Published in final edited form as:

Nat Rev Neurol. 2017 March ; 13(3): 131–132. doi:10.1038/nrneurol.2017.11.

CSF biomarkers for Alzheimer disease — approaching consensus

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Abstract

A European working group has provided a new set of recommendations for the use of cerebrospinal fluid (CSF) biomarkers in the diagnostic evaluation of Alzheimer disease and mild cognitive impairment. These recommendations represent an important step towards the implementation of CSF biomarker tests in the clinic, but several challenges remain.

Alzheimer disease (AD) is the most prevalent cause of dementia, but symptoms such as impaired memory and other cognitive skills, and the gradual loss of ability to perform functions of daily living, can occur in other dementias, especially early in the disease trajectory. The challenge of reinforcing a clinical diagnosis led two groups — the National Institute on Aging–Alzheimer’s Association workgroup¹, and the International Working Group for New Research Criteria for the Diagnosis of AD² — to develop research criteria for AD at the stage of dementia or earlier (mild cognitive impairment (MCI) or prodromal AD). When a need exists for more-accurate determination that AD is the cause of dementia, both groups recommended the inclusion of biomarkers, including reduced levels of amyloid- β_{1-42} ($A\beta_{1-42}$) and elevations of total tau (t-tau) and phosphorylated tau 181 (p-tau₁₈₁) in the cerebrospinal fluid (CSF), positive results on imaging tests such as amyloid PET, medial temporal lobe atrophy assessed by MRI, or a characteristic pattern of glucose

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Competing interests statement

The authors declare no competing interests.

Subject ontology terms

Health sciences / Neurology / Neurological disorders / Dementia / Alzheimer’s disease

[URI /692/617/375/132/1283]

Health sciences / Medical research / Biomarkers

[URI /692/308/53]

Biological sciences / Biochemistry / Proteins / Cerebrospinal fluid proteins

[URI /631/45/612/1224]

Health sciences / Health care / Medical imaging / Brain imaging

[URI /692/700/1421/65]

Competing interests statement

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hypometabolism measured by ^{18}F -FDG-PET^{1,2}. Similar guidelines have been endorsed by the European Federation of Neurological Societies.

To provide evidence-based guidance for the clinical utility of CSF $\text{A}\beta_{1-42}$, t-tau and p-tau₁₈₁ as AD biomarkers, a multidisciplinary working group of European investigators, as part of the BIOMARKAPD (Biomarkers for Alzheimer's and Parkinson's Disease) initiative, recently published recommendations for the use of these biomarkers in the diagnostic evaluation process for patients with a clinical diagnosis of AD or MCI^{3,4}. The working group employed a structured, well-organized and comprehensive approach, including an extensive literature search, prioritized clinical questions, and grading of the quality of evidence.

In the diagnostic work-up for suspected AD³, the evidence that these CSF biomarkers could identify or exclude AD was strong in mild dementia, but weaker in atypical or ambiguous cases. The investigators found weak evidence that CSF biomarkers could predict rates of clinical decline in mild AD or atypical or ambiguous dementia, and no evidence that their use could improve well-being or reduce health-care costs in these patients (although this question has received limited formal study). Also, comparisons with other biomarkers were limited, and were largely confined to brain MRI. For MCI⁴, the evidence indicates that CSF biomarkers can support or exclude AD as the likely underlying pathological process, and also have utility in predicting decline over 3 years.

Some evidence is scanty or missing: in particular, little information is available regarding the feasibility of lumbar puncture in the routine workflow for MCI and dementia, diagnostic and treatment outcomes after obtaining CSF biomarker data, and validation against gold standards such as autopsy. Nevertheless, the working group provides a compelling argument for incorporating CSF biomarkers into the initial diagnostic assessment of MCI, and of dementia in early, atypical or complex cases.

