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Perspective

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

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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)

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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.

Table 1
Meta-analyses and systematic reviews

Reference	Year	Type	Other markers	CSF marker	Timespan searched	Number of studies	Comments
Olsson et al. [7]	2016	Systematic review and meta-analysis	NFL NSE VLP-1 HFABP $A\beta_{1-40}$ $A\beta_{1-38}$ sAPPα sAPPβ Albumin ratio YKL-40/MCP-1 GFAP	$A\beta_{1-42}$ Tau P-tau	July 1984 to June 2014	131 151 89	A CSF signature of elevated tau and p-tau and reduced $A\beta_{1-42}$ is consistently observed in MCI patients who progress to AD. The other investigated markers need more research
Mo et al. [8]	2015	Systematic review and meta-analysis		$A\beta_{1-42}$	January 2004 to October 2013	17	Only one of the studies reported MCI to AD data
Ferreira et al. [9]	2014 (October)	Meta-analysis		$A\beta_{1-42}$ Tau P-tau	January 1990 to September 2013	12	The $A\beta_{1-42}$/p-tau ratio had the highest capability to predict conversion to AD
Ritchie et al. [10]	2014	Cochrane review		$A\beta_{1-42}$, CSF, and plasma	No restriction	14	CSF $A\beta_{1-42}$ levels cannot be recommended in an MCI population as a test for AD
Ferreira et al. [11]	2014 (March)	Systematic review		$A\beta_{1-42}$ Tau P-tau	January 1990 to September 2013	7 Systematic reviews or meta-analysis and 26 primary studies	Best performance for the prediction of conversion to AD was achieved with combinations of two or all three CSF markers
Noel-Storr et al. [12]	2013	Systematic review	FDG-PET PIB-PET MRI	$A\beta_{1-42}$	2000 to August 2011	37	Few large studies and variability in biomarker assessment
van Rossum et al. [13]	2010	Meta-analysis		$A\beta_{1-42}$ Tau P-tau	2002–2009	7 11 8	The combination of $A\beta_{1-42}$ and tau was the best predictor of conversion to AD
Schmand et al. [14]	2010	Meta-analysis	MRI MTL atrophy	$A\beta_{1-42}$ Tau P-tau	January 2003 to November 2008	14 14 14	CSF markers are abnormal slightly earlier than brain atrophy measured by MRI
Mitchell [15]	2009	Meta-analysis		P-tau	Until February 2009	6	P-tau was modestly successful in predicting progression to dementia
Diniz et al. [16]	2008	Systematic review and meta-analysis		$A\beta_{1-42}$ Tau P-tau	January 1999 to April 2007	4 5 3	MCI patients with high tau and p-tau and low $A\beta_{1-42}$ at baseline are more likely to convert to AD

Abbreviations: CSF, cerebrospinal fluid; NFL, neurofilament light protein; $A\beta_{1-42}$, amyloid-β 1-42; NSE, neuron-specific enolase; p-tau, phosphorylated tau; VLP-1, visinin-like protein; HFABP, heart fatty acid–binding protein; MCI, mild cognitive impairment; $A\beta_{1-40}$, amyloid β_{1-40}; AD, Alzheimer's disease; $A\beta_{1-38}$, amyloid β_{1-38}; sAPPα, soluble amyloid precursor protein α fragment; sAPPβ, soluble amyloid precursor protein β fragment; MCP-1, monocyte chemotactic protein 1 (also called YKL-40); GFAP, glial fibrillary acidic protein; FDG, fluorodeoxyglucose; PET, positron emission tomography; PIB, Pittsburgh compound B; MRI, magnetic resonance imaging; MTL, medial temporal lobe atrophy.

2. Methods

2.1. Working group composition and group process

For a detailed description of our application of the GRADE process, we refer to our recommendation article on dementia [22] and to previous methodological GRADE articles [19–21].

