Article

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SIMONSEN, Anja Hviid, *et al*.

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Reference

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Perspective

Recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia

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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 dementia. The recommendations were developed by a multidisciplinary working group based on the available evidence and consensus from focused discussions for (i) identification of Alzheimer's disease (AD) as the cause of dementia, (ii) prediction of rate of decline, (iii) cost-effectiveness, and (iv) interpretation of results. The working group found sufficient evidence to support a recommendation to use CSF AD

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biomarkers as a supplement to clinical evaluation, particularly in uncertain and atypical cases, to identify or exclude AD as the cause of dementia. Because of insufficient evidence, it was uncertain whether CSF AD biomarkers outperform imaging biomarkers. Operational recommendations for the interpretation of ambiguous CSF biomarker results were also provided.

Keywords: Alzheimer's disease; Biomarkers; CSF; Diagnosis; GRADE; Recommendations

1. Introduction

Dementia, or major neurocognitive disorder, represents a significant cognitive decline from a previous level of performance in one or more cognitive domains—such as complex attention, executive function, learning, memory, language or perceptual-motor, or social cognition—which interferes with independence in everyday activities [1,2].

Alzheimer's disease (AD) is the most common cause of dementia and accounts for 50%–70% of all diagnosed cases [3,4]. The symptoms of AD are impairments of memory and other cognitive skills and a gradual loss of ability to perform activities of daily living. Similar symptoms may occur, especially in the early course of the disease, in other dementias, such as the behavioral variant of frontotemporal dementia, dementia with Lewy bodies, and vascular dementia, and in a wide range of rarer conditions, and in atypical cases, the diagnosis may be challenging [5].

Therefore, the diagnostic criteria for AD dementia established recently by the National Institute on Aging and the Alzheimer's Association [6] and the research criteria by the International Working Group for New Research Criteria for the Diagnosis of AD [7] recommend the use of biomarkers, such as reduced levels of the 42-amino-acid form of amyloid-β ($A\beta_{1–42}$) and elevated levels of tau and phosphorylated tau (p-tau) in the cerebrospinal fluid (CSF), positive amyloid positron-emission tomography (PET) imaging, medial temporal lobe atrophy (as assessed by magnetic resonance imaging [MRI]), or a characteristic pattern of glucose hypometabolism (as assessed by fluorodeoxyglucose PET [FDG-PET]), when there is a need to increase the certainty that the underlying cause of a dementia syndrome is AD. Similar recommendations for biomarkers were presented in the most recent European Federation of Neurological Societies guidelines for the diagnosis and management of AD [8] and other dementias [9].

Reflecting the neuropathological hallmarks of AD, the levels of tau, p-tau, and $A\beta_{1–42}$ in the CSF are easily accessible biomarkers for AD [10]. However, there are no evidence-based guidelines available to guide the application and interpretation of CSF biomarkers in the diagnostic evaluation of patients with dementia. The present recommendations and corresponding recommendations for the application of CSF biomarkers in patients with mild cognitive impairment (MCI) [11], were developed by Biomarkers for AD and Parkinson's disease (PD; BIOMARKAPD), which is a research program funded by the EU Joint Program—Neurodegenerative Disease Research (JPND), with partners from 19 countries aiming to standardize (i) biomarker measurements, (ii) sample collection, and (iii) the interpretation of results.

The aim of this recommendation article was to provide consensus recommendations for the clinical use of CSF AD biomarkers in subjects with dementia, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method [12,13].

2. Methods

2.1. Working group selection and composition

The working group for this guideline comprised 28 international members, including neurologists, psychiatrists, specialists in clinical chemistry, epidemiologists, health economists, and researchers.

The evidence gathering, evaluation, and synthesis were led by five experts (SE, PJV, RH, S-KH, and AHS), and the development of clinical recommendations was chaired by GW.

2.2. Group process

All recommendations were developed by consensus conference [14]. Five face-to-face meetings were organized in the working group; between meetings, the progress was evaluated by e-mail.