MRI has value beyond the assessment of hippocampal or cortical atrophy, and CSF and MRI biomarkers are probably best deployed in a synergistic rather than a mutually exclusive fashion. Brain MRI or CT is recommended in the diagnosis of dementia to evaluate features such as mass lesions, vascular disease and certain types of CNS inflammation, which CSF-based AD biomarkers do not address. Conversely, although hippocampal atrophy or regional cortical thickness patterns on MRI can support a diagnosis of AD, they do not indicate whether amyloid or tau pathologies are driving these changes. In atypical presentations — for example, progressive aphasia or posterior cortical atrophy — biomarkers are complementary: MRI might demonstrate the regional atrophy pattern, and CSF biomarkers can clarify whether AD is the likely underlying pathology.

Before CSF $\text{A}\beta_{1-42}$, t-tau and p-tau₁₈₁ can move into clinical use, standardization of pre-analytical and analytical factors is an essential requirement for the provision of technically robust and reliable test methods. In the AD CSF biomarker research community, consensus has been growing around definitions of best-practice pre-analytical steps to handle CSF, and the need to move beyond 'research use-only' immunoassay methods for measurement of CSF $\text{A}\beta_{1-42}$, t-tau and p-tau₁₈₁. We look forward to the development and validation of

automated immunoassay methods according to strict *in vitro* diagnostic protocols, which should permit robust reproducibility across laboratories using the same assay methodology and analytical platform, and ultimately across different analytical platforms. Substantial progress in the development of certified reference methods and materials has been made for A β ₁₋₄₂, and similar efforts have been initiated for tau⁵⁻⁷.

An important question for any laboratory test is its interpretation: what pathological processes do the CSF analytes A β ₁₋₄₂, tau and p-tau₁₈₁ measure, what does an abnormal test imply, and how should cut-off points be established? The decreased levels of CSF A β ₁₋₄₂ in AD indirectly reflect aggregation and impaired clearance of A β ₁₋₄₂ in the brain. Depletion of A β ₁₋₄₂ in the CSF correlates with increased retention of amyloid PET tracers in the brain, although recent studies suggest that CSF A β ₁₋₄₂ levels begin to decrease before amyloid PET scans fall into the positive zone. Because A β ₁₋₄₂ is preferentially deposited in plaques in AD, normalization of A β ₁₋₄₂ against a less aggregation-prone A β peptide might improve diagnostic accuracy. Several recent studies support this idea: the CSF A β ₁₋₄₂:A β ₁₋₄₀ ratio was found to perform slightly more accurately than A β ₁₋₄₂ alone when calibrated against amyloid PET imaging, and in studies where people with AD were compared with those with other types of dementia and controls^{8,9}.

Increased levels of CSF tau suggest damage to neurons or axons and, when considered in the context of decreased A β ₁₋₄₂, provide support for ongoing neurodegeneration in AD. Evidence exists that the ratio of tau to A β ₁₋₄₂ has greater diagnostic utility than A β ₁₋₄₂ alone or the A β ₁₋₄₂:A β ₁₋₄₀ ratio. A systematic review with careful attention to analytical methodologies and study sample sizes will be needed to determine which combination of these biomarkers provides the best diagnostic and prognostic value.

The European working group has provided a conservative and thoughtful set of recommendations to move CSF biomarkers toward clinical implementation as indicators of the presence or absence of AD pathological processes in dementia and MCI^{3,4}. This carefully weighed evidence, together with the prospect of improved test methods that would be widely available in clinical laboratories, as well as universally applicable cut-off points, provides a basis for the realistic availability of these tests in the near future, but many challenges remain. For example, better tests or combinations of tests are needed for accurate prediction of rate of decline in MCI and patients with early AD. Also, studies comparing CSF biomarkers with various imaging modalities are required. In addition, the benefit to patients of CSF A β ₁₋₄₂ tau and p-tau₁₈₁ testing must be investigated. Ultimately, as the heterogeneity of pathology underlying dementia is increasingly recognized, an optimal biomarker panel may be tasked with detecting amyloid, tau and neurodegeneration¹⁰, as well as factors such as vascular or α -synuclein pathology, in order to personalize diagnosis and therapy.

Acknowledgments

The authors acknowledge grant support from the NIH National Institute on Aging (grant AG05131 to G.R.G. and grant U01 AG024904 to L.M.S.). [Au: OK?]

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