The working group for this guideline comprised 28 international members, including neurologists, psychiatrists, specialists in clinical chemistry, and epidemiologists. The evidence gathering, evaluation, and synthesis were led by five experts (MB, PJV, RH, S-KH, and AHS) and the development of clinical recommendations was chaired by GW. All recommendations were developed by consensus

conference. During the process, the group organized five face-to-face meetings; between the meetings, the progress was evaluated by e-mail. The face-to-face meetings were used to 1) establish a modified GRADE method for the development of recommendations for a diagnostic intervention; 2) to identify the most important clinical questions and outcomes; 3) to establish the methods for literature search and guidelines for evaluating the evidence; 4) to reach a consensus on each of the steps in GRADE, including the final recommendations; and 5) reach a consensus on operational aspects regarding the implementation of CSF biomarkers in clinical practice. The final draft of the manuscript was revised and commented on by all the coauthors.

First, the group applied the PICO format to select clinical questions on the use of CSF biomarkers taking into account the population (P), diagnostic strategy or intervention (I), comparison strategy (C), and patient outcomes (O).

For each clinical question defined in the PICO process, a MEDLINE search was conducted to identify relevant meta-analyses, systematic reviews, and research articles to address this question. More articles were then added from other sources including reference lists from articles in original search results.

MEDLINE search strings were as follows:

(Cerebrospinal fluid OR CSF) AND diagnos* AND (mild cognitive impairment OR MCI OR prodromal AD) AND (tau OR beta amyloid OR abeta) AND (sensitivity OR specificity)
(Cerebrospinal fluid OR CSF) AND diagnos* AND (mild cognitive impairment OR MCI OR prodromal AD) AND (tau OR beta amyloid OR abeta) AND (MRI OR PET OR SPECT)
(Cerebrospinal fluid OR CSF) AND diagnos* AND (mild cognitive impairment OR MCI OR prodromal AD) AND (tau OR beta amyloid OR abeta) AND added value.

After searching for evidence and identifying the relevant clinical questions, the GRADE level for each article that provided data to one of the clinical questions was assessed for each relevant outcome.

To ensure the consistency of the grading system, a grading algorithm was used as an aid. The article was assigned an upgraded level of quality for the patient population if

- it originated consecutively from a memory clinic, with at least 20 MCI cases;
- the diagnostic criteria both at the MCI stage and at follow-up were well described;
- the baseline and follow-up diagnoses were based on clinical specialist consensus according to well-defined criteria and blinded to the CSF result;
- detailed clinical and demographic data with clinical follow-up for at least 1 year;
- a detailed description of the analytical method used in a single laboratory with reported cut-off values and a high success rate; and
- autopsy-confirmed diagnosis.

The grading of each research article was added to the evidence tables. The overall quality of evidence for each clinical question was discussed in the meetings. Once the consensus decision was reached, the quality of the evidence for each relevant outcome was graded as "high," "moderate," "low," or "very low." Recommendations for questions, for which there was no available evidence, were developed after focused discussions in the working group at face-to-face meetings.

2.2. Operational aspects

In addition, the group discussed operational aspects, namely, 1) the possible complications of LP, 2) the interpretation of laboratory results, and 3) counseling of patients before and after the biomarkers analysis. Finally, based on the evidence and group discussion, a decision tree of using CSF biomarkers in the clinical assessment of MCI patients was drawn (Fig. 1).

3. Results

3.1. Steps 1–2: PICO definition of clinical questions

The working group identified six clinical questions to be addressed using the PICO method. The clinical questions were scored and ranked by importance, and the results are shown in Table 2. The highest rank was given to questions identifying or excluding AD (defined as a pathologically confirmed diagnosis) as the cause of MCI and predicting conversion to AD dementia (defined as an AD diagnosis based on clinical criteria) within 3 years followed by the prediction of functional or cognitive decline (even without dementia). The three other clinical questions on changing disease management, improving patient well-being, and reducing health care costs were discussed at length during the workshop. Because of the limited evidence available, a large number of the members ranked "improving patient well-being" as the most important question, whereas a slight majority ranked it the least important.

3.2. Step 3–4: Identifying the evidence and rating the quality

Table 1 lists all the identified systematic reviews and meta-analyses.

The first search for the predictive value of CSF biomarkers produced 137 articles and, in the end, 23 articles fulfilled the inclusion and exclusion criteria. The search for comparisons between CSF biomarkers and imaging biomarkers produced 117 articles, and 20 articles were included in the final data analysis. The search for the added value of CSF biomarkers produced 348 articles, of which 16 met the inclusion and exclusion criteria.