The face-to-face meetings were used to (i) establish a modified GRADE method for the development of recommendations for a diagnostic intervention; (ii) identify the most important clinical questions and outcomes; (iii) establish the methods for the literature search and guidelines for evaluating the evidence; (iv) reach a consensus on each of the steps in GRADE, including the final recommendations; and (v) reach a consensus on additional 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 co-authors.

2.3. Process of preparing recommendations according to GRADE

We used the GRADE approach for developing recommendations [12,13,15]. The GRADE method provides a systematic approach for guideline makers for first

formulating the correct questions to be addressed regarding a prespecified patient population and subsequently approaching those questions by searching for and grading the available evidence for making final recommendations. The method was originally developed for treatments and interventions. As our goal was to develop recommendations for the application of a biomarker in the diagnostic process, we modified the GRADE approach based on recommendations reported by Brozek et al. [13], as shown in Fig. 1.

The GRADE approach comprised eight steps (Fig. 1):

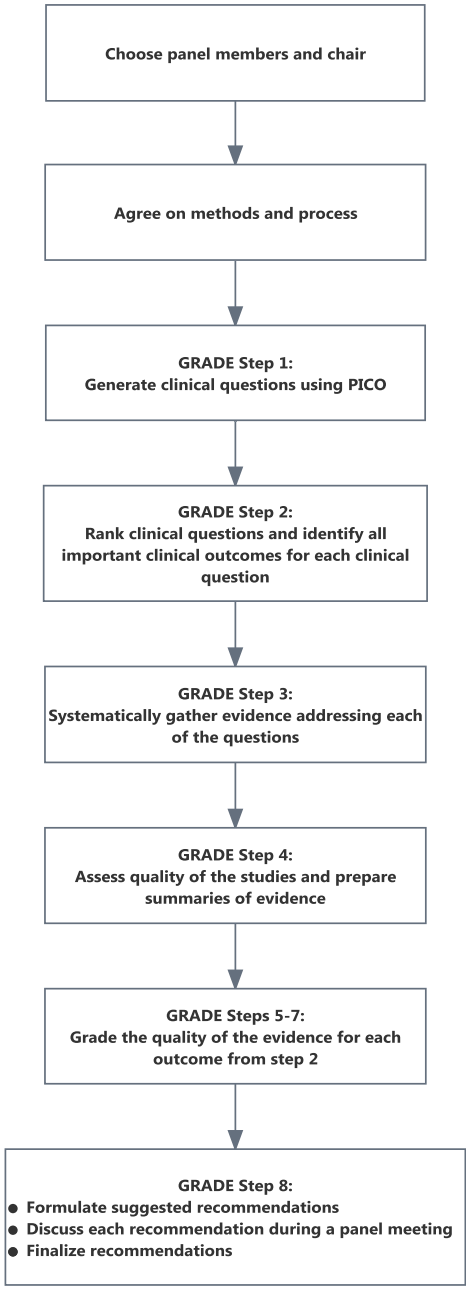

Fig. 1. Modified stepwise Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for the production of recommendations. PICO, population, diagnostic strategy or intervention, comparison strategy, and patient outcomes.

2.3.1. Step 1: Formulate and rank appropriate clinical questions for the application of GRADE

This group applied the PICO format that leads to focused clinical questions pertaining to a predefined population (P), diagnostic strategy or intervention (I), comparison strategy (C), and patient outcomes (O).

2.3.2. Step 2: Identify all important clinical outcomes, including harms, for each clinical question

The group identified and rated important clinical outcomes and discussed related operational procedures.

2.3.3. Step 3: Identify one or more high-quality systematic reviews and/or conduct a systematic review of the evidence

A systematic literature search to identify all the relevant meta-analyses and systematic reviews was conducted. For all the clinical questions, a MEDLINE search with predefined search strings was conducted, and more articles were then added from other sources, including reference lists from articles in the original search results. Finally, a second search was conducted to identify new articles that had been published after the first search round. Our literature search was performed so as to achieve the broadest coverage of published studies involving different aspects of the diagnostic performance of CSF biomarkers $A\beta_{1-42}$, total tau, and phosphorylated tau in patients with dementia.

