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LETTER TO THE EDITOR

Clinical usefulness of the CSF β-amyloid Aβ1-42/Aβ1-40 ratio for Alzheimer's disease diagnosis: a retrospective study in a Belgian academic hospital

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Dear Editor,

Diagnosing Alzheimer's disease (AD) can sometimes be challenging. In addition to clinical semiology and brain-imaging techniques, much emphasis has been put during the last years on the biological hallmarks of AD. The usual markers measured in cerebrospinal fluid (CSF) are Total-Tau (T-Tau), Phospo-Tau (P-Tau) and β-amyloid 1–42 peptide (Aβ42) [1]. The diagnostic performance of these CSF markers is quite acceptable when used and interpreted together [2, 3]. However, discrepancies between measurements of the Tau proteins and of Aβ-42 can occur and may complicate the diagnostic workup of AD patients. It is now also well established that the use of CSF β-amyloid Aβ1-42/Aβ1-40 ratio (Aβ42/40 ratio) increases the diagnostic performance of these biomarkers [4] most probably by reducing the inter-individual variability caused by the differences in production and clearance of all CSF Aβ species [5]. We, therefore, conducted a two-step retrospective study to assess the diagnostic performance and the clinical impact of the use of the Aβ42/40 ratio in a Belgian tertiary care hospital.

58 patients were included for the first part of this retrospective study. Patients underwent lumbar puncture at the Cliniques Universitaires Saint-Luc between 2018 and 2021. Patients underwent a complete clinical and paraclinical diagnostic workup, including medical history, neurological examination, neuroimaging (fluorodeoxyglucose (FDG)-PET scan and/or magnetic resonance imaging) and standard neuropsychological testing. Of these 58 patients, 29 presented with Alzheimer's clinical syndrome according to the 2018 definition of the NI-AA research framework [6] and 29 were age-matched controls (without established neurological disease). These 58 CSF samples were used to quantify Aβ42, Aβ1-40, T-Tau and P-Tau protein by chemiluminescent enzyme-immunoassay using the Lumipulse® G (Fujirebio Europe NV, Gent, Belgium). Statistical analysis was performed using the MedCalc Software (Ostend, Belgium), including receiver operator curve (ROC) and derived Youden's index to determine the optimal cut-off of the Aβ42/40 ratio. Our results showed that a Aβ42/40 ratio cut-off set at a value ≤ 0.053 presented the best discriminating performance between control and AD patients with the highest area under the curve (AUC) compared to other tested markers [AUC: 0.967 (0.883–0.996)] ($p < 0.001$) with a sensitivity and specificity of 100% and 93.1%, respectively (Fig. 1).

The second part of our study aimed at evaluating the clinical value of adding the Aβ42/40 ratio to the usual biomarker panel. To do so we retrospectively applied the previously determined cut-off of the Aβ42/40 ratio to 37 patients ($n = 37$) admitted to the department of neurology of our hospital. Of these 37 patients, 10 had Alzheimer's clinical syndrome and 27 were controls or non-AD. We then classified these 37 patients according to their AT(N) biomarker profile [6] using either the CSF Aβ42 level alone (cut-off previously determined < 437 pg/mL) [3] or the CSF Aβ42/40 ratio (Table 1). Among the patient with Alzheimer's clinical syndrome ($n = 10$), using CSF Aβ42 alone, 8 out of 10 patients with a clinical diagnosis of AD were categorized as Alzheimer's disease. Using the CSF Aβ42/40 ratio, 2 patients were successfully reclassified from non-AD

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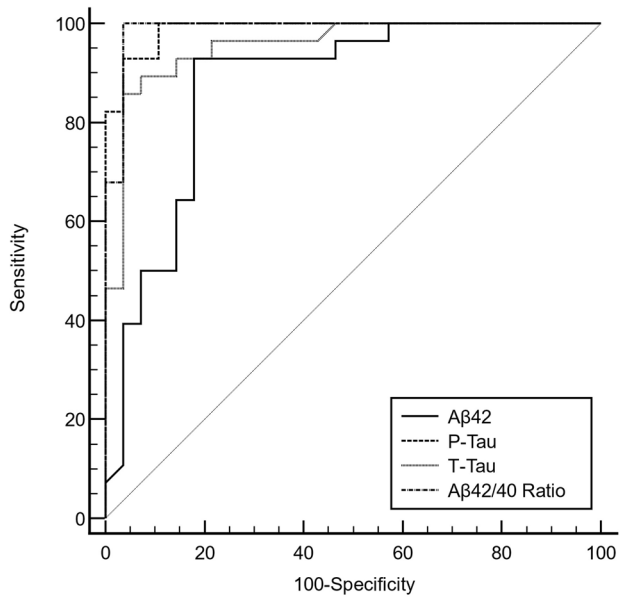