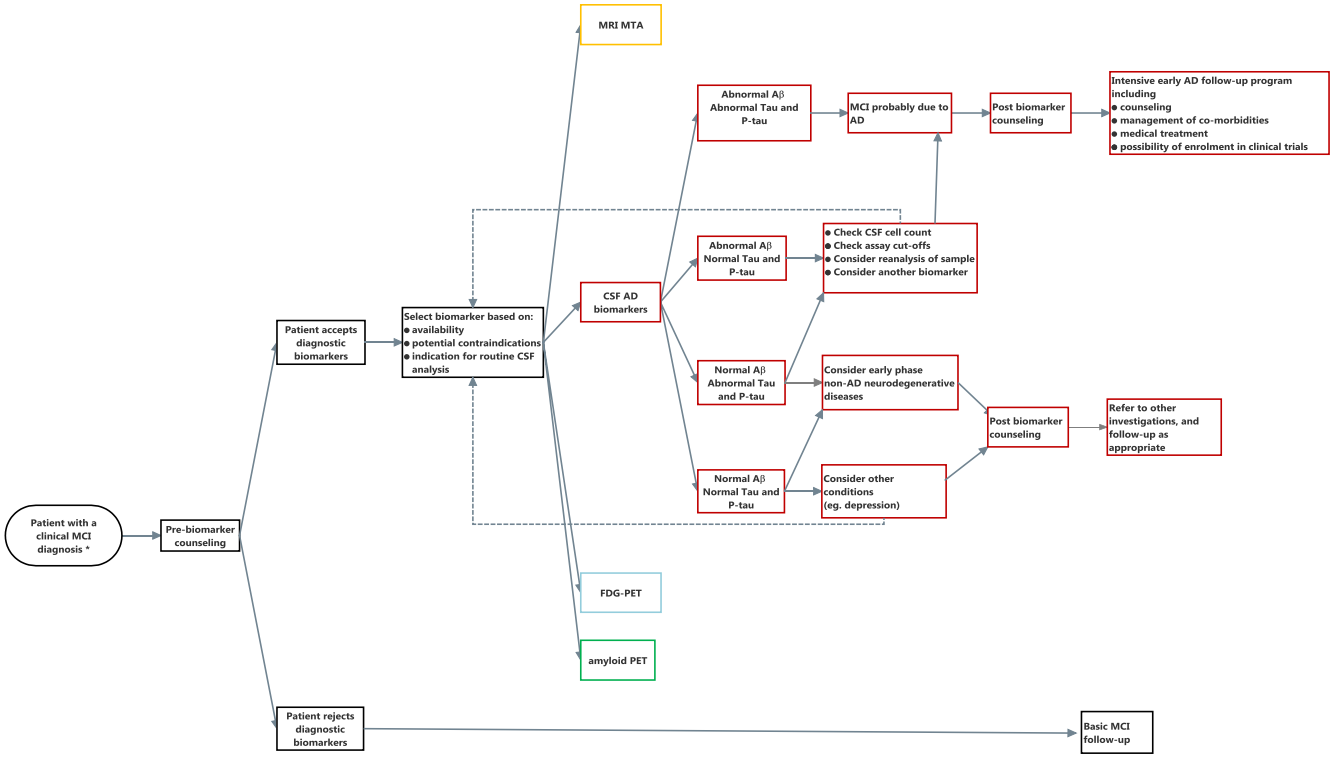

Fig. 1. Decision tree on the recommended use of the cerebrospinal fluid (CSF) biomarkers in diagnostic workup on patients with clinical diagnosis of mild cognitive impairment. *Diagnosis based on medical history, clinical and basic neuropsychological examination, and basic neuroimaging. MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MTA, medial temporal lobe atrophy; AD, Alzheimer's disease; FDG, fluorodeoxyglucose; PET, positron-emission tomography; Aβ, amyloid-β; P-tau, phosphorylated tau.

One article fulfilled the criteria for the health economy subsection. The information on the quality of evidence presented in the articles identified in each subsection is summarized in the Supplementary Tables 1–3.

No evidence tables were produced for clinical questions 5–6 concerning the effects on patient well-being and health economy, as during the search process, it was evident that there was very little or no evidence available.

