Neurobiology of Aging 52 (2017) 196–213

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Roadmap to Alzheimer's Biomarkers in the Clinic

Clinical validity of cerebrospinal fluid Aβ42, tau, and phospho-tau as biomarkers for Alzheimer's disease in the context of a structured 5-phase development framework

Niklas Mattsson [a,b,c,*], Anders Lönneborg [a], Marina Boccardi [d,e], Kaj Blennow [f], Oskar Hansson [a,b,*], for the Geneva Task Force for the Roadmap of Alzheimer's Biomarkers [1]

[a] Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden
[b] Memory Clinic, Skåne University Hospital, Malmö, Sweden
[c] Department of Neurology, Skåne University Hospital, Lund, Sweden
[d] Laboratory of Neuroimaging and Alzheimer's Epidemiology, IRCCS Fatebenefratelli, Brescia, Italy
[e] LANVIE, Laboratory of Neuroimaging of Aging, University of Geneva, Geneva, Switzerland
[f] Clinical Neurochemistry Laboratory, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Mölndal, Sweden

ARTICLE INFO

Article history:
Received 30 September 2015
Received in revised form 9 February 2016
Accepted 10 February 2016

Keywords:
Cerebrospinal fluid
Beta-amyloid
Tau
Phosphorylated tau
Biomarker development
Early diagnosis
Biomarker-based diagnosis
Alzheimer's disease
5-Phases

ABSTRACT

Novel diagnostic criteria for Alzheimer's disease (AD) incorporate biomarkers, but their maturity for implementation in clinical practice at the prodromal stage (mild cognitive impairment [MCI]) is unclear. Here, we evaluate cerebrospinal fluid (CSF) β-amyloid$_{42}$ (Aβ42), total tau, and phosphorylated tau in the light of a 5-phase framework for biomarker development. Ample evidence is available for phase 1 (identifying useful leads) and phase 2 (assessing the accuracy for AD dementia versus controls) for CSF biomarkers. Phase 3 (utility in MCI) is partially achieved. In cohorts with long follow-up time, CSF Aβ42, total tau, and phosphorylated tau have high diagnostic accuracy for MCI due to AD. Phase 4 (performance in real world) is ongoing, and phase 5 studies (quantify impact and costs) are to come. Our results highlight priorities to pursue and to enable the proper use of CSF biomarkers in the clinic. Priorities are to reduce measurement variability by introduction of fully automated assay systems; to increase diagnostic specificity toward non-AD neurocognitive diseases at the MCI stage; and to clarify the role of CSF biomarkers versus other biomarker modalities in clinical practice and in design of clinical trials. These efforts are currently ongoing.

1. Introduction

Novel diagnostic criteria published by the International Working Group (Dubois et al., 2007, 2010, 2014) and the National Institute of Aging-Alzheimer's Association (Albert et al., 2011) incorporate biomarkers for diagnosis of prodromal Alzheimer's disease (AD) or mild cognitive impairment (MCI) due to AD. Although the criteria differ in their details, a guiding thought is that biomarkers for amyloid pathology and neuronal injury may identify a subject who is more likely to have Alzheimer pathology as the underlying cause of his or her symptoms.

Cerebrospinal fluid (CSF) biomarkers have been explored for decades in AD. The most well-developed CSF AD biomarkers are β-amyloid-42 (Aβ42), total tau (T-tau), and phosphorylated tau (P-tau; Blennow et al., 2010). However, insufficient knowledge of the pathology and heterogeneity of AD and methodological challenges may hinder the implementation of these biomarkers in clinical practice, especially in early stages. To overcome a similar problem in the field of oncology, Pepe et al. (2001) suggested to systematize the investigation of cancer biomarkers based on a methodology used for pharmacologic investigations. A similar approach may boost the use of AD biomarkers for clinical practice, clinical research, and design of clinical trials. This is becoming

* Corresponding authors at: Memory Clinic, Skåne University Hospital, Lund 221 85, Sweden. Tel: +46 40-335036; fax: +46 40-335657.
E-mail addresses: niklas.mattsson@med.lu.se (N. Mattsson), oskar.hansson@med.lu.se (O. Hansson).
[1] http://centroalzheimer.it/public/MB/BM-Roadmap/The_Geneva_AD_Biomarker_Roadmap_Task_Force.docx.

0197-4580/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2016.02.034

increasingly relevant due to the development of novel putative disease-modifying treatments for neurodegenerative diseases, since the use of such treatments will benefit greatly from accurate diagnostics, especially at early disease stages. In this article, the Pepe et al. framework has been adapted to biomarkers for clinical diagnosis of AD at the MCI stage. This is a part of a multimodality Roadmap initiative that is described in detail in the accompanying articles (Boccardi et al., 2017; Frisoni et al., 2017) and as summarized in Section 2.5. While this review is focused on CSF AD biomarkers, other parts of the Roadmap initiative that are also published in this issue cover magnetic resonance imaging (MRI; Ten Kate et al., 2017), positron emission tomography (PET) and single-photon emission computed tomography (SPECT) biomarkers (Chiotis et al., 2017; Garibotto et al., 2017; Sonni et al., 2017), neuropsychology (Cerami et al., 2017), and ethical issues on the use of these biomarkers (Porteri et al., 2017).

