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What is the clinical impact of cerebrospinal fluid biomarkers on final diagnosis and management in patients with mild cognitive impairment in clinical practice? Results from a nation-wide prospective survey in France

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ABSTRACT

Objectives New diagnostic criteria for Alzheimer's disease (AD) include cerebrospinal fluid (CSF) biomarkers that allow diagnosis at the stage of mild cognitive impairment (MCI). However, the impact of CSF biomarkers in MCI populations in clinical practice has been poorly evaluated. The objective of this study is to assess the use and impact in clinical practice of AD CSF biomarkers in French memory clinics.

Design We performed a nation-wide, prospective survey between March 2012 and September 2014. Data over the same period was extracted from the French National Database (Banque Nationale Alzheimer, BNA) and compared with the results of the survey.

Setting 29 secondary and tertiary memory clinics in France.

Participants Clinicians prescribing lumbar puncture (LP) in order to measure AD CSF biomarkers. Clinicians completed a two-part questionnaire for each of their patients undergoing LP.

Primary and secondary outcome measures Assessment of diagnosis, level of confidence before and after CSF biomarkers and impact on management in patients who underwent LP for CSF AD biomarkers in clinical routine.

Results 977 questionnaires were completed, of which 61 were excluded because of unknown initial/final diagnosis or non-contributory CSF results. Of 916 patients reported, 153 (16.7%) had MCI as the initial diagnosis, of which 51 (33.3%) displayed an AD profile. CSF biomarkers resulted in a change in diagnosis in 44 patients (28.8%). Confidence level significantly increased after LP (8.3±1.4vs 6.73±1.18, p<0.0001), and CSF results modified management in 71/156 patients (46.4%), including 36 (23.5%) enrolled in clinical trials. Comparison of change in diagnosis with the BNA population revealed no difference (32.24%, p=0.4).

Conclusion This nation-wide survey, reflecting clinical practice in French memory clinics, describes the impact of CSF AD biomarkers in patients with MCI in clinical practice.

Strengths and limitations of this study

- First nation-wide survey evaluating clinical practice regarding the use of Alzheimer's disease cerebrospinal fluid biomarkers in memory clinics.
- 977 patients in 29 secondary and tertiary memory clinics over a 30-month period over the whole French territory.
- Results of the study corroborated by an analysis of the data from the French National Alzheimer Database over the same period.
- No central review of final diagnosis in order to reflect actual clinical practice.
- Practice in primary care memory clinics was not assessed by this study.

INTRODUCTION

Mild cognitive impairment (MCI) is a transitional state from normal cognition to dementia that may be due to various aetiologies.[1 2] During the past decades, cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) have been identified that reliably indicate neuropathological lesions.[3 4] Based on these advances, new criteria for the diagnosis of AD in clinical research, including CSF

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biomarkers, have been proposed.[1 5] Those criteria allow diagnosis at the very early stages of the disease (MCI due to AD/prodromal AD) (international working groups 1 and 2 and National Institute of Aging–Alzheimer Association criteria) and could predict progression to AD with good accuracy. Indeed it has been shown that a combination of low Abeta–42 and high tau and phospho-tau predicts evolution to AD with 95% sensitivity and 87% specificity in a population of patients with MCI over a course of 4–6 years, while variations are observed when biomarkers are performed in other populations (ie, healthy individuals).[6 7] Moreover, the incremental value of CSF biomarkers, in addition to clinical, neuropsychological and imaging work-up for the prediction of progression to AD in clinical practice setups, has been shown and estimated by several studies.[8 9] Thus, biomarkers are widely used in clinical research but also in a lesser extent in routine clinical practice.[10 11] French guidelines for the diagnosis and treatment of AD and associated disorders propose to assess CSF AD biomarkers 'in case of diagnostic uncertainty and particularly in young patients'.[12] Consequently, lumbar punctures (LPs) are performed on a daily basis in patients with cognitive troubles in French memory centres to measure AD biomarkers in the CSF. However, their actual impact on clinical practice regarding diagnosis, thinking efficacy and management in patients with MCI is unknown.