MEDLINE search strings are as follows:

- (Cerebrospinal fluid OR CSF) AND diagnos* AND (Alzheimer OR AD OR dementia) AND (tau OR beta amyloid OR abeta) AND (sensitivity OR specificity)
- (Cerebrospinal fluid OR CSF) AND diagnos* AND (Alzheimer OR AD OR dementia) AND (tau OR beta amyloid OR abeta) AND (MRI OR PET OR SPECT)
- (Cerebrospinal fluid OR CSF) AND diagnos* AND (Alzheimer OR AD OR dementia) AND (tau OR beta amyloid OR abeta).

Health economic evaluations of CSF were obtained by updating an existing systematic review [16] for which the search string is available on request.

Articles that included patients with several dementia disorders were included, but articles that focused solely on the comparison between AD and healthy aging were excluded from this review because our aim was to provide recommendations for differential diagnosis in patients with dementia.

2.3.4. Step 4: Assess the quality of the studies and summarize the evidence

After searching for evidence and identifying the relevant clinical questions, the level of quality for each article was assessed for each relevant outcome by a subset of the working group and presented to the whole group at one of the face-to-face meetings.

To ensure the consistency of the grading system, a grading algorithm was used as an aid. The article received an upgraded level of quality if the patient population was consecutively recruited from a memory clinic or consisted of diagnostic groups typical for memory clinics, with at least 20 cases per group. The diagnostic criteria had to be well-described, and the diagnosis had to be based on clinical specialist consensus according to well-defined criteria and blinded to the CSF results. If this was not the case, the level of quality was downgraded. Detailed clinical and demographic data with clinical follow-up for at least 1 year increased the level of quality. Furthermore, a detailed description of the analytical method used in a single laboratory with reported cut-off values was seen as essential for high quality. An autopsy-confirmed diagnosis was included as a further criterion that increased the level of quality.

The results of grading the quality of evidence in each research article were added to the evidence tables, and the overall quality of evidence for each clinical question was discussed in the face-to-face meetings and used to formulate the final recommendations.

2.3.5. Steps 5–7: Grade the quality of the evidence for each relevant outcome defined in Step 2 as "high," "moderate," "low," or "very low." Consider factors that may raise the quality of observational studies from low to moderate or high and grade the overall quality of evidence for each clinical question

Steps 5–7 were prepared by subgroups and approved by the working group as a whole.

2.3.6. Step 8: Determine the direction and strength of a recommendation

Determinants of strength of recommendations according to GRADE are quality of evidence, balance between desirable and undesirable effects, values and preferences, and costs [15]. Step 8 was carried out in the form of group discussions and voting at the final face-to-face meeting.

2.4. Operational aspects

In addition, the group discussed several operational aspects, namely (i) the possible complications of LP and (ii) the interpretation of laboratory results, which were judged as important for the application of CSF biomarker investigations in clinical practice even if there was no published evidence available. In these cases, recommendations were made after focused discussions in the working group.

3. Results

3.1. GRADE steps 1–2: PICO definition of clinical questions

During the first workshop meeting, the working group identified five clinical questions to be addressed using the PICO method. The target population was defined as patients with dementia, the diagnostic strategy was CSF AD biomarkers ($A\beta_{1-42}$, tau, and p-tau), and the comparison was either with clinical measures alone or with other (imaging) biomarkers. The clinical questions and their rank of importance are shown in Table 1. The working group agreed unanimously in the ranking of the clinical questions.

The highest rank of one was given to one clinical question: identifying or excluding AD as the cause of dementia. The rank of two was given to predicting the rate of clinical progression in patients with mild or atypical dementia.

The three clinical questions on changing disease management, improving patient well-being, and reducing healthcare costs were discussed at length during the workshop. Although it was evident that there would be very little evidence available, the working group agreed to grade them on their relative importance. The group was divided as regards the questions concerning disease management and patient well-being, as a large number voted for the highest rank whereas a slight majority voted for a rank of two.

