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ORIGINAL COMMUNICATION

Cerebrospinal fluid biomarkers and cognitive functions at multiple sclerosis diagnosis

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Abstract

Cognitive impairment (CI) is a frequent and disabling symptom in Multiple Sclerosis (MS). Axonal damage may contribute to CI development from early stages. Nevertheless, no biomarkers are at the moment available to track CI in MS patients. We aimed to explore the correlation of cerebrospinal fluid (CSF) axonal biomarkers, in particular: light-chain neurofilaments (NFL), Tau, and Beta-amyloid protein (Abeta) in MS patients with CI at the diagnosis. 62 newly diagnosed MS patients were enrolled, and cognition was evaluated using the Brief International Cognitive Assessment for MS (BICAMS) battery. CSF NFL, Abeta, and Tau levels were determined with commercial ELISA. Patients with CI (45.1%) did not differ for demographic, clinical, and MRI characteristics (except for lower educational level), but they displayed greater neurodegeneration, exhibiting higher mean CSF Tau protein (162.1 ± 52.96 pg/ml versus 132.2 ± 63.86 pg/ml p:0.03). No differences were observed for Abeta and NFL. The number of impaired tests and Tau were significantly correlated (r:0.32 p:0.01). Tau was higher in particular in patients with slowed information processing speed (IPS) (p:0.006) and a linear regression analysis accounting for EDSS, MRI, and MS subtype confirmed Tau as a weak predictor of IPS and cognitive impairment. In conclusion, CI has an important burden on the quality of life of MS patients and should be looked for even at diagnosis. Axonal damage biomarkers, and in particular Tau, seem to reflect cognition impairment in the early stages.

Keywords Multiple sclerosis · Biomarker · Cognition · Neurodegeneration · Tau · Neurofilaments

Introduction

Cognitive impairment (CI) is a frequent and disabling feature in Multiple Sclerosis (MS) patients [1]. Since cognitive deterioration may have a subtle and slow evolution over time, in the past, cognition was often not investigated until advanced diseases stages, particularly in progressive MS subtypes [2]. In contrast, CI involves information processing speed, episodic memory, and fluency with a high prevalence even in early disease stages [3]. Therefore, screening at MS diagnosis is recommended even in absence of patient complain [1–4]. Cognition may be evaluated with different neuropsychological test batteries in clinical practice. For the MS population, the most common test batteries are the Rao Brief Repeatable Battery (RBRB) which explores verbal learning and delayed recall, visuospatial learning and delayed recall, IPS, and verbal fluency on semantic input. Administration of RBRB takes about 45 min [5, 6]. The MACFIMS (Minimal Assessment of Cognitive Function in MS) battery explores, in 90 min, language, spatial processing, verbal memory and

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visuospatial memory, information processing speed, and executive functions using seven tests [6, 7]. Finally, the BICAMS (Brief International Cognitive Assessment in MS) test battery is recommended as an international, validated, and standardized brief cognitive evaluating information processing speed, verbal memory, and visuospatial memory [1, 8]. The BICAMS test battery only takes 15 min and is, therefore, feasible in clinical practice [6].

In MS, the precise mechanisms of CI are still to be recognized but growing evidence suggested that both inflammation and neurodegeneration have a substantial role. MS is an inflammatory disease with focal inflammation due to lymphocytes infiltration in both the white and grey matter of CNS [9]. MRI studies highlighted that a disconnection syndrome resulting from white and grey matter focal inflammation may represent a key mechanism underlying CI [9, 10], but most attention has been directed to the role played by the neuronal and axonal loss [11, 12]. Axonal damage may result in both global brain and spinal cord atrophy as well as focal cortical (e.g. temporal lobe) and subcortical (e.g. thalamus) atrophy [9]. Since patients display variable levels of inflammation and neurodegeneration, the presence of specific soluble biomarkers capable to mark and/or predict the development of CI would be extremely useful to the clinician. No specific soluble biomarkers are available for CI in MS, whereas cerebrospinal (CSF) Tau and Beta-amyloid (Abeta) are routinely used in other neurodegenerative diseases such as Alzheimer's disease. In MS, high levels of CSF Tau and Abeta seem to mark high neurodegeneration and poor prognosis [13], but only one study described a correlation of CSF Abeta levels with CI [14]. Moreover, CSF and serum neurofilaments light-chain (NFL) have been extensively investigated in MS as a marker of axonal damage following acute inflammation (high correlation with gadolinium-enhancing lesions and relapses), as well as brain volume loss [15] and treatment response, but little is known about its ability to trace CI [11, 16–23]. Only a few reports involving small cohorts of patients reported a possible association of high levels of NFL with CI, but results were not consistent [11, 16–23].