METHODS

We conducted a prospective nation-wide survey between March 2012 and September 2014. An invitation was sent to the 400 French memory clinics, including the 28 French tertiary centres where most LPs for CSF biomarkers are performed. Secondary and tertiary memory centres were recruited on a voluntary basis. Detailed data regarding participating clinicians have been described previously.[13]

Survey design

In participating centres, clinicians completed a two-part questionnaire for every patient they considered eligible for CSF biomarkers according to national guidelines.[9] The first part of the questionnaire was to be completed before LP. In this part, clinicians had to indicate all their diagnostic hypotheses, including their main hypothesis and, finally, their level of confidence in the proposed diagnosis on a 10-point scale. In the second part (completed after CSF biomarker results), clinicians indicated the biological profile (AD profile, non-AD or non-conclusive), their final diagnosis, their level of confidence in the final diagnosis and the impact of the CSF results on the management of patients (ie, enrolment in a clinical trial and financial assistance).

CSF biomarkers and diagnosis

CSF biomarker measurements were performed in local laboratories. The AD profile was considered when all three biomarkers were abnormal according to local laboratories cut-offs (low Abeta, high tau and phospho-tau). In order not to interfere with clinical practice, no inclusion criteria were provided to the clinician regarding diagnostic workup and diagnosis of MCI, and the diagnoses of MCI, AD and other pathologies were made by the clinician according to the international criteria without validation by an external committee.

External validity

To evaluate the external validity of our results, we compared our data with those of the French National Database (Banque Nationale Alzheimer, BNA, records of memory clinics through the whole French territory) during the same period.[14] Patients who had received a main diagnosis of MCI and in which LP had been performed for the assessment of CSF AD biomarkers during the study period were included in the analysis. A change in diagnosis was defined as a modification from the main diagnosis of MCI to any other main diagnosis during follow-up.

Statistics

Main confidence levels before and after LP were compared in the survey population. Rates of diagnosis change and reclassification as AD after LP were compared between survey and BNA populations. We compared the continuous quantitative variables using one-way analysis of variance and qualitative variables using χ^2 tests. Statistics were performed using GraphPad Prism V.6.

Patient and public involvement

No patients were directly involved in the design, recruitment or conduct of the study. The results of this study will not be disseminated to patients about whom clinicians fulfilled the survey questionnaires.

RESULTS

As shown in the study flowchart (figure 1), 977 questionnaires were prospectively collected from 29 participating memory clinics during the survey period. Sixty-one (6.2%) were excluded due to unknown initial/final diagnosis or non-contributory CSF results due to interpretation or technical problem. There was no significant difference in the ratio of patients with MCI has main initial diagnostic hypothesis between those included and excluded (13, 21.3%) from the study (p=0.35).

Among 916 patients included in the analysis, 153 (16.7%) had MCI as the main initial diagnosis. The mean age was 70 years and 81 patients (52.9%) were women. These characteristics did not differ from the general population of the study (69.2 years and 50.2% women). Among patients with MCI, 51 (33.3%) displayed a CSF AD profile, while 89 (58.2%) had a profile not in favour of AD and 13 (8.5%) had non-contributory CSF biomarkers.

Overall, a change in diagnosis following the CSF results occurred in 44 (28.8%) patients. Final diagnoses depending on CSF results are shown in figure 2A. The

