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Perspective

Recommendations for cerebrospinal fluid Alzheimer's disease biomarkers in the diagnostic evaluation of mild cognitive impairment

Sanna-Kaisa Herukka[a], Anja Hviid Simonsen[b], Niels Andreasen[c], Ines Baldeiras[d], Maria Bjerke[e], Kaj Blennow[f], Sebastiaan Engelborghs[e,g], Giovanni B. Frisoni[h,i], Tomasz Gabryelewicz[j], Samantha Galluzzi[i], Ron Handels[k], Milica G. Kramberger[l], Agnieszka Kulczyńska[m], Jose Luis Molinuevo[n,o], Barbara Mroczko[m,p], Agneta Nordberg[q], Catarina Resende Oliveira[d], Markus Otto[r], Juha O. Rinne[s], Uroš Rot[l], Esen Saka[t], Hilkka Soininen[a], Hanne Struyfs[e], Silvia Suardi[u], Pieter Jelle Visser[v,w], Bengt Winblad[x], Henrik Zetterberg[f,y], Gunhild Waldemar[b,*]

[a]*Department of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland*
[b]*Danish Dementia Research Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark*
[c]*Department of Geriatric Medicine, Karolinska University Hospital, Huddinge, Sweden*
[d]*Neurochemistry Laboratory, Faculty of Medicine, CHUC—Coimbra University Hospital, CNC, CNC.IBILI—Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal*
[e]*Reference Center for Biological Markers of Dementia (BIODEM), Institute Born-Bunge, University of Antwerp, Antwerp, Belgium*
[f]*Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden*
[g]*Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Antwerp, Belgium*
[h]*Geneva Neuroscience Center, University Hospitals and University of Geneva, Geneva, Switzerland*
[i]*IRCCS Fatebenefratelli, Brescia, Italy*
[j]*Department of Neurodegenerative Disorders, Mossakowski Medical Research Centre Polish Academy of Sciences, Warsaw, Poland*
[k]*Alzheimer Centre Limburg, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands*
[l]*Center for Cognitive Impairments, Department of Neurology, University Medical Center Ljubljana, Ljubljana, Slovenia*
[m]*Department of Neurodegeneration Diagnostics, Medical University of Białystok, Białystok, Poland*
[n]*Alzheimer's Disease and Other Cognitive Disorders Unit, Hospital Clinic i Universitari, IDIBAPS, Barcelona, Spain*
[o]*Beta Brain Research Center, Fundació Pasqual Maragall, Barcelona, Spain*
[p]*Department of Biochemical Diagnostics, University Hospital in Białystok, Białystok, Poland*
[q]*Department of NVS, Center for Alzheimer Research, Translational Alzheimer Neurobiology, Karolinska Institutet, Huddinge, Sweden*
[r]*Department of Neurology, University of Ulm, Ulm, Germany*
[s]*Turku PET Centre, Turku University Hospital and University of Turku, Turku, Finland*
[t]*Department of Neurology, Hacettepe University Hospitals, Ankara, Turkey*
[u]*Neuropathology Laboratory, Neurological Institute C. Besta, Milan, Italy*
[v]*Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands*
[w]*Department of Neurology, Alzheimer Centre, VUMC, Amsterdam, The Netherlands*
[x]*Department NVS, Karolinska Institutet, Center for Alzheimer Research, Division of Neurogeriatrics, Huddinge, Sweden*
[y]*Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK*

Abstract This article presents recommendations, based on the Grading of Recommendations, Assessment, Development, and Evaluation method, for the clinical application of cerebrospinal fluid (CSF) amyloid-β_{1-42}, tau, and phosphorylated tau in the diagnostic evaluation of patients with mild cognitive impairment (MCI). The recommendations were developed by a multidisciplinary working group and based on the available evidence and consensus from focused group discussions for 1) prediction of clinical progression to Alzheimer's disease (AD) dementia, 2) cost-effectiveness, 3)

*Corresponding author. Tel.: +45 35452580, +45 26302580 (mobile); Fax: +45 35452446.
E-mail address: gunhild.waldemar.01@regionh.dk

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interpretation of results, and 4) patient counseling. The working group recommended using CSF AD biomarkers in the diagnostic workup of MCI patients, after prebiomarker counseling, as an add-on to clinical evaluation to predict functional decline or conversion to AD dementia and to guide disease management. Because of insufficient evidence, it was uncertain whether CSF AD biomarkers outperform imaging biomarkers. Furthermore, the working group provided recommendations for interpretation of ambiguous CSF biomarker results and for pre- and post-biomarker counseling.

