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Featured Article

The ALFA project: A research platform to identify early pathophysiological features of Alzheimer's disease

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Abstract

Introduction: The preclinical phase of Alzheimer's disease (AD) is optimal for identifying early pathophysiological events and developing prevention programs, which are shared aims of the ALFA project, including the ALFA registry and parent cohort and the nested ALFA+ cohort study.
Methods: The ALFA parent cohort baseline visit included full cognitive evaluation, lifestyle habits questionnaires, DNA extraction, and MRI. The nested ALFA+ study adds wet and imaging biomarkers for deeper phenotyping.
Results: A total of 2743 participants aged 45 to 74 years were included in the ALFA parent cohort. We show that this cohort, mostly composed of cognitively normal offspring of AD patients, is enriched for AD genetic risk factors.
Discussion: The ALFA project represents a valuable infrastructure that will leverage with different studies and trials to prevent AD. The longitudinal ALFA+ cohort will serve to untangle the natural history of the disease and to model the preclinical stages to develop successful trials.

Keywords: Alzheimer's disease; Dementia; Cohort studies; Cognition; Prevention; Biomarkers; Risk factors

1. Introduction

The increase in average life expectancy that has occurred in developed countries during the last 50 years has been accompanied by an increment in the prevalence of age-associated disorders. Alzheimer's disease (AD), more specifically, late-onset AD (LOAD) is the first cause of neurological disability in the elderly causing enormous social and economic burden in modern societies [1]. Currently, >45 million people suffer from dementia worldwide and with the progressive aging of the population, this figure is expected to increase to up to 130 million in 2050 [2]. Despite having described the AD clinicopathological hallmarks over a century ago, its precise etiology remains unknown. It is noteworthy that, to date, all clinical trials evaluating disease-modifying drugs performed have failed [3].

In the last decade, several *in vivo* AD biomarkers, such as β-amyloid (Aβ) and tau concentration in cerebrospinal fluid (CSF [4]), hippocampal atrophy [5,6], temporoparietal hypometabolism [7,8], and cerebral amyloid deposition measured by positron emission tomography (PET [9,10]), have been extensively characterized. The results of these

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studies show that AD pathology develops for several years or even decades before clinical symptoms appear; this silent asymptomatic period of the disease is referred to as the preclinical stage of AD [11]. The detection of this preclinical stage opens up novel opportunities for the development of new therapeutic strategies. If new treatments capable of delaying the evolution of the disease and the appearance of dementia emerge in the next years, they will be especially useful during the preclinical phase of the disease [12]. In fact, as AD burden increases with the aging of the population, a treatment capable of delaying the onset of dementia by only a few years would have a tremendous impact on the social cost of the disease. Indeed, it has been calculated that a delay in dementia's onset of only 5 years could reduce a 33% of the economic cost of AD [13]. In this scenario, it has been hypothesized that, to increase the possibilities of success, drugs that have failed in trials performed on AD patients should be essayed in cognitively healthy subjects that are at elevated risk of developing AD. Even more, the preclinical stage could be the optimal timeframe to evaluate new therapeutic strategies directed against targets not only related to the amyloid cascade but also focused on delaying neuronal loss [14]. Moreover, interventional preventive strategies may help to better understand the relationship between the different medical, environmental, and genetic factors and the onset of symptoms.

The setup of preventive studies requires the identification of individuals with an increased risk of developing AD in the near future that are suitable to be recruited as asymptomatic subjects in clinical trials. With this in mind, a number of research projects have been designed and are currently ongoing such as the Wisconsin Registry for Alzheimer's Prevention program [15], the Adult Children Study [16], and the more recently developed PREVENT programme [17] and the longitudinal cohort study of the European Prevention of Alzheimer's Dementia (EPAD) project [18], among others.

Following the same rationale and aiming at increasing our knowledge of the pathophysiology and pathogenic factors emerging at early preclinical AD stages, the Barcelonaβeta Brain Research Center (BBRC) started the ALFA (for Alzheimer and Families) project for the prospective follow-up of a cohort of cognitively normal subjects, most of which are the offspring of AD patients. The ALFA project consists of the ALFA registry, the ALFA parent cohort, and the nested ALFA+ cohort study. The ALFA registry contains basic demographic data of persons willing to participate in future BBRC projects. The ALFA parent cohort is composed of cognitively normal participants aged between 45 and 74 years, who were administered a series of cognitive tests and from which we collected their clinical history and information related to lifestyle and a blood sample for further genetic analysis. The ALFA parent cohort will serve as the basis for the establishment of research protocols and studies, both observational and interventional, of preclinical participants at risk of cognitive impairment due to AD. Furthermore, it will be replenished over time through new recruitment and from the ALFA registry. Participants of the ALFA parent cohort will be offered the option of entering currently active projects at the BBRC such as EPAD [18] or future clinical trials and other research studies.

A subset of the ALFA parent cohort participants will be invited to take part in a nested longitudinal long-term study, named the ALFA+ study, in which a more detailed phenotyping will be performed. On top of a similar characterization as in the ALFA parent cohort, it will entail the acquisition of both wet (CSF, blood, and urine sample collection) and imaging (magnetic resonance imaging [MRI] and PET) biomarkers.

In this article, the ALFA parent cohort and the longitudinal ALFA+ study are introduced. Furthermore, a basic sociodemographic profile and a description of AD risk-associated variables of the ALFA parent cohort participants at baseline are also presented.

2. Methods

2.1. The ALFA parent cohort

The ALFA parent cohort represents a research platform that will supply related studies such as the longitudinal ALFA+.

2.1.1. Inclusion and exclusion criteria

Inclusion criteria were being cognitively normal Spanish and/or Catalan-speaking persons aged between 45 and 74 years that agreed with the study procedures and tests: clinical interview and questionnaires associated to risk factors, cognitive tests, a blood sample extraction for DNA analysis, and MRI. Furthermore, a close relative was involved in the volunteer's functional evaluation and both of them had to grant their consent. A high percentage of the individuals recruited were cognitively normal offspring of AD patients.

Exclusion criteria were (1) Cognitive performance falling outside the established cutoffs: Mini-Mental State Examination [19,20] (MMSE) <26, or Memory Impairment Screen [21,22] (MIS) < 6, or Time-Orientation subtest of the Barcelona Test II [23] (TO-BTII) <68, or semantic fluency [24,25] (animals; SF) < 12. (2) Clinical Dementia Rating scale [26]; CDR > 0. (3) Major psychiatric disorders (according to DSM-IV-TR) or diseases that could affect cognitive abilities (current major depression or general anxiety disorder, bipolar disorder, schizophrenia, and dementia). The Goldberg Anxiety and Depression Scale [27,28] (GADS) was used to screen for mood disorders. Whenever the scores were dubious, the rater assessed whether the subject met the DSM-IV-TR criteria for general anxiety disorder or major depressive episode and was excluded if this was the case. (4) Severe auditory and/or visual disorder, neurodevelopmental and/or psychomotor disorder. (5) Significant diseases that could currently interfere with cognition (renal failure on hemodialysis, liver cirrhosis, chronic lung disease with oxygen therapy, solid organ transplantation, fibromyalgia, active cancer in treatment, or any