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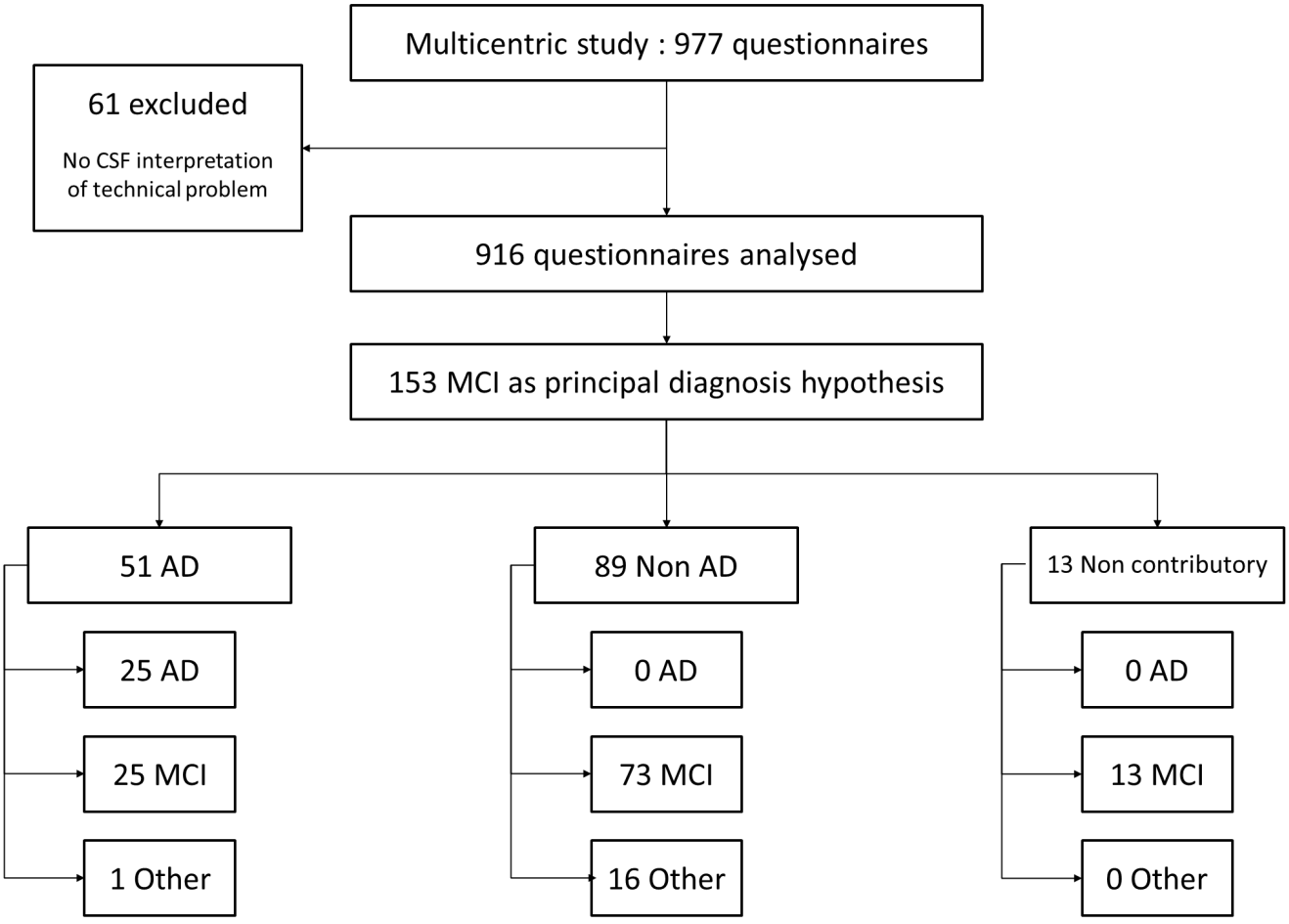


Figure 1 Study flowchart. AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment.

highest incidence of change in diagnosis was observed when the biological profile was in support of AD. In those patients, clinicians changed their diagnosis in 51% of the cases (in 26 patients, 25 patients were reclassified as having AD and 1 patient received a diagnosis of primary progressive aphasia). Among the 89 patients with MCI with non-AD biological profiles, 73 (82%) remained having MCI, while 16 patients (18.0%) were reclassified as having cognitive troubles of other origin. All patients with non-contributory CSF profile remained having MCI.

Mean diagnosis confidence levels before and after CSF analysis are displayed in figure 2B. The mean confidence level before LP was 6.73±1.8. CSF biomarkers resulted in a significant increase in the mean confidence level in the proposed diagnosis (8.3±1.4, p<0.0001). Subgroup analysis showed a similarly significantly increased mean confidence level of 8.2±1.5 in patients with non-AD CSF profiles and 8.8±1.5 in patients with the AD CSF profiles (p<0.05) and a non-significantly increased confidence level in the group with non-contributory CSF profile (7.077±1.7).

Symptomatic treatment by cholinesterase inhibitor was introduced in 30 patients (19.6%) after LP. Most patients who received cholinesterase inhibitors after LP had CSF biomarkers indicative of AD (28/51, 54.9%), among whom 17 (60.7%) had been reclassified as having AD. In addition, the management of the patients was modified after CSF results for 71/153 patients (46.4%): full health insurance cover for 19 patients (12.5%), social support aids for 10 patients (6.5%), enrolment in a clinical trial for 36 patients (23.5%) and other measures in 33 patients (21.6%). The impact of CSF results on patient management was even higher in the group of patients with CSF results in favour of AD, with a change in management in 32 of those patients (62.7%): full health insurance cover for 16 patients (31.4%), social support aids for 8 patients (15.7%), enrolment in a clinical trial for 17 patients (33.3%) and other measures for 13 patients (25.5%).