The working group identified possible complications of lumbar puncture and interpretation of conflicting biomarker results as two other important aspects to be taken into account. Recommendations on these operations aspects are provided as an adjunct to the recommendations.

3.2. GRADE steps 3–4: Evidence gathering and quality rating

The search for systematic reviews and meta-analyses produced 12 results that are summarized in Table 2.

The search for the diagnostic value of CSF biomarkers produced 344 articles, of which 57 fulfilled the inclusion criteria. The search for comparisons between CSF biomarkers and imaging biomarkers produced 913 articles, of which 5 articles were included in the final data analyses. The search for the added value of CSF biomarkers produced 1277 articles, of which 22 were selected for data analyses. There were no articles that fulfilled the criteria for the health economy subsection. A summary of the information on the articles identified for each subsection is shown in the Supplementary Tables 1–3.

During the initial search process, it was evident that there was very little or no evidence available for clinical questions

Table 1
The clinical questions and their rank of importance, based on workshop discussion (score 1: most important, score 3: least important)

In patients with mild dementia or dementia with atypical symptoms or an ambiguous dementia subtype diagnosis, will AD CSF biomarkers (alone or in combination) compared with (A) clinical measures and/or (B) other imaging biomarkers …	Rank
1. Identify or exclude AD as the cause of dementia?	1
2. Predict the rate of clinical decline?	2
3. Guide management?	2
4. Improve well-being?	2
5. Reduce healthcare costs?	3

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid.

Table 2
Systematic reviews and meta-analyses describing the performance of CSF AD biomarkers in the differential diagnosis of dementia

Reference	First author	Year	Type	Timespan searched	Other markers	CSF marker	Number of studies	Diagnosis of AD vs. normal aging	Diagnosis of AD vs. other dementias	Comment
[17]	Olsson	2016	Systematic review and meta-analysis	July 1984 to June 2014	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	131 151 89	+ + +		A CSF signature of elevated tau and p-tau, and reduced $A\beta_{1-42}$ is consistently observed in AD. The other investigated markers need more research.
[18]	Mo	2015	Systematic review and meta-analysis	January 2004 to October 2013		$A\beta_{1-42}$	17	+	+	Aβ has a potential utility for the differential diagnosis of AD.
[19]	Liu	2014	Meta-analysis	Not mentioned		Tau	16	+	+	Tau levels can distinguish between AD and VaD in the Chinese population.
[20]	Rosa	2014	Systematic review and meta-analysis	January 1990 to August 2013		$A\beta_{1-42}$	41	+		Aβ can discriminate AD patients from healthy controls with good sensitivity and specificity.
[21]	Ferreira	2014	Systematic review	January 1990 to September 2013		$A\beta_{1-42}$ Tau P-tau	7 Systematic reviews or meta and 26 primary studies	+	+	CSF biomarkers fail in distinguishing AD from other dementias.
[22]	Gaugler	2013	Meta-analysis	Until January 2012	FDG-PET	Tau	41 (7 meta-analyses and 34 reviews)	+	+	CSF tau and PET had comparable diagnostic performance.
[23]	Agarwal	2011	Meta-analysis	1998–2009		$A\beta_{1-42}$ Tau	7 11	+	+	The combination of high tau and low levels of Aβ might be useful in differential diagnoses if AD. High variation between studies, more studies are needed.
[24]	Bloudek	2011	Systematic review and meta-analysis	January 1990 to March 2010	MRI, CT, FDG-PET, SPECT	$A\beta_{1-42}$ Tau P-tau $A\beta_{1-42}$ and tau	20 30 24 12	+	+	SPECT and p-tau performed equally and better than the other biomarkers for the differentiation between AD and non-AD dementias.
[25]	van Harten	2011	Systematic review and meta-analysis	Until July 2010		Tau P-tau	52 28		+	Tau has insufficient diagnostic accuracy. P-tau had slightly higher accuracy.
[26]	Mitchell	2009	Meta-analysis	Until February 2009		P-tau	18	+	+	The clinical utility of p-tau for the differentiation between AD and other dementias was satisfactory to poor.
[27]	Formichi	2006	Systematic review	Not mentioned		$A\beta_{1-42}$ Tau P-tau $A\beta_{1-42}$ and tau combination	14 41 12 9	+	+	Aβ and tau not specific enough to distinguish between AD and other dementias. P-tau increases specificity for AD differential diagnosis.

