Prevention strategies may be required to successfully tackle AD.Preclinical AD applies to over half of all healthy elderly subjects and manifests by signs of amyloid deposition and/or neuronal injury in the brain, preceding the stage in which symptoms of dementia, cognitive and functional impairment become observable. Prevention trials in preclinical AD require longer and larger clinical trials using biomarkers and cognitive endpoints, which requires collaboration across academia, government and industry.

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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative condition. Currently 35 million patients suffer from AD and this number is estimated to rise to 115 million patients worldwide by 2050 [1,2]. At microscopic level, AD is characterized by the presence of large numbers of neuritic plaques, neurofibrillary tangles and by neuronal cell loss beginning in the hippocampus [3]. Clinically AD manifests itself by progressive decline of memory and other cognitive functions. Mild cognitive impairment (MCI) is considered to reflect a transitional stage between normal aging and dementia [4].

Recently, an asymptomatic phase, preclinical AD, has been defined as the stage preceding MCI and AD [5,6]. Subjects in the preclinical stage are at risk for AD, as shown by biomarkers signaling amyloid deposition in the brain (low amyloid-beta in cerebrospinal fluid [CSF] or increased binding to amyloid ligands in positron emission tomography [PET]) and signs of neuronal injury, such as high tau or phospho-tau in CSF, as well as signs of cortical thinning and hippocampal atrophy on structural magnetic resonance imaging (MRI) [7].

At present, five stages describe the potential recognition of approx. 96% of all healthy older adults (>65 years) 54% of whom are at risk developing AD before they express MCI, based on assessment of amyloid accumulation in the brain in the first stage, signs of neuronal injury in the second stage and subtle cognitive impairment in the third stage [9••] (see Table 1).

Preclinical Alzheimers disease

The categorization of preclinical AD is based on new research criteria commissioned by the National Institute on Aging and the Alzheimer's Association (NIA-AA), which distinguish three advancing stages (1–3) of preclinical AD from normality (stage 0) [6] in addition to the description of Suspected Non-AD Pathophysiology (SNAP) and a remaining unclassified category [9••]. SNAP is defined by presence of neuronal injury markers and absence of amyloid with or without signs of cognitive impairment. The unclassified category is defined by presence of subtle cognitive impairment and absence of amyloid with or without markers of neuronal injury. The stages at which cognitive and behavioral symptoms become manifest, are MCI and probable AD. The latter represents what is known in NINCDS ADRDA as clinical diagnosis of probable AD. Prodromal MCI is defined as clinically abnormal performance on tests of episodic memory along with evidence of amyloid deposition in the brain [11].

Vos *et al.* [10••] describe a longitudinal study carried out at the Knight Alzheimer's Disease Research Center (KADRC) at Washington University in St. Louis, Missouri, of 311 cognitively normal elderly people. Participants were older than 65 and had a Clinical Dementia Rating (CDR) of 0 at baseline, indicating normal cognition. Amyloid pathology and neurodegeneration were assessed from CSF, measured by amyloid-beta and tau, respectively. The results of classification into stages of preclinical AD was very similar to that reported by the Mayo Clinic Study of Aging (MCSA) in a separate population of cognitively healthy older adults using amyloid imaging. The average of these classifications are shown in Table 1. These studies show that preclinical AD is common and can be diagnosed by markers in CSF [9••,10••]. A strong association was shown between

Table 1

Characterization of stages from normality to AD

Condition	Stage	Avg. % in cohort studies	Molecular biomarkers		Cognitive impairment	Clinical Dementia Rating	Years to probable AD [8]
			Amyloid deposition	Neuronal Injury			
Normal	Stage 0	42%	−	−	−	0	
Preclinical AD	Stage 1	15.5%	+	−	−	0	17–23
	Stage 2	12%	+	+	−	0	7–13
	Stage 3	3.5%	+	+	+	0	6–10
	SNAP	23%	−	+	−/+	0	
	Unclassified	4%	−	−/+	+	0	
Prodromal AD	MCI due to AD		+	+	+	0.5	5–8
Probable AD	Mild to moderate AD		+/−	+/−	+	≥1	0

