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Can we rely only on ratios of cerebrospinal fluid biomarkers for AD biological diagnosis?

New recommendations for Alzheimer's disease (AD) diagnostic criteria include cerebrospinal fluid (CSF) biomarkers results [1]. This represents a major step forward for AD biological diagnosis which would rely on a decrease of amyloid peptides (Aβ42), an increase of tau and phosphorylated-tau (p-tau) proteins in the CSF. A major issue is represented by the debate over the definition of a proper CSF "Alzheimer profile" and its optimal use in clinical practice. Most of the studies compared, on prospective or retrospective cohorts, the accuracy of the biomarkers to discriminate AD from non-AD patients, or to predict conversion of mild cognitive impairment (MCI) patients. Many combinations based on either simple ratios or complex algorithms have been evaluated. Recently, Duits et al. [2] reported that a simple ratio, tau/Aβ42, was as efficient as complex algorithms to identify AD patients. These authors therefore suggested using this ratio with a cut-off >0.52 for differentiating AD patients from other patients and for predicting dementia due to AD in MCI patients. Using existing data, we also computed the accuracy of the different combination of biomarkers (see Table 1). The difference in accuracy between ratios (tau/Aβ42, p-tau/Aβ42) and more complex algorithms was in fact nonsignificant. There was however a trend in favor of regression approaches, a finding also reported in previous works [3–6]. Of note, the fixed cut-off tau/Aβ42 ratio proposed by Duits et al. [2] was not optimal in our cohorts even though we followed recommended standard operating procedures (SOPs) [7]. This illustrated the limits in using a fixed tau/Aβ42 ratio of CSF biomarkers, which in fact presents several caveats as highlighted below.

First of all, using solely the tau/Aβ42 ratio implies that p-tau measurement is pointless. However, we have shown, as other authors, that p-tau is an important asset as it demonstrates a very high specificity for AD [4,5,8,9]. p-tau appears also helpful in mixed situations when tau increase is linked to neuronal damages, like in prion

Table 1
Diagnostic accuracy of biomarkers for distinguishing AD patients from controls and other dementia patients

	AD patients vs. Control					AD vs. Other dementia patients				
	ROC-AUC	% SE	% SP	% PPV	% NPV	ROC-AUC SE	% SE	% SP	% PPV	% NPV
Aβ42	0.82 (0.78-0.85)	79 (74-84)	81 (75-86)	86 (81-90)	73 (66-79)	0.76 (0.73-0.80)	86 (82-90)	65 (60-69)	62 (57-67)	88 (83-91)
tau	0.89 (0.85-0.91)	81 (76-86)	86 (80-90)	89 (85-93)	76 (69-81)	0.85 (0.82-0.87)	82 (76-86)	79 (74-83)	72 (67-77)	86 (82-90)
p-tau	0.89 (0.86-0.92)	82 (76-86)	86 (82-92)	91 (86-94)	76 (70-82)	0.87 (0.84-0.90)	76 (70-81)	90 (87-93)	83 (78-88)	85 (81-88)
tau/Aβ42	0.91 (0.88-0.93)	87 (83-91)	88 (83-92)	91 (87-95)	83 (77-88)	0.86 (0.84-0.89)	85 (80-89)	80 (76-84)	74 (69-79)	89 (85-92)
tau/Aβ42 (>0.52)	/	81 (76-85)	92 (87-95)	94 (90-96)	77 (70-82)	/	81 (76-85)	83 (79-87)	76 (71-81)	87 (83-90)
p-tau/Aβ42	0.92 (0.89-0.95)	86 (81-90)	91 (86-95)	93 (90-96)	81 (75-86)	0.89 (0.86-0.91)	85 (80-89)	84 (80-88)	78 (73-83)	89 (86-92)
PLM scale	0.93 (0.90-0.95)	83 (78-87)	91 (86-95)	93 (89-96)	78 (72-84)	0.89 (0.87-0.91)	83 (78-87)	87 (83-90)	81 (76-86)	88 (85-92)
Aβ42/pTau decision tree	0.87 (0.83-0.90)	93 (89-96)	80 (74-86)	87 (83-91)	89 (83-93)	0.83 (0.80-0.85)	91 (87-94)	74 (69-78)	70 (65-75)	93 (89-95)
Hulstaert	0.90 (0.86-0.92)	86 (81-90)	91 (86-95)	93 (89-96)	82 (76-87)	0.85 (0.82-0.88)	85 (80-89)	82 (78-85)	76 (70-80)	89 (85-92)
Schoonenboom	0.93 (0.90-0.95)	86 (82-90)	91 (86-95)	94 (90-96)	82 (76-87)	0.90 (0.87-0.92)	82 (77-86)	89 (85-92)	83 (78-87)	88 (84-91)
Spies	0.93 (0.90-0.95)	88 (83-91)	90 (85-94)	93 (89-96)	83 (78-88)	0.90 (0.87-0.92)	83 (78-88)	89 (85-92)	83 (78-87)	89 (85-92)

Abbreviations: AD, Alzheimer's disease; ROC, receiver operating characteristics; AUC, area under the curve; SE, sensitivity; SP, specificity; PPV, positive predicting value; NPV, negative predicting value; Aβ42, amyloid-β42; p-tau, tau phosphorylated at threonine 181. Values in brackets represent the 95% confidence intervals of the different items.

NOTE. The population used to calculate AUCs, SE, SP, PPV and NPV values is fully described in the article by Gabelle et al. [4]. The PLM scale was calculated as described in [5], the Aβ42/pTau decision tree as in [9], the Spies regression as in [6], the Schoonenboom regression and the Hulstaert formula as in [2]. The " tau/Aβ42 (>0.52)" condition corresponds to the accuracy of the tau/Aβ42 ratio with a cut-off >0.52 as recommended in [2].

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diseases where the tau/p-tau ratio has demonstrated its relevance [10]. Because these situations are rare (estimated <5%), the statistical differences of methods combining three rather than two biomarkers is often not significant (Table 1), but, based on our routine practice, it is still very useful for individual cases.

The second issue of using a fixed ratio resides in the challenge of having similar values, and not only the cut-offs, for Aβ42 and tau in the different laboratories. Even after implementing optimal SOPs and the future development of a reference methods (for Aβ42 only), the availability of different commercial Aβ42-tau kits with their own standards, antibodies, ranges and cut-offs is an additional factor suggesting that values and ratio harmonization between centers is not attainable in the near future.

Finally, the yes/no answer, regarding the presence of AD based on CSF biomarkers, is commonly used to assess biomarkers' accuracy. However, neurologists/practitioners in direct contact with patients and families are rather using a multimodal probabilistic approach to establish an AD diagnosis. Hence, the probabilistic use of biomarkers as reported in the leading work from Spies [6] probably represents a good answer to the clinical needs. In a recent work [5], we have defined a diagnostic scale for AD using the multicenter data of our national network Paris-Lille-Montpellier (PLM). This PLM scale is based on the number of pathologic biomarkers Aβ42, tau and p-tau, ranging therefore from 0 to 3. Its ranking is therefore homogeneous between centers with different cut-offs, and its use is convenient for physicians. Furthermore, this scale exhibited the highest accuracy (see [5] and Table 1) and is compatible with different assays. We believe that this type of probabilistic approach, which could at some point include additional informative data (imaging, genetics, vascular risk factors), is of high interest to implement CSF biomarkers for AD in clinical practice and for clinical trials design.

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