Fig. 1 Receiver-operating characteristic curves obtained for Amyloïd β1–42 peptide (Aβ42), Phospho-Tau (P-Tau), total-Tau protein (T-tau) and the Aβ42/Aβ40 ratio for discriminating Alzheimer disease patients vs. control subjects

pathologic change to Alzheimer's disease, in concordance with the clinical diagnosis. Regarding the AT(N) categorization of controls or non-AD patients ($n=27$) using the CSF Aβ42 alone, 10 patients were categorized with normal AD biomarkers, 6 with non-AD pathologic change, 8 with Alzheimer's pathologic change, 2 with Alzheimer's and concomitant suspected non-Alzheimer's pathologic change and 1 with Alzheimer's disease (a case of mild cognitive impairment). 6 non-AD patients were reclassified from Alzheimer's pathologic change to normal AD biomarkers and 2 further non-AD patients from Alzheimer's and concomitant suspected non-Alzheimer's pathologic change to non-AD pathologic change. Only two patients out of 27 (7.4%) presented with isolated CSF Alzheimer's pathologic change, whereas a clinical diagnosis of dementia was ruled out.

Altogether, the AT(N) classification of patients using the CSF Aβ42/40 ratio instead of CSF Aβ42 alone resulted in better concordance in 10 out of 37 cases (27%). There was a significant association between a CSF Aβ42/40 ratio ≤ 0.053 and the diagnosis of Alzheimer's clinical syndrome (Table 2a, Fisher's exact test p value < 0.0001), whereas CSF Aβ42 levels did not discriminate as well AD from non-AD patients (Table 2b).

In conclusion, these results demonstrate that the use of the Aβ42/40 ratio significantly improves the biological interpretation of CSF AD biomarkers with a greater concordance in about 27% of patients. Thus, the isolated measurement of CSF β-amyloid 1–42 levels should be substituted by the calculation of the Aβ42/40 ratio.

Table 1 Patient classification according to their Biomarker category derived from their AT(N) profiles using CSF Aβ42 alone or the CSF Aβ42/40 ratio

AT(N) classification	Clinical diagnosis			
	AD ($n=10$)		Non-AD ($n=27$)	
	CSF Aβ42	CSF Aβ42/40 ratio	CSF Aβ42	CSF Aβ42/40 ratio
Alzheimer's disease A + T + (N) + or A + T + (N) −	8	10	1	1
Alzheimer's pathological change A + T − (N) −	0	0	8	2
Non-AD pathologic change A − T − (N) +, A − T + (N) − or A − T + (N) +	2	0	6	8
Alzheimer's and concomitant suspected non-Alzheimer's pathologic change A + T − (N) +	0	0	2	0
Normal AD biomarkers A − T − (N) −	0	0	10	16

Table 2 Categorization of clinical AD versus non-AD patients, according to the AT(N) biomarker category classification using either the CSF Aβ42/40 ratio ((a) Fisher's exact test $p < 0.0001$) or CSF Aβ42 levels alone, (b) Fisher's exact test non-significant)

AT(N) biomarker category reclassification using the CSF Aβ42/40 ratio (cut-off ≤ 0.053)	Clinical diagnosis	
	AD ($n = 10$)	Non-AD[1] ($n = 26$)
(a) Fisher's exact test $p < 0.0001$		
Alzheimer's continuum	10	2[2]
Non-AD	0	24
AT(N) biomarker category classification using CSF Aβ42 (cut-off < 437 pg/mL)[3]	Clinical diagnosis	
	AD ($n = 10$)	Non-AD[1] ($n = 26$)
(b) Fisher's exact test non-significant		
Alzheimer's continuum	8	10
Non-AD	2	16

Alzheimer's continuum includes biomarker categories demonstrating aggregated Ab or associated pathologic state (A+), aggregated tau (T+), neurodegeneration or neuronal injury (N+) in the following combinations: A + T + (N) +, A + T + (N −), A + T − (N) + or A + T − (N)-

[1]Excluding the case diagnosed with mild cognitive impairment ($n = 1$)

[2]Two patients out of 26 (7.7%) had isolated CSF Alzheimer's pathologic change, whereas a clinical diagnosis of dementia was ruled out

[3]See reference [3]

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The patients included signed an internal regulatory document, stating that residual samples used for diagnostic procedures can be used for retrospective academic studies, without any additional informed consent (ethics committee approval 2007/10SEP/233).

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