Keywords: Alzheimer's disease; Biomarkers; CSF; Diagnostics; GRADE; Mild cognitive impairment; Recommendations

1. Introduction

The neuropathological hallmarks of Alzheimer's disease (AD) are neuronal and synaptic degeneration accompanied by intracellular neurofibrillary tangles comprised hyperphosphorylated tau and extracellular plaques comprised amyloid-β ($A\beta_{1–42}$) protein [1]. The symptoms of AD develop insidiously and progress slowly, most commonly starting with memory impairment followed by deterioration in other cognitive skills, resulting in progressive dementia with a gradual loss of ability to perform activities of daily living.

An early diagnosis is crucial for counseling, for planning treatment and care, and for advance directives. Scientifically, the possibility of making an early (predementia) diagnosis is essential for the clinical evaluation of novel, potentially disease-modifying drugs against AD. The term "mild cognitive impairment" (MCI) is often used to refer patients with objective cognitive impairment and normal capabilities for activities of daily living, who do not meet the criteria for dementia [2–4]. MCI is a significant risk factor for dementia and may in some cases represent the prodromal phase of AD or other neurodegenerative disorders. Approximately 35% of MCI patients progress to AD dementia within a 3-year follow-up with an annual conversion rate of 5%–10% [5]. However, there are many causes of MCI, not all are related to progressive neurodegenerative disorders. Thus, diagnosing the underlying etiology is very challenging in an individual patient with cognitive impairment, and there is a need for more accurate diagnostic tests to identify MCI patients in whom AD may be the underlying cause, early in the course of the disease.

Consequently, international working groups have developed clinical criteria for the diagnosis of MCI because of AD, which include the option to improve prognostic accuracy, with the use of biomarkers [2,6]. Currently, the most validated biomarkers for early detection in clinical use include markers of neuronal injury and of $A\beta_{1–42}$: medial temporal lobe atrophy (as assessed on magnetic resonance imaging [MRI]), a characteristic pattern of cerebral glucose metabolism (as assessed on fluorodeoxyglucose positron emission tomography [FDG-PET]), amyloid deposition in the brain (as assessed by amyloid-PET), and lower levels of $A\beta_{1–42}$ together with elevated levels of tau and phosphorylated tau (p-tau) in the cerebrospinal fluid (CSF).

In the diagnostic criteria for MCI because of AD, developed by the National Institute on Aging and the Alzheimer's Association (NIA-AA), a positive Aβ biomarker (either by amyloid-PET or CSF) together with the presence of a neuronal injury biomarker, such as medial temporal lobe atrophy or elevated levels of tau and p-tau in the CSF, indicates that the MCI syndrome may be because of AD, whereas negative Aβ biomarkers suggest that MCI is unlikely because of AD [2]. The international working group 2 criteria for prodromal AD are 1) the presence of episodic memory decline of the hippocampal type as the leading clinical symptom and 2) positive biomarker evidence from either CSF or imaging that supports the presence of underlying AD pathology [6].

Although brain imaging with MRI, FDG-PET, and amyloid PET often require advanced imaging analyses, which may not be easily accessible everywhere, a lumbar puncture (LP) may be done in many different clinical settings and CSF samples can, if needed, easily be shipped to a central laboratory for analysis. Numerous articles, including large multicenter studies and meta-analyses and systematic reviews (see Table 1), have confirmed the predictive value of CSF biomarkers in patients with MCI. However, there is a need to reach a consensus on the application of CSF biomarkers in clinical practice because it currently varies from country to country, and even from site to site, and because early predementia diagnosis of AD is associated with unique clinical challenges and ethical concerns [17,18].

The aim of this recommendation article was to provide consensus recommendations on the clinical use of CSF biomarkers in subjects with MCI using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method [19–21].

The present recommendations and the corresponding recommendations for the application of CSF biomarkers in patients with dementia [22] were developed by Biomarkers for AD and Parkinson's disease (BIOMARKAPD), a project supported by the EU Joint Program—Neurodegenerative Disease Research (JPND) involving clinicians and researchers from 19 countries with the aim to standardize the assessment of established and new fluid biomarkers for AD and PD.