[28]	Sunderland	2003	Meta-analysis	August 1989 to March 2003	$A\beta_{1-42}$ Tau	17 34	+	Clear reduction of Aβ levels and increase in tau levels in AD patients compared with controls.

Abbreviations: CSF, cerebrospinal fluid; AD, Alzheimer's disease; NFL, neurofilament light protein; $A\beta_{1-42}$, amyloid-β_{1-42}; p-tau, phosphorylated tau; NSE, neuron-specific enolase; VLP-1, visinin-like protein; HFABP, heart fatty acid–binding protein; $A\beta_{1-40}$, amyloid-β 1–40; $A\beta_{1-38}$, amyloid-β 1–38; sAPPα, soluble amyloid precursor protein alpha fragment; sAPPβ, soluble amyloid precursor protein beta fragment; MCP-1, monocyte chemotactic protein 1 (also called YKL-40); GFAP, glial fibrillary acidic protein; VaD, vascular dementia; FDG, fluorodeoxyglucose; PET, positron-emission tomography; MRI, magnetic resonance imaging; CT, computerized tomography; SPECT, single photon emission computerized tomography.

3–5. Therefore, it was decided in the workshop that these questions would be discussed using the indirect evidence available and group discussions.

When grading the evidence, it became apparent that there were many articles that did not fulfil the inclusion criteria, especially in the subsection comparing the diagnostic value of CSF biomarkers with that of imaging biomarkers, as the data given for each modality was insufficient. Furthermore, the articles included in the Supplementary Tables 1–3 present their data on diagnostic accuracy in many different forms, which made it difficult to directly compare the results. Another limitation was that the diagnoses were based on clinical criteria, and pathological studies have shown that about 20% of these diagnoses may be incorrect.

3.3. GRADE 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 the diagnostic performance of CSF AD biomarkers (S1), the comparison of CSF AD biomarkers with imaging biomarkers (S2), and the added value of CSF biomarkers over clinical measures (S3). The overall quality of the evidence was rated high in terms of identifying AD pathology as the cause of dementia. There were 10 studies where patients had been followed until autopsy, in addition to 33 studies with long-term clinical follow-up of the patients. However, in terms of the direct comparison of CSF AD biomarkers with imaging biomarkers in the diagnostic evaluation of a mixed group of patients with dementia, there were only a few studies available. There were three studies comparing CSF AD biomarkers with hippocampal atrophy on MRI, one study comparing them with medial temporal lobe atrophy on CT, one study comparing them with FDG-PET, and one study comparing them with hexamethylpropyleneamine oxime-single photon emission computerized tomography. The results of these studies were conflicting; so, the evidence was graded as moderate to low. We did not find any studies comparing CSF biomarkers with amyloid PET imaging.

Furthermore, there was only little evidence regarding whether CSF biomarkers alone or in combination with imaging biomarkers could predict the rate of progression in patients with dementia because cognitive decline was not quantified in most identified studies.