Table 2
The clinical questions and their rank scores in order of importance based on workshop discussions (rank 1: most important)

Clinical questions: in patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers …	Rank
1. … identify or exclude AD as the cause of MCI?	1
2. … predict conversion to AD dementia within 3 years?	1
3. … predict functional or cognitive decline?	2
4. … change disease management?	3
5. … improve patient well-being?	3
6. … reduce health care costs?	4

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment.

3.3. Steps 5–7: Rating the quality of evidence for each clinical question

The Supplementary Tables 1–3 show the articles included in the evidence for clinical questions 1–3. When possible, the number of cases with each possible patient outcome in the test was calculated. Using the predefined grading algorithm, each article was given a GRADE level of "high," "moderate," "low," or "very low" for each clinical question. There was no evidence for the diagnostic value of CSF biomarkers in identifying AD pathology as the cause of MCI, as there were no studies with CSF AD biomarkers available with follow-up to neuropathological confirmation of the diagnosis. For the question on predicting functional decline or progression to AD-type dementia diagnosis during a 3-year follow-up, the overall quality of the evidence was in terms of the following:

- high and consistent for prediction by CSF alone;
- high and consistent for added value of CSF over clinical measures alone; and
- conflicting and rated as low quality for added value over other hypometabolism on FDG-PET and hippocampal atrophy on MRI. There was only one high-quality article comparing diagnostic accuracy of CSF biomarkers and amyloid-PET imaging in MCI,

Table 3
Final recommendations and recommendation strengths

Clinical question: in patients with MCI, will CSF biomarkers as compared with (A) clinical measures alone and/or (B) other biomarkers …	a) Compared with clinical measures alone		b) Compared with other biomarkers	
	Direction of recommendation	Strength of recommendation	Direction of recommendation	Strength of recommendation
1. … identify or exclude AD as the cause of MCI?	NA		NA	NA
2. … predict functional or cognitive decline?	Yes	Strong	Hippocampal atrophy: yes FDG-PET: no Amyloid-PET: no	Hippocampal atrophy: weak FDG-PET: weak Amyloid-PET: weak
3. … predict conversion to AD dementia >3 years?	Yes	Strong	Hippocampal atrophy: yes FDG-PET: no Amyloid-PET: no	Hippocampal atrophy: weak FDG-PET: weak Amyloid-PET: weak
4. … change disease management?	Yes	Weak	NA	
5. … improve quality of life?	Yes	Weak	NA	
6. … reduce health care costs?	No	Weak	NA	

Abbreviations: MCI, mild cognitive impairment; CSF, cerebrospinal fluid; AD, Alzheimer's disease; NA, not addressed; FDG-PET, fluorodeoxyglucose positron-emission tomography.

suggesting equal sensitivity but slightly higher specificity than amyloid-PET in predicting progression to AD dementia [23].

3.4. Step 8: Developing the recommendations

3.4.1. The role of CSF biomarkers in the diagnostic evaluation of MCI patients

The final recommendations for each clinical question and the strength of each recommendation, reflecting the strength of the scientific evidence, are shown in Table 3. There was no evidence for the diagnosis of AD pathology as the underlying cause of MCI; so, no recommendation was given. The working group recommended using the CSF biomarkers in MCI as an add-on to clinical evaluation alone for predicting functional decline or progression to AD dementia and, based on the available evidence, the recommendation was strong. However, in comparison with the outcome of using hippocampal atrophy as a biomarker, the working group issued a weak recommendation to incorporate CSF biomarkers in the diagnostic workup compared with hippocampal atrophy. Because of insufficient evidence, the working group could not recommend CSF biomarkers as an alternative to FDG-PET or amyloid-PET in predicting future decline or conversion. The working group recommended using CSF biomarkers to inform future disease management, but the strength of this recommendation was weak because of the small amount of evidence. Clinical questions 5–6, concerning the use of CSF biomarkers to improve patient well-being and reduce health care costs, were discussed by the working group, and recommendations were given based on expert opinion as presented in Table 3.

In summary, the working group recommended that patients with mild cognitive symptoms should be offered diagnostic evaluation to identify specific and potentially reversible causes that require specific treatment and follow-up. A summary of the operational recommendations of clinical use of CSF biomarkers in clinical use is provided in the decision tree (Fig. 1).