Biomarkers have a long history in AD research. In 1998, the Reagan Working Group stated in a consensus report that the ideal biomarker for AD should detect a fundamental feature of neuropathology and be validated in neuropathologically confirmed cases, have a sensitivity >80% for AD and a specificity >80% for other dementias, and be reliable, reproducible, noninvasive, simple to perform, and inexpensive (Anonymous, 1998). The Reagan report was written before the now widespread understanding of AD as a disease that spans a continuum from asymptomatic brain changes to symptomatic stages, including both MCI and advanced dementia. During the last decade, CSF AD biomarker research has been extended to the MCI stage of the disease. Although several novel CSF biomarkers may identify MCI due to AD (e.g., CSF neurogranin [Kvartsberg et al., 2015] and CSF heart fatty acid-binding protein [Olsson et al., 2013]), the accumulated data for CSF Aβ42, T-tau, and P-tau are vastly more extensive than for any other CSF biomarker. Therefore, these 3 biomarkers (here collectively called "CSF AD biomarkers") are the focus of this review. This investigation of the state of maturity of the CSF AD biomarkers was performed through a literature review, where evidence was interpreted under the light of the Pepe et al. framework.

2. Methods

2.1. Target

As mentioned previously, this study was performed with reference to a model imported from the oncology field (Pepe et al., 2001) and adapted to the field of dementia, specifically to the aim of performing the differential diagnosis of AD at the prodromal stage of the disease. The terms of this framework are described and summarized in this section. The target population is subjects with MCI as defined below. Only sporadic (not familial) AD was considered. Besides neuropathology, we considered clinical diagnosis of AD to be the reference standard, using the Standards for Reporting of Diagnostic Accuracy (STARD) criteria terminology (Bossuyt et al., 2003). When considering diagnosis of AD at the MCI stage, we only included studies with at least 2 years of follow-up of all cognitively stable MCI cases since the prodromal stage of AD may last for at least 10 years (Bateman et al., 2012; Buchhave et al., 2012; Jack and Holtzman, 2013).

2.2. Glossary

2.2.1. Alzheimer's disease

By Alzheimer's disease, we refer to the Alzheimer's pathology consisting of brain Aβ and tau pathology and neurodegeneration, usually with mediotemporal and temporoparietal distribution. The term is independent of the clinical manifestation of the disease.

2.2.2. AD dementia

The clinical syndrome featuring both cognitive impairment and functional disability is distinguished from the pathology per se. Due to imprecision of clinical diagnostic methods, not all patients with a clinical diagnosis of AD dementia have AD as the underlying neuropathology.

2.2.3. Mild cognitive impairment

We use MCI to indicate a population with acquired cognitive impairment but no functional disability. Besides prodromal AD (about 50%), this category also includes cases with no neurodegenerative disorder (about 35%–40%) and non-AD neurodegeneration (about 10%–15%; Bennett et al., 2002; Jack et al., 2008; Rowe et al., 2010).

MCI cases with AD biomarker positivity are defined as prodromal AD in clinical criteria (Dubois et al., 2010).

2.2.4. Non-AD neurocognitive disease

The disorders that we include as non-AD differential diagnoses include vascular pathology, hippocampal sclerosis, frontotemporal lobar degeneration, other tauopathies (progressive supranuclear palsy and corticobasal degeneration), Lewy body disease, and other alpha-synucleinopathies such as multiple system atrophy.

2.2.5. Non-AD dementia

The clinical syndromes caused by non-AD neurocognitive diseases featuring both cognitive impairment and functional disability are called "dementias" to distinguish them from the etiopathologies per se.

2.2.6. CSF AD biomarkers

Aβ42, T-tau, and P-tau are measured in CSF.

2.3. Conceptual framework

The main phases for the development of the biomarkers resemble the phases covered in oncology and routinely used for pharmaceuticals development. The shift of the reference methodological model from the field of oncology to that of dementia and from the aims of screening to those relating to diagnosis is thoroughly described in the study by (Frisoni et al., 2017). Here, we summarize the resulting points of this translation, addressing the steps to be covered for a systematic development of CSF AD biomarkers for their proper use in clinical routine for the diagnosis of dementia. The present review assesses the maturity of CSF AD biomarkers relative to each of the following steps. All aims and subaims are specifically addressed and qualified as "fully achieved," "partly achieved," "preliminary evidence," or "not achieved" based on the available evidence. The evaluation terms and assessments are reported in detail in Table 1.

2.3.1. Phase 1

Studies aimed to identify the rationale of the CSF AD biomarkers, based on pathology findings, and consisting of preclinical exploratory studies.

2.3.2. Phase 2

Studies aimed to define the ability of the CSF AD biomarkers to discriminate patients with AD dementia from controls and non-AD dementias. It focuses on defining the clinical assay allowing reliable discrimination. This phase also aims at identifying possible differential effects of covariates in patients and controls, which may influence the thresholds for positivity.