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► To cite this version:

Constance Delaby, Charlotte E Teunissen, Daniel Alcolea, Elodie Bouaziz Amar, Anne Beaume, et al.. International Initiative for Harmonization of Cerebrospinal Fluid Diagnostic comments in Alzheimer's Disease. AAIC Alzheimer's association, Jun 2021, VIRTUAL CONFERENCE, United States. hal-04842812

HAL Id: hal-04842812

<https://hal.science/hal-04842812v1>

Submitted on 17 Dec 2024

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International Initiative for Harmonization of Cerebrospinal Fluid Diagnostic comments in Alzheimer's Disease.

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Introduction/background

The quantification of cerebrospinal fluid (CSF) biomarkers (Amyloid beta peptides [Aβ1-40 and Aβ1-42], tau protein and its phosphorylated form phospho-tau (ptau181)) is progressively implemented in specialized laboratories as an aid for the multidisciplinary diagnosis of Alzheimer's disease (AD). However, no consensus has yet been reached between the different laboratories involved to define the most appropriate conclusions/comments based on the profile of the quantified biomarkers. Therefore, although the methods of biomarker analysis are often similar between the laboratories involved in this clinical task, the conclusions reported to the responsible physician (neurologist or psychiatrist) may be very different. Harmonization of this report is therefore necessary so that the management and stratification of patients in research protocols can be similar regardless of where the analysis is performed. The objective of the present work, supported by the ISTAART Biofluid Based Biomarkers PIA, is to propose a harmonized report between the different specialized laboratories involved in accordance with their own practice, and to whom the report is transmitted.

Methods

Clinical centers
A total of 34 specialized laboratories (involved in CSF biomarkers measurement) across the world accepted to be part of our project of diagnostic's comments harmonization (represented countries: Austria, Belgium, Canada, France, Germany, Italy, Netherland, Poland, Spain, Sweden, United Kingdom, USA).

Questionnaire sent to laboratories
As a first step, we defined the 5 most typical biochemical profiles, according to the level of CSF biomarkers and their combination. For each profile, each laboratory was asked to provide us with the comments/conclusions given in routine clinical practice. We then compiled all the comments into a single file and asked participants to rank their top three comments for each profile according to their use in clinical practice. The next step will be to discuss and decide on the most relevant reports at a consensus conference.

Recipients of CSF biomarker interpretation reports
As the report may need to be adapted to the recipients, we also asked the participants to answer a series of additional question such as: who requests the analysis, what is the delay before sending back the results, to whom is the report addressed, is clinical information available to the biologist/pathologist.

Report comments classification for each biochemical profile defined

Laboratories were initially asked to indicate, according to their own practice: the **analytical approach** used to quantify the CSF biomarkers, the **cut-off** value of normality for each biomarker (and the way of its obtention), the **comments/report transmitted** for each biochemical profile defined. In a second step, we pooled the 34 answers obtained and proposed to each laboratory to choose, among the most frequent reports (with indicated frequency among the laboratories), the **2 most relevant for each biochemical profile**, according to their reliability in clinical practice (see table above and example for the "only amyloid" situation).

Biochemical profile N: >cut-off, P: <cut-off	All normal	All pathologic	Only amyloid	Total Tau alone	Tau/p-Tau
Ratio Aβ42/40 or Aβ42	N	P	P	N	N
t-tau	N	P	N	P	P
p-tau	N	P	N	N	P
PROPOSED COMMENTS Select 1 or 2 preferred comments and order them #1 and #2	Biochemical profile not evocative of AD (30%)	Biochemical profile suggestive of AD (26%)	Profile compatible with an amyloidopathy (36,6%) #1	Isolated increase of Tau (if Tau>1200, it confirms a CJD suspicion) (20%)	Atypical profile, likely compatible with tauopathy (30%)
	Biochemical profile not suggestive of AD (16%)	Profile evocative of AD (19%)	Isolated amyloidopathy indicative of AD pathologic change in the AD continuum (6,5%)	Profile non evocative of AD, but compatible with tauopathy or important cytotoxicity (stroke, trauma, epilepsy, vascular dementia, paraneoplastic syndromes)... (16,5%)	Atypical profile, which can not rule out AD (13%)
	No biomarker evidence of Alzheimer's pathology (13%)	Biochemical profile of CSF compatible with AD (16%)	Isolated decrease of Aβ1-42. Biochemical profile not indicative of AD (6,5%)	Isolated increase of tau, evocative of massive neuronal death (16,5%)	Biochemical profile possibly suggestive of AD (10%)
	Biochemical profile of normal CSF (10%)	Biomarker profile characteristic of AD (10%)	Profile compatible with amyloidopathy (very low levels of Aβ may suggest pre-analytical concerns). Lower Aβ ratio as a sign for probable AD (6,5%)	Isolated increase of Tau. Profile not evocative of AD, other causes should be considered (16,5%)	Isolated increased total and phosphorylated Tau, not fully conclusive. Consider interpretation ratio of pTau/Aβ1-42 for more diagnostic certainty on AD (10%)
	Normal Profile, not indicative (evocative) of AD (10%)	Consistent with a clinical diagnosis of AD (10%)	If Aβ42 or Aβ42/40 is only in borderline zone: neurochemically improbable AD; If Aβ42 or Aβ42/40 in definite pathological zone: neurochemically possible ASD (6,5%)	Isolated elevation of Tau very likely in conditions with neuronal death such as stroke or CJD (13%)	Atypical profile, likely compatible with tauopathy, AD could be suggested if high value of Aβ1-40 (6,5%)
	Biochemical profile not compatible of AD (6%)	Profile of probable AD (6%)		No biomarker evidence of an amyloid-β pathology. Isolated increase in total tau: tau is a non specific marker of any cause of neuronal injury, damage or inflammation (6,5%)	Isolated increase of Tau and pTau : profile of non-AD pathologic change (6,5%)
			Not compatible with AD, other causes should be considered (6,5%)	Biochemical profile evocative of non-amyloid neurodegenerative pathology (6,5%)	

CSF obtention and report transmission

The diagnostic comments may be influenced by various parameters, that each laboratory was asked to precise:

- The **way CSF is addressed to the specialized laboratories / identification of the initial requester**: hospital unit, AD specialized unit (memory center...), general practitioner, private consultation neurologist, other (such as retirement home).
- The **way the report is transmitted**: delay necessary for transmission, nature of results transmitted: (raw data alone, comments alone, both), to whom the report is transmitted (initial requester, patient)

Conclusion

This is the first time that harmonized reports may be proposed across the different specialized laboratories involved in the biochemical diagnosis of AD. This initiative is very promising, as harmonized reports may facilitate more direct comparison of biomarker-stratified patient and research participant outcomes across centers.

Perspectives

The next step will consist of proposing various reports, adapted to the interlocutors involved (initial requester of the analysis and final receiver of the comments), so they are suitable to each laboratory's own practice. This work will be later extended to blood biomarkers.