Our study aims to investigate the correlation of CSF NFL, Tau, and Abeta protein levels with CI in MS patients at diagnosis.

Materials and methods

Study population and CSF collection

We enrolled 62 consecutive newly diagnosed MS patients in our Center (AOU Maggiore della Carità—Novara). We included patients who underwent lumbar puncture performed on the suspicion of MS as part of the usual diagnostic workup from January 2015 to December 2020. Time at lumbar puncture was considered our baseline and inclusion criteria were: diagnosis of MS according to Mc Donald Criteria 2010 or 2017 revision [24, 25], age ≥ 18 years old, signed informed consent for both diagnostic and research purpose at the moment of lumbar puncture, and presence of a cognitive evaluation not later than 1 month from baseline. We excluded patients with a history of alcohol, drug abuse, and behavioral or psychiatric diseases, patients with exposure to immunosuppressive, immunomodulant treatments before or at the moment of the baseline, and none of the patients was under steroids at the moment of lumbar puncture or cognitive evaluation. We collected clinical-demographic data such as gender, age of onset, age at diagnosis, MS phenotype, and expanded disability status score at diagnosis (EDSS). Brain and spinal MRI was performed within 3 months before or following baseline, according to Italian guidelines [26]. We recorded T2 white matter lesion load with a cut-off of ten lesions to define high and low lesion load [27], the presence or absence of spinal lesions, and the presence or absence of gadolinium-enhancing (gd +) lesions.

CSF analysis and biomarkers determination

CSF was obtained via LP and after centrifugation at 8000 r/min for 10 min and supernatants were aliquoted in polypropylene tubes. Samples were stored at − 80 °C until use. As part of the diagnostic MS procedure, every patient was tested for cell counts, glucose, and protein CSF concentration, oligoclonal bands detection via isoelectrofocusing (Sebia), albumin, IgG Index, and kappa free light chain index via nephelometry [28–30]. CSF Abeta and total Tau and NFL were measured using three commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits: (i) INNOTEST® beta-AMYLOID 1–42 kit (Fujirebio Diagnostics, Ghent, Belgium) which has a calibrator range (CR) between 62.5 and 4000 pg/mL and low detection limit (LLoQ) of 65 pg/ml; (ii) INNOTEST® hTAU antigen kit (Fujirebio Diagnostics, Ghent, Belgium) which measures the six tau isoforms from 352 to 441 amino acids and has a LLoQ of 34 pg/ml and CR of 50–2500 pg/ml; (iii) NF-light® ELISA kit (UmanDiagnostics AB, Umeå, Sweden) with a CR between 100 and 1000 pg/ml and a LLoQ of 32 pg/ml and a variability intra-measurement inter-measurements below 10%. Duplicate testings requiring 25 ml × 2 were performed for both kits. CSF samples were analyzed by board-certified laboratory technicians, blinded to clinical data and all experiments were performed according to manufacturers' instructions. CSF Abeta under 500 pg/ml are considered pathological independently from age, whereas Tau levels over 300 pg/ml were considered pathological in subjects under 50 years old.

Cognitive evaluation

The Beck Depression Inventory was used to screen patients for depression. Patients with total scores of ≥ 14 were excluded from the final analysis [31]. Then, the BICAMS test battery was performed by the same neurologist administrating the three subsequent tests: the Symbol digit Modalities Test (SDMT) as a measure of information processing speed, the California Verbal Learning Test-2 (CVLT2) as a measure of verbal memory, and the Brief Visuospatial Memory Test-Revised (BVMT-R) for visuospatial memory. According to the Italian normative values, raw scores were corrected for educational level, age, and gender. Regression-based *T* scores and *z* scores were thus obtained [8]. A composite *T* score and *z* score were also calculated as the mean of the three single normalized scores of the patient. The presence of a specific cognitive domain impairment was defined by the failure of the corresponding test (*T* score ≤ 35 and *z* score ≤ -1.5) [8]. Overall CI was defined by the presence of impairment in at least one out of three tests and/or the presence of the composite corrected score below the cut-off.

