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Review Article

Preclinical Alzheimer's disease: A systematic review of the cohorts underlying the concept

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Abstract Preclinical Alzheimer's disease (AD) is a relatively recent concept describing an entity characterized by the presence of a pathophysiological biomarker signature characteristic for AD in the absence of specific clinical symptoms. There is rising interest in the scientific community to define such an early target population mainly because of failures of all recent clinical trials despite evidence of biological effects on brain amyloidosis for some compounds. A conceptual framework has recently been proposed for this preclinical phase of AD. However, few data exist on this silent stage of AD. We performed a systematic review to investigate how the concept is defined across studies. The review highlights the substantial heterogeneity concerning the three main determinants of preclinical AD: "normal cognition," "cognitive decline," and "AD pathophysiological signature." We emphasize the need for a harmonized nomenclature of the preclinical AD concept and standardized population-based and case-control studies using unified operationalized criteria.

Keywords: Preclinical Alzheimer's disease; Systematic review; Cohort; Clinical trial; Longitudinal; Cross-sectional; Biomarker; Cognition; Familial Alzheimer's disease; Neuropathology

1. Introduction

The positivity of biomarkers of Alzheimer's disease (AD) before the occurrence of first clinical symptoms and dementia supports the concept that AD is a continuum and that it could be diagnosed before its clinical expression [1]. Intervention at such an early stage of the disease is considered to improve the chance of success because it would target potentially still reversible and less established and extensive pathological processes. The lack of clinical efficacy of trials using monoclonal antibodies targeting amyloid at a mild or moderate stage of the illness is further encouragement to shift the attention to the preclinical stage of the disease.

The concept of a preclinical stage of AD emerged mainly from clinicopathological studies describing apparently cognitively normal individuals with the possibility of AD hallmark lesions in the brain [2–5]. The International Working Group-2 (IWG-2) and later the National Institute on Aging-Alzheimer's Association (NIA-AA) consortium each proposed a definition of the preclinical stage of AD [6,7]. The recent release of consensual criteria should facilitate the harmonization and the quality of epidemiological and interventional research on preclinical AD [1].

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Until now, little is known about the natural history of the preclinical state. Large epidemiological studies have been conducted or are still ongoing regarding the risk of dementia in the general population, but they are not strictly focusing on AD and even less on the identification of subjects with the preclinical form of the disease using AD biomarkers (for review, see Tang et al. [8]).

Per definition, people with preclinical AD lack the classical symptoms of the disease. However, the NIA-AA defines a stage of preclinical AD, with "subtle cognitive decline" [7]. This is because of the fact that most longitudinal epidemiological studies show the occurrence of decline, mainly in terms of psychomotor speed and executive functions, years before the diagnosis of dementia [9,10]. There is no consensual definition for "subtle cognitive changes" (i.e., "normal cognition" and "cognitive decline"). Likewise, an AD physiopathological biomarker profile was not required for study inclusion in these studies.

The present article, based on a systematic review of the literature on preclinical AD, aims at identifying the diagnostic approaches used by the leading groups in the field at this early stage of the disease. In particular, three main issues concerning the concept of preclinical AD must be clarified: 1) the level of cognitive performance considered as normal cognition, 2) the changes in cognitive performance considered as cognitive decline, and 3) the best biomarkers or the best combination of them able to identify the "AD pathophysiological signature" in vivo. This review could support future clinical research in the field especially if a disease-modifying drug demonstrates its efficacy.

2. Methods

2.1. Search strategy and selection criteria

The PubMed database and ClinicalTrials.gov were searched for the terms "Preclinical Alzheimer's disease," "Preclinical Alzheimer disease," "Presymptomatic Alzheimer's disease," "Presymptomatic Alzheimer disease," "Asymptomatic Alzheimer's disease," and "Asymptomatic Alzheimer disease," up to June 2015, without any language restriction. The terms had to be in the title or even in the abstract of the manuscript to include articles that would only refer to the concept of preclinical AD without studying it.

2.2. Search strategy results and further classification of studies

We identified 361 articles reporting "preclinical AD." They were categorized as "reviews" (for review, conceptual and perspective articles), "out of topic" (when despite the title or abstract of the article, no preclinical AD subject was included in the study), "neuropathological" (when AD diagnosis was pathologically established in subjects who died within 1 year of a cognitive evaluation considered as unimpaired), "genetic" when the study dealt with

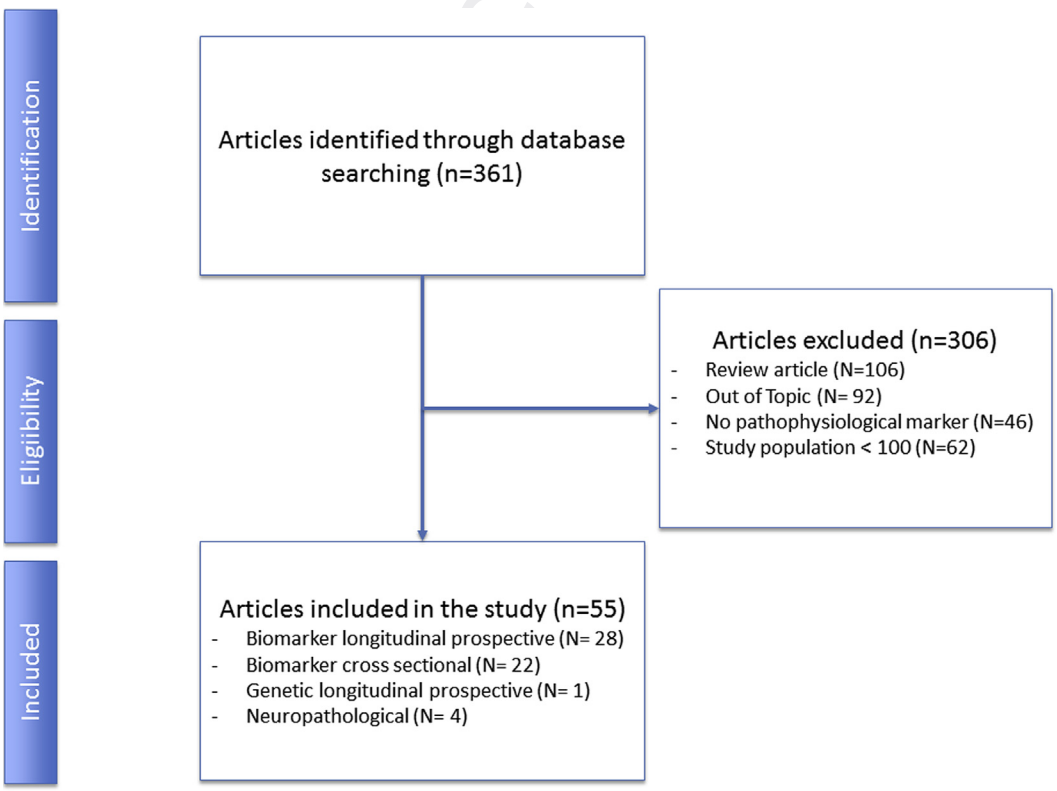

Fig. 1. PRISMA (2009) flow diagram of article selection.