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Review

Biological markers of amyloid β-related mechanisms in Alzheimer's disease

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ABSTRACT

Recent research progress has given detailed knowledge on the molecular pathogenesis of Alzheimer's disease (AD), which has been translated into an intense, ongoing development of disease-modifying treatments. Most new drug candidates are targeted on inhibiting amyloid β (Aβ) production and aggregation. In drug development, it is important to co-develop biomarkers for Aβ-related mechanisms to enable early diagnosis and patient stratification in clinical trials, and to serve as tools to identify and monitor the biochemical effect of the drug directly in patients. Biomarkers are also requested by regulatory authorities to serve as safety measurements. Molecular aberrations in the AD brain are reflected in the cerebrospinal fluid (CSF). Core CSF biomarkers include Aβ isoforms (Aβ40/Aβ42), soluble APP isoforms, Aβ oligomers and β-site APP-cleaving enzyme 1 (BACE1). This article reviews recent research advances on core candidate CSF and plasma Aβ-related biomarkers, and gives a conceptual review on how to implement biomarkers in clinical trials in AD.

Contents

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Introduction

We face a global epidemic of Alzheimer's disease (AD) as the world's population ages. In 2006, the worldwide prevalence of AD was 26.6 million, and by 2050 the prevalence will quadruple. The current worldwide cost related to dementia is approximately $160 billion (Wimo et al., 2006). Without a significant improvement in prevention and treatment of AD, our healthcare and socioeconomic systems will not be able to carry the financial burden of AD in the future. However, interventions that delay disease onset or progression by only 1 year would reduce the disease prevalence by more than 9 million cases in 2050. Effective strategies for preventing and treating AD are therefore urgently needed before the national economies are overwhelmed by the financial burden of this growing epidemic.

Intense research efforts over the last 3 decades have given detailed knowledge on the molecular pathogenesis of AD. AD is a complex progressive condition with sequentially interacting pathological cascades, including the aggregation of amyloid β (Aβ) with plaque development, hyperphosphorylation and aggregation of tau protein with formation of tangles, together with downstream processes such as inflammation and oxidative stress, all of which contribute to loss of synaptic integrity, effective neural network connectivity and progressive regional neurodegeneration (Blennow et al., 2006). Research advances from pathological, neurochemical and genetic studies give increasing support to the "amyloid cascade hypothesis" (Hardy and Selkoe, 2002), which states that an imbalance between the production and clearance or degradation or clearance of Aβ in the brain is the initiating event in AD, ultimately leading to synaptic and neuronal dysfunction and degeneration with subsequent cognitive disturbances (Fig. 1).

These research advances have been translated into several new drug candidates with disease-modifying potential, several of which are now evaluated in clinical trials (Wisniewski and Konietzko, 2008). This foreshadows a new era of causal mechanistic treatment beyond symptomatic therapy. This new type of disease-modifying drugs can be expected to be most effective if initiated very early in the disease process, before the neurodegenerative process is too severe. However, current diagnostic manuals, such as the DSM-IV and ICD-10, warrant dementia, i.e., an advanced stage and severity of the disease, to make a clinical diagnosis of AD. Thus, there is a great need for improved diagnostic tools. New research criteria for diagnosis of AD implementing biomarkers to allow early identification have recently been proposed (Dubois et al., 2007).

Novel concepts of disease-modifying treatment also challenge current approaches for drug development. Drug trials on clinically diagnosed AD cases employing outcome measures based on clinical rating scales will not be sufficient to identify an effect of the new type of drugs in short-term and small-medium sized clinical trials. Biomarkers may speed up this process by serving as alternative outcomes to clinical measures. More accurate outcomes may also be achieved by enriching the population with patients with a disease-specific biomarker pattern, thus minimizing the risk of including patients who do not suffer from AD.

Biomarkers for AD

This review is focused on biochemical markers for the amyloidogenic process in AD in cerebrospinal fluid (CSF) and plasma. We use the term "biomarker" in a general sense to describe any measurable neurochemical indicator that is used to assess the risk or presence of disease. Biomarkers may facilitate the ability to reliably diagnose AD in the very early and perhaps even pre-clinical disease stages. They may also provide objective and reliable measures of drug safety and disease-modifying treatment efficacy in clinical drug trials in AD. Since the neuropathological changes of AD likely precede symptoms by years or decades, and it may well be optimal to treat the neuropathology as early as possible, biomarkers of pre-clinical AD are likely to play a pivotal role in the development of the next generation of therapies.

Criteria for an ideal biomarker for AD have been proposed by a consensus group on molecular and biochemical markers of AD (authors, 1998). The key features of an ideal AD biomarker are that it should detect a fundamental feature of the neuropathology, and have a diagnostic sensitivity for AD exceeding 80% together with specificity above 80% for distinguishing AD from other dementias. It should also be reliable, reproducible, non-invasive, simple to perform, and inexpensive. Recommended steps to establish a biomarker include confirmation by at least two independent studies conducted by qualified investigators with the results published in peer-reviewed journals, and validation in neuropathologically confirmed cases. Beyond these criteria for early and accurate diagnosis, it would be especially useful if the biomarker could track natural disease progression as well as the beneficial effect of disease-modifying therapies.

To facilitate clinical drug development for AD, it is of particular importance to be able to make accurate diagnoses early in the disease process, and to have biochemical measures that reflect the pharmacodynamic effects of treatment. For these reasons the National Institute on Aging (NIA) commissioned a working group on biomarkers as part of its Alzheimer's Disease Neuroimaging Initiative (ADNI) (Frank et al., 2003). A wide range of biological measures with possible relevance to AD were considered and then classified into categories of "Feasible, core," "Feasible, non-core" and "Uncertain feasibility." Feasibility was determined by the availability of a validated assay for the biological measure in question, with properties that included high precision and reliability of measurement, where reagents and standards were well described. Core analytes were those judged by the group to have reasonable evidence for association with key mechanisms of pathology implicated in AD, while non-core analytes were felt to be less clearly connected with mechanisms of pathogenesis or neurodegeneration in AD.

Development of feasible, core biological markers of Aβ-related mechanisms in AD

Key neuropathological hallmarks of AD are amyloid plaques and neurofibrillary tangles (Braak and Braak, 1991; Thal et al., 2002).