3.4. GRADE Step 8: Recommendations

The final recommendations for each clinical question and the strength of each recommendation, which reflects the strength of the scientific evidence, are shown in Table 3. The working group recommended the use of CSF AD biomarkers in patients with dementia to identify or exclude AD as the underlying cause of dementia. Based on the evidence, the recommendation was strong for patients with mild dementia but weak for patients with atypical or

Table 3
Final recommendations and recommendation strengths

	a) Relative to clinical measures		b) Relative to other biomarkers	
Clinical question	Answer	Strength of recommendation	Answer	Strength of recommendation
… identify or exclude AD as the cause of dementia?	Yes	In mild dementia: strong In atypical or ambiguous dementia: weak	No	In mild dementia: weak In atypical or ambiguous dementia: weak (no evidence)
… predict rate of clinical decline?	Yes	Weak	No	Weak (no evidence)
… guide management?	Yes, in ambiguous cases	Weak (no evidence)	No	Weak (no evidence)
… improve well-being?	No	Weak (no evidence)	No	Weak (no evidence)
… reduce healthcare costs?	No	Weak (no evidence)	No	Weak (no evidence)

Abbreviation: AD, Alzheimer's disease.

NOTE. In patients with mild dementia or dementia with atypical symptoms or an ambiguous dementia subtype diagnosis, will cerebrospinal fluid biomarkers (alone or in combination) as compared with (A) clinical measures and/or (B) other biomarkers ….

ambiguous dementia. The working group also recommended the use of CSF AD biomarkers to predict the future rate of clinical decline, but because of the lower amount of quality evidence, the strength of the recommendation was weak. In ambiguous cases of dementia, the working group recommended using CSF AD biomarkers to guide disease management, although the strength of this recommendation was weak because of the lack of evidence. The working group did not find sufficient evidence to recommend the use of CSF AD biomarkers to improve the patient's well-being or to reduce healthcare costs.

As the evidence regarding the comparison of CSF AD biomarkers with imaging biomarkers was conflicting, the working group could not recommend CSF biomarkers above any imaging biomarker.

3.5. Operational aspects of the application of CSF biomarkers in patients with dementia

3.5.1. Role of CSF biomarkers in the diagnostic evaluation of patients

Patients with dementia should be offered a thorough diagnostic evaluation to identify possible causes that require specific treatment and follow-up. This evaluation would at least include obtaining medical and family history from an informant, a psychiatric evaluation, a physical (including neurological) examination, neuropsychological testing, a cranial CT or MRI, and laboratory screening tests [8]. Adding CSF or another AD biomarker study to the primary diagnostic evaluation will help identify patients with dementia because of AD and thereby patients who may potentially benefit from cholinesterase inhibitors and memantine. This may also serve as a way to exclude AD in atypical cases. The available evidence does not support the choice of one biomarker above another. Thus, the choice of biomarker may depend on cost, availability, and other indications for performing the biomarker study (e.g., lumbar puncture in patients with possible inflammatory disease).

3.5.2. Interpretation of CSF biomarker results in patients who meet general dementia criteria

In cases where CSF biomarker results indicate dementia because of AD: in patients where the CSF levels of $A\beta_{1–42}$ are decreased and the levels of tau and phospho-tau are increased in relation to predefined cut-points, there is a greater probability that dementia is caused by AD. In such cases, the patient should be offered treatment with cholinesterase inhibitors or memantine and nonpharmacological treatment and counseling. Also, patients with dementia because of AD may be offered the possibility to participate in clinical trials with new, potentially disease-modifying drugs that target the neuropathological hallmarks of AD, of which the biomarkers are in vivo correlates.

In cases where the levels of CSF $A\beta_{1–42}$, tau, and p-tau levels are conflicting: in patients with reduced CSF $A\beta_{1–42}$, but normal tau and/or p-tau levels, AD as the cause of dementia is still a possibility, although less likely. In these cases, it is recommended that the CSF cell count and albumin quotient and the cut-offs for CSF $A\beta_{1–42}$ are checked. A CSF reanalysis may be considered and another (imaging) biomarker may be added to clarify the diagnosis. In patients with elevated tau or p-tau, but normal $A\beta_{1–42}$, other neurodegenerative disorders may be considered and other biomarkers such as $A\beta_{1–40}$ or imaging biomarkers may be added to clarify the diagnosis [29,30].

In cases where the levels of CSF $A\beta_{1–42}$, tau, and phospho-tau are normal: it is unlikely that AD is the cause of dementia. Other biomarker modalities may be used to clarify the diagnosis.

