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Review Article

Neuroscience learning from longitudinal cohort studies of Alzheimer's disease: Lessons for disease-modifying drug programs and an introduction to the Center for Neurodegeneration and Translational Neuroscience

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Abstract The development of disease-modifying therapies for Alzheimer's disease is an urgent public health emergency. Recent failures have highlighted the significant challenges faced by drug-development programs. Longitudinal cohort studies are ideal for promoting understanding of this multifactorial, slowly progressive disease. In this section of the special edition, we review several important lessons from longitudinal cohort studies which should be considered in disease-modifying therapy development. In the final section, we introduce the clinical cohort of the Center for Neurodegeneration and Translational Neuroscience. This newly established longitudinal study aims to provide new insights into the neuroimaging and biological marker (biomarkers) correlates of cognitive decline in early Alzheimer's disease and Parkinson's disease (PD).

Keywords: Neuroscience; Longitudinal cohort; Alzheimer's disease; Disease-modifying therapy

1. Introduction

Affecting more than 45 million people worldwide, Alzheimer's disease (AD) is the most common neurodegenerative disease of the central nervous system. The morbidity, mortality, and costs associated with caring for those afflicted by this disease have been well established [1]. With estimates predicting a tripling in prevalence rates by 2050, the search to find disease-modifying therapies (DMTs) has become an urgent global health emergency. Longitudinal cohort studies have been an important source of information regarding the complex chain of events that occur in AD. The insights gleaned from these studies have been used to inform a new generation of increasingly sophisticated clinical trials that have permitted testing of candidate agents earlier in the disease course [2]. Despite significant advances in our understanding of disease, it has been more than 14 years since the last symptomatic agent was approved, and no agent has ever demonstrated disease-modifying effects in clinical trials. The recent spate of high-profile failures [3] has highlighted the challenges for DMT development and thrown into question some of the most fundamental assumptions about AD therapeutics [4].

As part of this special issue introducing the newly established Center for Neurodegeneration and Translational Neuroscience (CNTN), we present five learnings from longitudinal cohort studies and briefly discuss their application in clinical trials. In the final section, we introduce the clinical core of the CNTN. The clinical core of CNTN is a newly established longitudinal cohort study that integrates lessons learned from other cohort studies and brings several new contributions to the field. The following are some among these contributions: (1) an "ADNI approach" to studying cognition in Parkinson's disease (PD); (2) an expanded battery of cognitive testing to better elucidate executive

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dysfunction in mild cognitive impairment (MCI); (3) positron emission tomography (PET) imaging of microglial activation in the AD and PD disease continuum; and (4) a multimodal recruitment and retention strategy focused on minority recruitment.

2. Longitudinal cohort studies in AD research

Randomized controlled trials (RCTs), which attempt to limit bias and confounding through balanced randomization of carefully selected cohorts, have long been considered the "gold standard" for medical evidence [5]. Any DMT will only be approved based on the results of a well-conducted RCT [2]. The application of RCTs to a slowly progressive disease such as AD is challenging and typically requires enrolling thousands of participants (across hundreds of clinical trial sites) to achieve the requisite statistical power. The degree of complexity required for running large, complicated RCTs has led to a skyrocketing of expenses, and it is now estimated to cost more than $5 billion to bring a DMT to market [6]. It is, therefore, critical that RCTs be informed with a robust knowledge of disease progression and pathogenesis.

Longitudinal cohort studies in AD represent an important resource of information for designing clinical trials. The questions addressed in longitudinal cohort studies of individuals with AD (or at high risk for developing disease) are often different from those of RCTs (regarding, for example, disease trajectory, biomarker evolution, and population-based outcomes) but are no less important. When collected over large periods of time, cohort studies can detect outcomes that appear slowly or inconsistently. These outcomes may not be detected in more narrowly focused clinical trials. Cohort studies, which are often not subject to the same rigorous balanced randomization requirements of RCTs, may also include a wider diversity of participants, more reflective of "typical" rather than "ideal" patient populations [7]. Over the past 3 decades, longitudinal cohort studies have provided key insights into the biological markers (biomarkers), risk factors (environmental and genetic), epidemiology, and disease trajectory of AD.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) serves as a model for conducting longitudinal cohort studies in AD. Launched in 2005, ADNI is a multicenter, longitudinal observational study of cognitive normal elderly, MCI, and early AD [8]. An important contribution of ADNI is its approach to data integrity. Using a study protocol that emphasizes standardized data collection across all clinical sites, ADNI is conducted like a clinical trial but has no intervention. Rigorous adherence to a study protocol improves the reproducibility of data [9]. Now in its third iteration and having expanding to sites all over the world, the ADNI dataset represents a rich repository of multimodal imaging, AD biomarkers, genetics, neuropathology, and neuropsychological testing that is freely and openly shared with collaborators through the ADNI website.

In the following sections, we highlight several lessons learned from both ADNI and other longitudinal cohort studies of AD and consider their impact on DMT development.

2.1. Even at the most experienced academic medical centers, misdiagnosis rates for AD consistently exceed 20%. Eligibility for DMT clinical trials should be confirmed by diagnostic biomarkers

Neuropathology has long been considered the "gold standard" for the diagnosis of AD. The National Alzheimer's Coordinating Center includes a large neuropathology dataset that allows for examination of clinicopathological correlates [10]. An important lesson from the National Alzheimer's Coordinating Center is the significant number of participants who present phenotypically with AD but lack amyloidosis. These individuals are described as having suspected non-Alzheimer pathology (SNAP) [11]. Individuals with SNAP are unlikely to respond to antiamyloid therapies [12]. Looking at a sample of 919 demented subjects, Beach et al. [13] found that a clinical diagnosis of "possible" or "probable" AD was 71% to 87% sensitive and 44% to 71% specific for AD. The authors, furthermore, estimated that the positive predictive value of a clinical diagnosis of AD was 83% (for moderate plaque load, Braak stage III or IV). Although 80% hit rate may appear reasonable, in the context of a clinical trial, this level of misdiagnosis is problematic (again, assuming a poor response rate in non-AD individuals). For example, applied to a trial with a 50% response rate, a 20% misdiagnosis rate would effectively reduce the response rate by 10% [13]. To achieve the same statistical power, recruitment to the trial would need to be doubled. Studies examining misdiagnosis rates in clinical trials have reported even higher numbers, particularly when applied to populations earlier in the AD continuum [14]. These findings are highly supportive that clinical trial populations be enriched by AD diagnostic biomarkers. A recent examination of the AD drug-development pipeline, however, revealed that less than half of phase II and III DMTs used diagnostic biomarkers as entry criteria [15].

2.2. Variability in clinical progression is common in AD, particularly early in the disease continuum. To detect drug-placebo treatment differences, multimodal stratification strategies should be incorporated into the trial design so as to increase the likelihood that participants will progress during the course of the trial

AD is now conceptualized as a clinicobiological entity progressing seamlessly from an asymptomatic high-risk state to MCI and finally ending in dementia. A growing consensus suggests that DMTs must be introduced at a time point when the pathological processes can still be overcome. Testing therapeutics in participants with minimal (or no) symptoms represents a significant paradigm