3.4.2. Complications of an LP

The CSF biomarker test for AD in MCI patients is not an indispensable test, and the possible contraindications (increased intracranial pressure, coagulopathy, and a skin infection at the injection site) must be assessed carefully. For example, the current use of anticoagulants is a contraindication for LP, and the risk of stopping medication for LP because of an AD biomarker test must be considered. Transient back pain and headache may be reported after LP [24]. The considerations in the multidisciplinary working group concerning possible were described in the recommendation article on dementia [22].

3.4.3. Counseling of patients before an LP

The working group agreed on the following recommendations concerning information to be provided during counseling before asking for consent to the LP in a patient with MCI:

- CSF may help to identify rare conditions, such as neuroinflammatory or infectious diseases that can be treated;
- CSF biomarkers may identify the risk of symptom progression and confirm AD as the cause of the symptoms: with unknown biomarker status, the 3-year risk of progression to dementia is approximately 35%, with negative biomarkers it is 14%, and with positive AD biomarkers it is 54% [25];
- in the case of positive AD biomarkers, a personal follow-up plan will be offered and appropriate support

will be initiated in the case of symptom progression. In addition, such information may be important for personal planning; and
- in the case of negative AD biomarkers, an intensive follow-up plan may not be necessary (if no additional symptoms that may indicate a neurodegenerative disorder other than AD present) and such information may be important for personal planning and well-being.

3.4.4. Interpretation of CSF biomarker results

The cut-off points for CSF $A\beta_{1–42}$, tau, and p-tau have varied considerably between laboratories. In general, European laboratories have operated with cut-off points for $A\beta_{1–42}$ that were too low, resulting in the underdiagnosis of AD [26]. The BIOMARKAPD consortium has recently developed recommendations for appropriate cut-off points [26–28].

We recommend to use the same cut-off points regardless of apolipoprotein E (*APOE*) genotype. $A\beta_{1–42}$ levels are highly associated with *APOE* genotype and individuals carrying the *APOE* ε4 allele (a major susceptibility gene for AD) may have low CSF $A\beta_{1–42}$ without the clinical symptoms of AD [29–32]. However, CSF $A\beta_{1–42}$ is strongly associated with cortical Aβ accumulation independent of *APOE* genotype, and the association of *APOE* ε4 with low CSF $A\beta_{1–42}$ simply reflects this association. Similarly, although Aβ decreases with age in the normal population, this again reflects increasing amyloid accumulation in the brain as seen with aging [33]. The strategy for interpreting normal CSF biomarker results, conflicting CSF biomarker results, and abnormal CSF biomarker results is shown in the decision tree (Fig. 1).

3.4.5. CSF biomarker results that are conflicting with other AD biomarker results

In these cases, biomarkers as a whole may be less informative as to the cause and prognosis of the MCI syndrome. However, even with negative biomarkers and conflicting biomarkers, there is still a risk of progression to AD dementia, albeit much smaller [25]. It is essential to interpret biomarker results close to the cut-off points with care. Analytical variation (often around 10%) in the biomarker measurements may result in a fairly significant gray zone within which it is impossible to tell whether the individual patient is positive or negative for a certain biomarker [28]. In such cases, repeated testing and clinical evaluation should be provided.

3.4.6. Counseling of patients with positive biomarkers after CSF biomarker study—disclosure of results

The working group recommended that counseling is offered to inform the patient with MCI what to do to stay well for as long as possible (e.g., intervention to reduce life style–related risk factors and offer multimodal training [34]) and to provide a follow-up program to:

- offer continuous counseling and support,
- monitor the development of symptoms and functional status,
- treat comorbidities,
- offer pharmaceutical treatment as early as possible; and
- offer participation in intervention trials.

3.4.7. Cost and availability

The considerations in the multidisciplinary working group concerning cost and availability were described in the recommendation article on dementia [22]. A routine clinical CSF biomarker test is available in every hospital as the CSF samples can be sent to outside laboratory for analysis of $A\beta_{1–42}$, tau, and p-tau. The cost is relatively low [35,36], but LP requires personnel with the appropriate training and facilities. Routine LP might therefore raise logistical issues of upscaling that must be addressed [37] in relation to availability of other (imaging) biomarkers.