In cases where the levels of CSF $A\beta_{1–42}$, tau, and phospho-tau are close to the cut-off points: results close to the cut-off points should be interpreted with care. An inherent analytical variability of 10% for the used assays results in a gray zone with uncertain biomarker values [31]. In these cases, another (imaging) biomarker may be added to clarify the diagnosis or the analysis may be repeated.

3.5.3. Complications of lumbar puncture

The possible contraindications (increased intracranial pressure, coagulopathy, and a skin infection at the injection site) must be assessed thoroughly. For example, the current use of anticoagulants is a contraindication for LP, and the risk of cessation of anticoagulants for LP because of an AD biomarker test must be carefully considered. Of all the patients included in a multicenter LP feasibility study (n = 3868), 17% reported back pain, 19% reported headache, and 9% reported typical post-LP headache. An atraumatic needle and an age of >65 years were preventive [32]. When LP is performed correctly, in compliance with the consensus recommendations for the LP procedure, it is generally well tolerated and accepted with a low complication rate. Hence, in patients with dementia, although possible contraindications should be considered carefully in the individual patient, the value of a lumbar puncture for diagnostic purposes usually exceeds the risk of complications from the procedure.

3.5.4. Costs and availability

CSF biomarker cost estimates range from €130–622 [33–35]. The estimates are lower than related biomarkers in FDG-PET ($1671 [1999] [36], $1661 [assumed in 2001] [37], €507 [assumed in 2004] [38]). A routine clinical CSF biomarker test is readily available, and the samples can be sent for analyses elsewhere. However, LP requires personnel with the appropriate training and facilities. The introduction of lumbar punctures into the routine clinical diagnostic workup would therefore raise logistical issues of upscaling that must be addressed [39].

One study researched the cost-effectiveness of CSF biomarkers [40]. Several aspects limited the generalizability of the study. The use of the intermediate outcome of additional costs per additional correct diagnosis in combination with the unknown maximum willingness to pay for one additional correct diagnosis limits the advising of adopting the CSF test in clinical practice from a societal perspective. Furthermore, the CSF test was simulated as a replacement test in the current diagnostic workup. Therefore, the results of this study are not considered as evidence for cost-effectiveness in terms of dementia in a clinical setting.

Because of a lack of evidence, the group could not recommend the use of CSF biomarkers to reduce healthcare costs.

4. Discussion

This article presents the outcomes of an expert working group, established under the JPND BIOMARKAPD program, which aimed to produce recommendations for the clinical application of CSF biomarkers in the differential diagnosis of patients with dementia. By applying the GRADE method and a systematic literature search, a consensus was reached on the recommendations for several aspects of the clinical application of CSF biomarkers in this group of patients.

An accurate and early diagnosis is important to be able to differentiate patients with AD from patients suffering from dementia because of other causes and to ensure appropriate pharmacological treatment, counseling, and inclusion in clinical trials.

The application of CSF AD biomarkers in the clinical routine has been hampered by a lack of harmonization and standardization. There is also uncertainty about the role of CSF in relation to other biomarkers. The use of biomarkers in patients with subjective cognitive complaints or MCI to predict future dementia or diagnose AD at a very early stage is associated with a range of unique ethical and logistical challenges that are discussed in a separate article [11]. For patients who have already developed dementia and are referred to diagnostic evaluation, the differential diagnosis of AD versus other dementia disorders may be challenging, particularly in atypical and uncertain cases.

Hence, the most important clinical question was defined by the GRADE working group as "in patients with mild dementia or dementia with atypical symptoms or an ambiguous dementia subtype diagnosis, will CSF biomarkers for AD compared with clinical measures alone or other (imaging) AD biomarkers identify or exclude AD as the cause of dementia?"