Over the study period, in the BNA, 39 651 memory clinic visits of patients with an initial diagnosis of MCI were recorded. Among them, 763 (1.92%: 48.49% women, mean age 70.58 years) underwent LP for AD biomarkers. This resulted in a change in diagnosis in 246 patients (32.24% of patients with MCI who underwent LP). Of those patients, 61.38% were reclassified as having AD, while 38.62% received a different diagnosis. There were no significant differences between our survey and BNA

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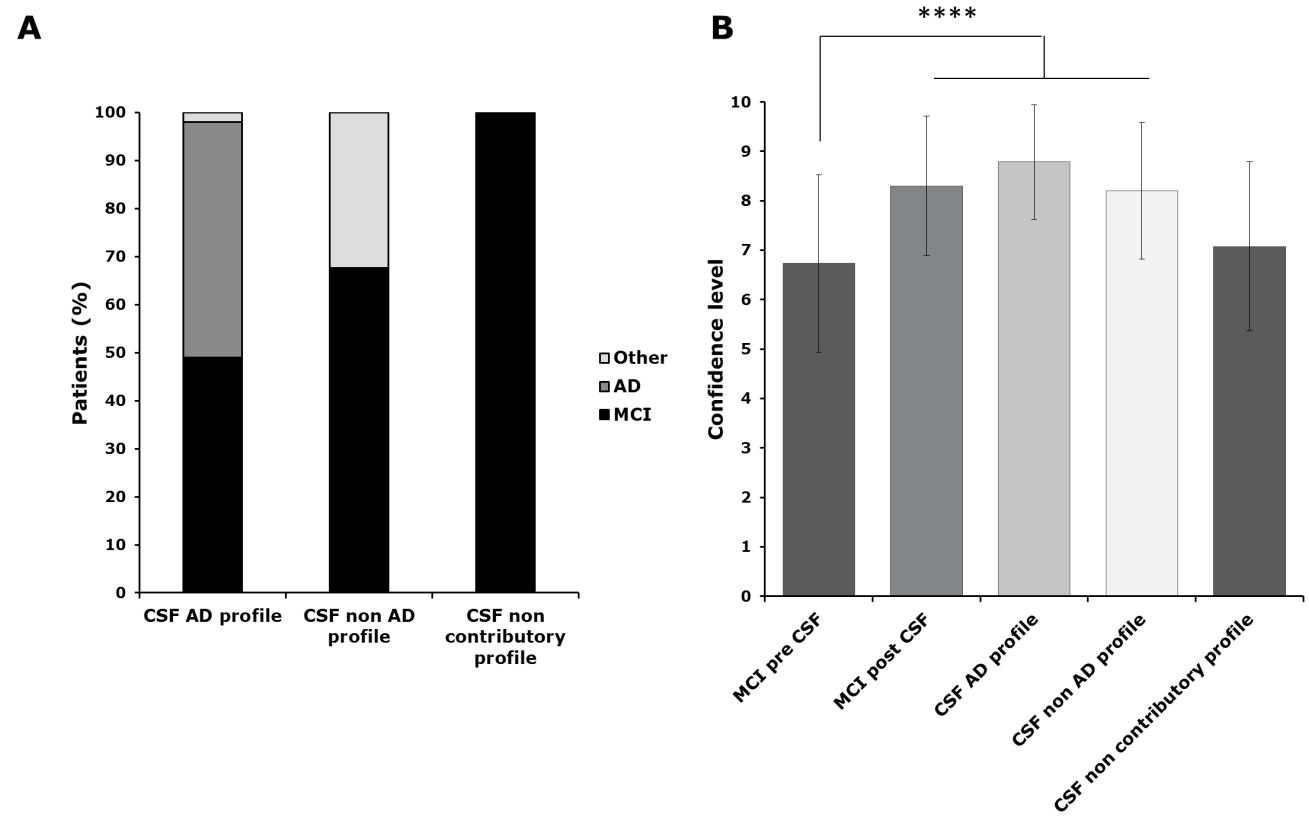


Figure 2 (A) Main diagnosis after CSF AD biomarkers, depending on the CSF profile in patients with MCI. (B) Confidence level in the proposed diagnosis before and after CSF AD biomarkers in the MCI population, depending on the CSF profile. AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment.

populations for the rate of diagnosis change and reclassification as AD (p=0.40 and p=0.57, respectively).