4. Discussion

We aimed to produce recommendations for the clinical application of CSF AD biomarkers in the diagnostic evaluation of patients with MCI under the JPND BIOMARKAPD program. Using the GRADE method, we systematically searched the literature and reached a consensus on the recommendations for the clinical application of AD CSF biomarkers among patients with cognitive impairment who do not meet the criteria for dementia. In patients with MCI, will CSF biomarkers, compared with clinical measures alone and/or other imaging biomarkers, 1) identify or exclude AD as the underlying cause of MCI and 2) predict conversion to AD dementia within 3 years? These questions were defined and ranked as the most important clinical questions by the multidisciplinary working group, before initiating the search and evaluation of scientific literature. The working group found high-quality evidence that supports the use of CSF biomarkers alongside clinical measures to predict cognitive decline and conversion to AD over a 3-year follow-up period. However, when CSF biomarkers were compared with various imaging biomarkers, the amount of evidence was significantly lower, largely because of limited number of studies, which were sometimes also contradictory. We therefore could not recommend one AD biomarker over another to predict cognitive decline and conversion to AD. Based on expert opinion discussed at face-to-face meetings, the working group also developed a decision tree for the interpretation of results and recommended pre- and post-biomarker counseling. There was little or no evidence available for evaluation of the value of CSF biomarkers in changing disease management, improving patient well-being, or reducing health care costs.

From a clinical point of view, it is important to identify patients at risk for the development of AD-type dementia to

recognize the patients in need of medical or other interventions. An increasing number of patients are referred to memory clinics with very mild symptoms that may be because of AD, and many of these patients request a thorough diagnostic evaluation and information about their diagnosis, that is, the cause of their symptoms. CSF and other AD biomarkers may help to identify the subgroup of patients with MCI because of AD, although with some uncertainty, and such patients may need intensified follow-up and intervention. Also, patients with an early diagnosis of MCI because of AD may be offered the possibility of participating in clinical trials with new potentially disease-modifying drugs and in nonpharmacological interventions. Without biomarkers, there is a risk of overdiagnosing AD in MCI cases where progression to dementia is unlikely. For patients with dementia, international guidelines recommend the use of CSF biomarkers and/or other AD biomarkers to support the AD diagnosis [38–40]. However, for patients with mild impairment who do not meet the clinical criteria for dementia, there are no clinical guidelines concerning the utility of CSF biomarkers.

So far, the application of biomarkers in the clinical routine is hampered by a lack of harmonization and standardization and by the varying access to biomarkers. Furthermore, although an early diagnosis may pave the way toward early treatment and support, there are also ethical issues associated with establishing a very early diagnosis in an incurable disease.

There was strong evidence for the use CSF biomarkers in addition to clinical measures when predicting functional or cognitive decline or the conversion to AD dementia in patients with MCI. Notably, the available evidence relates to the prediction of clinical outcome, not to predicting underlying pathology, which is one of the major limitations discussed during the development of the present recommendations. Although there are some articles available on the comparison between CSF biomarkers and neuropathological results in dementia, there are no studies where MCI patients with CSF and other biomarkers were followed to a final clinical diagnosis and autopsy with a neuropathological confirmation of the diagnosis. Therefore, the working group could not give recommendation on the use of CSF biomarkers for identifying the AD-type neuropathology. However, the follow-up period of patients was relatively long in many studies, which increases the reliability of information concerning the conversion to clinical AD or remaining as stable MCI in the course of the disease. Furthermore, circumstantial evidence suggests that of the three studied biomarkers, CSF $A\beta_{1–42}$ is associated with AD pathology in the brain of subjects with MCI. CSF $A\beta_{1–42}$ correlates strongly with PET-amyloid deposition, and PET-amyloid strongly correlates with brain amyloid, also in subjects with MCI [23,27,41]. Thus, it is likely that CSF $A\beta_{1–42}$ correlated with brain Aβ in subjects with MCI.

