Experiences with cerebrospinal fluid analysis in Dutch memory clinics

Running head: CSF analysis in memory clinics

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Abstract

Background: Evidence on cerebrospinal fluid (CSF) analysis to demonstrate Alzheimer's disease has not yet been implemented in diagnostic guidelines.

Methods: We investigated the use of CSF analysis in a survey among all known memory clinics in the Netherlands, of which 85 of 113 (75.2%) responded.

Results: Sixty percent of respondents used CSF analysis, in 5% (median) of patients. The analysis almost always confirmed the working diagnosis in 68.4% and sometimes changed it in 28.2%. Complications occurred very infrequently (0%, median) and were mild. Reasons not to perform CSF analysis included the lack of clear recommendations in diagnostic guidelines.

Conclusions: These results ask for a guideline update to clarify the use of CSF analysis as an add-on diagnostic method.

Introduction

Recent hypothetical models on Alzheimer's disease (AD) biomarker dynamics regard cerebrospinal fluid (CSF) biomarker analysis of amyloid β_{42} ($A\beta_{42}$), phosphorylated tau (p-tau) and total tau (t-tau) to demonstrate AD as evidence based.[1] Most diagnostic guidelines, however, have not yet implemented this evidence. In contrast to the latest AD research criteria,[2] the most frequently used AD-criteria, NINCDS-ADRDA and DSM-IV-TR, do not include CSF biomarkers.

Triggered by the gap between biomarker evidence and guidelines, we aimed to investigate the current use of CSF analysis in the diagnostic work up of Memory Clinic (MC) patients and the clinician's opinion on reasons to use CSF analysis.

Methods

A questionnaire was sent to all known MCs in the Netherlands, i.e. all centres known to perform early dementia diagnostics in a multidisciplinary context. MCs that were approached were requested to check our list of MCs to see if any centres were missing. The questionnaire was distributed by e-mail and could be returned by e-mail or on paper. Participants not responding within two weeks were approached by phone or in writing. Approval of this study was not needed in accordance with local regulations.

With respect to CSF analysis, questions were asked about frequency of use; type of patients in whom lumbar puncture was performed; influence of the results on diagnosis; reasons to apply or not to apply this method; and frequency and type of complications.

One hundred and thirteen MCs were approached, of which 85 responded (75.2%), and 84 completed at least part of the questions on CSF analysis. Sixty-two MCs of these 84 were based in general (54) or academic (8) hospitals.

Results

Fifty MCs (59.5% of respondents, 46 hospital based) used CSF analysis, in 5% (median, range 0.01-75%) of patients, most often in patients suspected of mild dementia (table 1). Most of the MCs found that the results almost always confirmed the working diagnosis (68.4%) and hardly ever changed it (53.8%), although change was reported to occur sometimes by 28.2% of MCs. The results hardly ever contradicted the working diagnosis, according to 61.5% of MCs.

Reasons to perform CSF analysis were diagnostic uncertainty; to differentiate between dementia types; or to exclude certain diseases such as Creutzfeldt-Jakob disease or neurolues; young age of onset; positive family history; the desire for more diagnostic certainty, e.g. in case of implications of the diagnosis for the patient's employment. Research on new biomarkers was not mentioned in this sample of memory clinics. Reasons not to perform CSF analysis included the lack of clear recommendations in guidelines; not being convinced of the diagnostic advantage; other diagnostic methods being more accessible; the procedure being too invasive; the presence of contra-indications for lumbar puncture such as an intracerebral tumor or use of anticoagulants.

Lumbar puncture failed in 0% (median, range 0-10%). Five percent (median, range 0-50%) of patients refused to undergo lumbar puncture. Complications occurred in 0% (median, range 0-10%). Post-puncture headache was the only complication reported.

Discussion

This survey shows that CSF analysis to diagnose dementia has found its way into clinical practice, although there is a wide range in the frequency of use. The proportion of centres using CSF analysis in the Netherlands is largely the same as the proportion of expert centres across Europe using CSF analysis routinely.[3] The analysis was most often found to confirm the diagnosis, and not to contradict it, although it sometimes led to a change in diagnosis. We may conclude that in clinical practice, CSF analysis is perceived as sufficiently valid to change the pre-test probability of AD and of inflammatory diseases, and thus to change the diagnostic hypothesis. The biomarkers $A\beta_{42}$, p-tau and t-tau are analysed in two core laboratories in the Netherlands (located in Nijmegen and Amsterdam), of which the Nijmegen laboratory is certified as the national reference laboratory for CSF analyses for AD, which diminishes the analytical variance that is still seen in AD biomarker analyses among various laboratories. Newsletters with reference standards are regularly sent out from the reference centre to reduce heterogeneity in interpretation of the biomarker values. However, the interpretation of the data itself could not be controlled for in this study.

We did not ask MCs to specify the exact analyses that were performed. In an unknown proportion of MCs the standard AD biomarkers $A\beta_{42}$, p-tau and t-tau may have been used, but in some MCs other unspecified CSF analyses may have been applied. Chosen analyses depend on the clinical context. As shown by the stated reasons to perform CSF analysis, this is both used to exclude diseases and to gain more certainty about the presence of AD pathology. The percentages of confirmation and change may therefore reflect test characteristics of the analysis, but also the selection of patients in whom lumbar puncture is performed. Complications occurred infrequently and were mild, which confirms previous reports suggesting high safety of lumbar puncture.[4]

The lack of clear recommendations in dementia guidelines, the uncertainty perceived in clinical practice and the heterogeneity of the application of CSF diagnostics found in this survey all ask for a dementia guideline update, in which the use of CSF analysis as an add-on diagnostic method should be clarified. Although relatively high inter-assay variability of CSF biomarker analyses will make it impossible to provide a single reference value in a guideline, a high diagnostic performance of CSF biomarkers in diagnosing the neurodegenerative diseases causing dementia can be reached when laboratories establish their own reference values.[5,6] Studies on cost-effectiveness of CSF analysis and other AD biomarkers are urgently needed to elucidate the most efficient diagnostic pathway, considering all currently available diagnostic biomarkers.

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Conflict of interest

No conflict of interest

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Table 1. Characteristics of the type of patients and results of using CSF biomarkers in dementia diagnostics in Dutch memory clinics

	Median (range)	**No. of MCs[a] that responded (%[b])**
Type of patient		
Subjective complaints	0% (0-75%)	26 (52%)
Cognitive disorder, no dementia	5% (0-95%)	32 (64%)
Mild dementia	15% (0-100%)	33 (66%)
Moderate-severe dementia	2% (0-80%)	29 (58%)
Failing procedure	0% (0-10%)	25 (50%)
Refusal patient	5% (0-50%)	30 (60%)
Complications	0% (0-10%)	23 (46%)
CSF confirms diagnosis	**N (%[c])**	38 (76%)
Never	1 (2.6%)	
Hardly ever	0 (0%)	
Sometimes	11 (28.9%)	
Almost always	26 (68.4%)	
Always	0 (0%)	
CSF changes diagnosis		39 (78%)
Never	6 (15,4%)	
Hardly ever	21 (53,8%)	
Sometimes	11 (28,2%)	
Almost always	1 (2,6%)	
Always	0 (0%)	
CSF contradicts diagnosis		39 (78%)
Never	5 (12,8%)	

Hardly ever	24 (61,5%)
Sometimes	10 (25,6%)
Almost always	0 (0%)
Always	0 (0%)

[a] MC = memory clinic

[b] percentage of the MCs responding to the specific question

[c] percentage of the 50 MCs using CSF analysis