We found sufficient evidence to support the use CSF biomarkers alongside clinical measures to identify or exclude AD as the underlying cause of dementia. In terms of comparing the diagnostic performance of CSF biomarkers to other AD biomarkers, medial temporal lobe atrophy on MRI, FDG-PET, or amyloid PET, there were only a few articles on the topic, and the results were conflicting as to the superiority of CSF AD biomarkers. Thus, the working group did not find sufficient evidence to support a recommendation of CSF biomarkers above any other (imaging) biomarker for to identify or exclude AD as the cause of dementia.

Furthermore, we did not find any published studies on the potential effect of CSF biomarkers on disease management, improving the quality of life or healthcare costs. Hence, these questions were indirectly assessed in light of the available literature and group discussions. The working group recommended the application of AD CSF biomarkers to guide disease management in ambiguous dementia cases. However, the group did not find evidence to support any recommendation of using AD CSF biomarkers to improve patient well-being or reduce healthcare costs.

Many of the studies found in our literature search described the diagnostic accuracy of CSF biomarkers in the differentiation between AD and healthy ageing, and only a few studies addressed the differentiation between AD and other dementia diseases. For clinicians managing patients with dementia, differentiation between healthy ageing and AD is not highly relevant, whereas it is important to obtain a reliable differential diagnosis between different diseases causing dementia.

In this article, the evidence for the CSF AD biomarkers was presented separately from the value of analyzing other CSF measures with potential diagnostic importance. The analysis of CSF for AD biomarkers is an easily accessible test, particularly in terms of patients for whom lumbar puncture with routine CSF analysis is already indicated. Thus, CSF analyses may serve several diagnostic purposes at the same time, for example, investigation of the blood-brain barrier integrity, presence of neuroinflammation, or infection and elucidation of whether AD is the cause of dementia.

The strength of our set of recommendations was developed using a systematic approach, the GRADE method, and by an international, multidisciplinary team with long-term clinical and research experience and based on the review and evaluation of a vast amount of research evidence and five face-to-face consensus meetings. The GRADE method was originally developed for therapeutic interventions, and the translation to diagnostic interventions is complex, particularly in a field, as the present, with significant gaps in evidence. Even with the application of a systematic approach, it is a potential limitation that the outcome of the consensus method is sensitive to the composition of the group and to group dynamics.

Our literature search emphasized a need for more studies that compare the value of CSF and imaging biomarkers in the differential diagnosis of patients with dementia and to fill the gap of missing evidence on the important clinical question of improving patient well-being (clinical validity and utility). More evidence would help inform clinicians about the choice of biomarkers, which should be based on evidence and on potential contraindications, availability, and cost.

In conclusion, using a GRADE-based approach based on currently available evidence, the BIOMARKAPD working group recommended the use of CSF AD biomarkers in the diagnostic evaluation of patients with dementia as a supplement to clinical evaluation, particularly in uncertain and atypical cases, to identify or exclude AD as the underlying cause, after having ranked this clinical question as the most important. The working group also recommended the use of CSF biomarkers to predict the rate of clinical decline. CSF AD biomarkers are readily accessible and may help to identify or exclude AD as the cause of dementia with important implications for treatment. However, no recommendations could be given on the choice of CSF biomarkers versus other potential AD biomarkers because of insufficient or conflicting evidence.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2016.09.008.

RESEARCH IN CONTEXT

1. Systematic review: The authors developed recommendations for use of CSF AD biomarkers in diagnostic evaluation of dementia, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method based on systematic review of the literature and structured group discussions. Despite numerous clinical studies on CSF AD biomarkers, there were no evidence-based recommendations available to guide the application and interpretation of CSF biomarkers in the evaluation of patients with dementia.
2. Interpretation: The group recommends the use of CSF AD biomarkers as a supplement to clinical evaluation, to identify or exclude AD as the cause of dementia, for prognostic evaluation, and for guiding management of patients, particularly in atypical and uncertain cases.
3. Future directions: Studies comparing the diagnostic value of CSF and imaging biomarkers for AD are needed, as well as studies assessing whether the application of biomarkers in diagnostic evaluation can improve patient well-being as a final outcome.

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