Comparing the diagnostic performance, in patients with MCI, of CSF biomarkers to other AD biomarkers, temporal lobe atrophy on MRI, FDG-PET, or amyloid-PET, there were fewer articles, and the results were conflicting. Especially in case of CSF tau and p-tau, there were very few studies fulfilling the search criteria. Thus, the group was not able to recommend one biomarker modality above another and noted that more research studies with direct comparison of the added value of CSF and imaging biomarkers are needed. In the current clinical practice, the availability of PET imaging in the close proximity or an expert laboratory on CSF analysis near the treating clinician may in reality play a role in selection of a biomarker used. However, particularly in patients in whom LP with CSF routine analysis is already indicated, the analysis of CSF for AD biomarkers is an easily accessible study.

One study researched the cost-effectiveness of CSF biomarkers in dementia [42]. Several aspects limited the generalizability of that study. It tested the effect of CSF measures alone on costs in relation with off-label treatment with donepezil in subjects with dementia. This is a highly unlikely scenario for subjects with MCI as acetylcholinesterase inhibitors are not recommended in MCI. Evidence from the literature revealed that CSF AD biomarker information most likely does not have a direct effect on health [43,44] because no effective pharmacological treatment is available in MCI [45–47]. Several studies revealed positive, neutral, and negative reactions during interviews after patients received a diagnosis of MCI, but these reactions have not been tested after disclosure of AD as the most likely cause of this syndrome [48–50]. Reactions after disclosure of the MCI diagnosis included relief of not having dementia, worrying if dementia because of AD will develop over time, planning activities, and stress, and it is likely that similar reaction will apply after disclosure of CSF biomarker status in MCI. Concerns about stigmatization have also been addressed [51]. These reactions, however, regard the diagnosis of the MCI syndrome.

The strength of this article is the participation of a large international multidisciplinary team. The work was based on a systematic review of a vast amount of research evidence, and the development of the recommendations was based on the GRADE method and face-to-face consensus meetings.

Our literature searches highlighted the need for more studies where MCI patients have been followed until autopsy and prospective studies where the diagnostic and prognostic performance of the CSF biomarkers compared with other biomarker modalities. A new international task force "Roadmap to the Biomarker-Based Diagnosis of Alzheimer's Disease" aims to 1) identify the gaps of evidence to full clinical validity of AD biomarkers (neuropsychology, CSF, and imaging) for the etiologic diagnosis of AD at the MCI stage and 2) prioritize them into a coherent and cost-effective roadmap, to form a strategic research agenda. As already pointed out for CSF biomarkers in our recommendation, the roadmap initiative has revealed a relative lack of evidence concerning prospective studies in patients with MCI on clinical validity and clinical utility for most AD biomarkers (Frisoni G., personal communication).

In conclusion, the BIOMARKAPD working group used the GRADE method to develop recommendations for the application of CSF biomarkers in patients with MCI. The working group identified the most important PICO questions as: in patients with MCI, will CSF biomarkers, compared with clinical measures alone, and/or other imaging biomarkers identify or exclude AD as the cause of MCI and predict conversion to AD within 3 years? Based on currently available evidence and focused face-to-face consensus meetings, the working group recommended the use of CSF AD biomarkers for the prediction of clinical progression or conversion to AD dementia in patients with MCI with appropriate pre- and post-biomarker counseling. No recommendations could be given on the priority of CSF biomarkers versus other potential AD biomarkers because of insufficient or conflicting evidence. More studies are needed on the clinical validity and utility of CSF and other biomarkers in predicting clinical progression to AD dementia in patients with MCI.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2016.09.009.

RESEARCH IN CONTEXT

1. Systematic review: The authors developed the recommendations for the clinical use of CSF biomarkers in diagnostic evaluation of MCI patients based on systematic review of literature and application of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method.
2. Interpretation: Based on the published scientific evidence and group discussions, the group recommends the use of CSF biomarkers in predicting the functional or cognitive decline or conversion to AD dementia within 3 years. Furthermore, the group recommends counseling both before and after the biomarker evaluation.
3. Future directions: Studies with follow up from the MCI stage of the disease to dementia and autopsy are necessary to get direct evidence on whether or not these biomarkers can identify AD pathology as the underlying cause of MCI. Also, more studies comparing different biomarker modalities within the same patient populations are needed to compare their performance in predicting AD dementia in MCI patients.

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