DISCUSSION

The aim of this prospective national study was to understand current practice regarding the use and impact of CSF AD biomarkers in the care of patients with cognitive troubles in memory clinics. These questions are of particular interest in patients with MCI as MCI is often associated with high diagnosis uncertainty regarding the underlying cause. Moreover, early diagnosis of AD in patients with MCI may have a dramatic impact on the management of patients. For instance, early results of the Imaging Dementia - Evidence for Amyloid Scanning (IDEAS) Study that evaluates the impact of amyloid positron emission tomography (PET) imaging on patient management in patients with MCI and atypical dementia showed that PET imaging resulted in a change in 67.8% of patients with MCI as compared with 65.9% of patients with dementia.[15] It also has direct consequences on their ability to participate in clinical trials and on the statistical power of those trials.[16]

Results of this study suggest that patients with MCI represent a minority of those undergoing LP for CSF AD biomarker evaluation among patients consulting in secondary and tertiary memory centres in France. This is in accordance with the French national recommendations but in contradiction with the apparent positive impact of CSF biomarker results on diagnosis and management that we report. Indeed, while diagnosis reclassification rates appear lower in patients with MCI than in the general population of the study,[13] confidence levels in the proposed diagnosis after CSF show a trend for higher confidence in the MCI population (8.035, p=0.06), and impact on management is significantly higher in patients with MCI than in patients without MCI (only 310/916 patients (33.8%) in the whole cohort had a change in management after CSF results, $p=2.65\times10^{-5}$). Of note is the fact that clinicians relied on CSF results to prescribe cholinesterase inhibitors, the main symptomatic treatment for AD in 93.3% of patients (28/30 patients in which this treatment was introduced).

Surprisingly, while the percentage of biomarker non-contributory results is low, only half of the patients with MCI with a CSF profile indicative of AD receive a final diagnosis of AD. This observation may be a consequence of the coexisting and overlapping concepts of MCI due to AD and prodromal AD. Thus, it possibly reflects the difficulties for clinicians to deal with these competing concepts in everyday practice.[1 5] A study by Vos *et al* compared the main diagnostic criteria for AD in patients with MCI and analysed their properties and

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respective abilities to predict evolution towards AD. This work well underlines the overlaps and differences that exist between criteria and supports the use in clinical practice according to the National Institute of Aging Alzheimer Association criteria.[17]

Importantly, the rates of CSF biomarkers indicative of AD and of change in diagnosis we report are highly reminiscent of those published in previous works.[11 18] Moreover, data regarding diagnosis reclassification rates and reclassification to AD in our detailed survey are in line with those of the French national database. This indicates a good external validity of our result and confirms the impact of CSF biomarker results in clinical practice in France. Interestingly, recent cost–utility analyses, although based only on expert assumptions of health related outcomes, suggested that performing CSF AD biomarkers in patients with MCI might also be cost-effective.[19 20] Logically, this effect would be reinforced in case of a disease-modifying treatment availability.[21]

This is the first nation-wide prospective survey exploring the impact of CSF biomarkers on diagnosis and management of patients with MCI in clinical practice. With almost 1000 patients included and good external validity, we consider that our results accurately reflect the clinical practice in France. However, this study has several limitations. First, it is a declarative survey on a voluntary basis that limits its exhaustiveness. It is also possible that responders might have a more 'biomarker-based' practice than non-responders. However, as this study focuses on the actual impact of CSF AD biomarker results on clinical practice and consequences on clinician decisions rather than the use of CSF biomarkers, we assume that this would not skew the conclusions of this study. Additionally, the transversal character of the study hinders the analysis of the long-term impact of CSF biomarker results on the diagnosis and the management of patients.

However, the study results definitely show that LP results can change the diagnosis and management in MCI populations in clinical practice. Altogether, our results support the need for further large-scale studies on the impact of CSF biomarkers on health outcomes in patients with MCI.

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Contributors EC analysed the data and wrote the manuscript. FML contributed to the constitution of the database and wrote the first draft of the manuscript. A-CT contributed to the constitution of the database. DW, JD, EM, ED, AG, BC, VdlS, AJ, FB, EA-B, CM-A, MQ, SS, NP, EB, FP, DH, JH and ePLM participants performed lumbar puncture, managed the patients and filled in the questionnaires. PR extracted the data from the French National Alzheimer Database. CP conceived and coordinated the study and supervised the writing of the manuscript. All authors revised the manuscript.

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