SNAP = Suspected Non-AD Pathophysiology; AD = Alzheimers disease; MCI = mild cognitive impairment
Cohort studies: MCSA = Mayo Clinic Study of Aging [9••]; KADRC = Knight Alzheimer's Disease Research Center of the Washington University School of Medicine (St. Louis, MO, USA) [10••].

preclinical AD and future cognitive decline in both MCSA and KADRC studies [10••,12]. The KADRC study also showed a strong association between preclinical AD and mortality and this adds to the importance of preclinical AD as a target for therapeutic intervention. Because of observed differences in rate of progression, it is argued that in prevention trials subjects can best be stratified by preclinical AD stage [10••].

Clinical trials before Alzheimers disease

In the past decades, clinical drug trials have been carried out in patients with mild to moderate AD and this has only yielded the currently registered drugs, the cholinesterase inhibitors and an NMDA blocker, which act at best symptomatic, that is, they temporarily stop or attenuate decline but do not halt it. Since recently, clinical trials of disease modifying agents are currently being carried out in prodromal AD. Although no clinical trials are known to date to be carried out in preclinical AD, the door to this has been opened by a recent new Food and Drug Administration (FDA) guidance on developing drugs for treatment of preclinical AD [13]. The possibility of clinical drug trials is suggested in subjects with only subtle cognitive deficits in the absence of any detectable functional impairment. An effect on a valid and reliable cognitive assessment used as a single primary efficacy measure would be considered for approval by FDA [14]. In relation to the staging descriptions above, this applies to subjects in preclinical AD, in whom cognitive decline would be prevented. Decline can also be described as poor performance on more challenging cognitive tests [6]. The preclinical criteria emphasize memory. However, declines in other domains may be the initial cognitive signal of impending AD [15,16].

Cognitive assessments

The instrument hitherto most used to assess changes in cognition in trials in mild to moderate AD is the Cognitive subscale of the Alzheimers Disease Assessment Scale, or ADAS-Cog [17]. However, due to a restriction of range in test scores (ceiling-effect), it lacks sensitivity to detect changes in earlier stages such as MCI and preclinical AD [18]. The Clinical Dementia Rating scale, in particular its so-called Sum of Boxes score (CDR-SB), has been proposed as primary assessment instrument in prodromal AD [19•]. However, because of its expected value of zero in preclinical AD, CDR-SB is not expected to be targeting cognitive performance in that range. The studies in preclinical AD described here in the MCSA cohort [9••] and in the KADRC cohort [10••], have used neuropsychological test batteries to detect signs of subtle cognitive impairment in stage 3 of preclinical AD. In both studies detection was set at scores below the 10th percentile, which resembled an approx. 1.25 SD deviation from reference values in normal controls. In the MCSA study a global composite cognitive score comprising the executive, language, visuospatial and memory domains, was used after it was established that a similar result would be obtained when using a memory domain score [9••]. In the KADRC study an episodic memory composite score was used as the measure of cognition to define stage 3 of preclinical AD [10••].

Cognition and amyloid

Although previous studies had observed only moderate negative relationships between amyloid-beta and cognition and/or episodic memory, a recent meta-analysis established a modest significant relationship between amyloid-beta and cognition [20]. In the Australian Imaging, Biomarker and Lifestyle (AIBL) study, more decline was reported in preclinical AD subjects with high amyloid-beta after 18 months on memory and language (fluency) and similar memory decline was also seen in individuals genetically at risk as determined by presence of a ApoE4 allele(s) [21,22•]. These studies suggest that in preclinical AD, elevated amyloid-beta load is associated with subtle AD-related cognitive impairment. It was also concluded that the relationship between amyloid-beta and cognitive decline in preclinical AD may be best understood from prospective studies [21]. Data from prospective studies suggest that high amyloid-beta does increase the risk of progression to MCI [23], and that