Data availability and statistical analysis

Upon CSF sampling, patients gave written consent to CSF storage for research purposes. The study was conducted in accordance with the declaration of Helsinki guidelines and approved by the ethical committee of the University Hospital of Novara. Collected data were used to produce a pseudonymized dataset, available under reasonable request to the corresponding author. Statistical analysis was performed using SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA) and Graphpad Prism 9 for Windows (Graphpad Software, La Jolla, CA, USA). We checked the normality distribution of data with the Kolmogorov–Smirnov Test and Shapiro–Wilk Test. We presented categorical data with median, range, and interquartile range (IQR), proportions as numbers and percentages, and continuous data with mean and standard deviation (SD). Mann–Whitney U test and Kruskal–Wallis test were used for comparison between continuous variables; Chi-Squared test and Fisher test for categorical variables. Bonferroni correction was applied when appropriate for multiple comparison analysis. Spearman's rank correlation coefficient test was used for the correlation between continuous variables and partial correlation with correction for EDSS and MRI status. Linear regression analyses including EDSS, type of MS, and MRI characteristics at baseline as independent variables and BICAMS normalized scores as dependent variables were run to identify the best predictors of CI. All tests were two-sided and the significance threshold was set to $p < 0.05$.

Results

Patient characteristics

The majority of patients were female with relapsing–remitting (RR) disease course (96.8%). The mean age at diagnosis was 39.1 ± 11.2 years, median EDSS was 1.5 ± 0.8, and 38.7% showed at least one gd + lesion. In the whole cohort, mean CSF Tau, Abeta and NFL concentrations were 145.69 ± 50.58 pg/mL, 647.82 ± 283.52 pg/mL, 2248.88 ± 2230.07 pg/mL, respectively. The main demographic and clinical characteristics are summarized in Table 1, whereas results from BICAMS are reported in Table 2. Information processing speed and verbal memory were impaired in 15/62 patients (24%) showing *T* score ≤ 35, and 28/62 (45.1%) patients showed CI (at least impairment in 1 test). Moreover, 11/62 patients (17.7%) displayed impairment in the composite score (11/62, 17.7%) indicating a variability in each patient between different domains Patients with or without CI did not differ for

Table 1 Demographic, clinical, MRI characteristics, and CSF mean levels of biomarkers of the study population (*N*:62)

Demographic characteristics	
Age at onset (yrs); mean ± SD	36.43 ± 9.99
Age at diagnosis (yrs); mean ± SD	39.16 ± 11.22
Female *n*, (%)	41, (66.1%)
Educational level (yrs) mean ± SD	12.91 ± 3.34
EDSS; mean ± SD (median; range)	1.5 ± 0.8 (1.5; 0–4)
MS type (*n*; %)	
RR	60; 96.8%
PP	2; 3.2%
Clinical characteristics at onset (*n*; %)	
Sensory/pyramidal syndrome	23; 37.2%
Brainstem/cerebellar syndrome	19; 30.6%
Optic neuritis	10; 16.1%
Myelitis	8; 12.9%
Progressive course	2; 3.2%
MRI characteristics (*n*; %)	
> 9 T2 brain lesions	41; 66.1%
≤ 9 T2 brain lesions	21; 33.9%
Gd + lesions	24; 38.7%
Spinal lesions	43; 69.4%
Biomarker (mean ± SD)	
CSF Tau pg/ml	145.69 ± 50.58
CSF Abeta pg/ml	647.82 ± 283.52
CSF NFL pg/ml	2248.88 ± 2230.07

Abeta beta amyloid, *CSF* cerebrospinal fluid, *EDSS* expanded disability status score, *Gd* + gadolinium enhancing, *NFL* neurofilament light chain, *RR* relapsing remitting, *SD* standard deviation, *PP* primary progressive, *yrs* years

Table 2 Neuropsychological results at the BICAMS evaluation

Cognitive domain	Test	Raw score (mean ± SD)	*z* score (mean ± SD)	*T* score (mean ± SD)	Score < cut-off (*n*; %)
IPS	SDMT	46.70 ± 12.58	− 0.62 ± 1.12	43.76 ± 12.58	15/62; 24.2%
VM	CVLT-II	50.48 ± 12.22	− 0.54 ± 1.23	44.56 ± 12.30	15/62; 24.2%
VSM	BVMT-R	22.80 ± 9.10	− 0.51 ± 1.08	44.84 ± 10.86	11/62; 17.7%
Overall cognition	Composite score	NA	− 0.53 ± 0.88	44.39 ± 8.97	11/62; 17.7%
Cognitive impairment					28/62; 45,1%

Results are presented as raw scores for each test and normalized *z*-scores and *T*-scores for each test. Number and percentage of the altered test (normalized score below cut-off) are also shown. Cognitive impairment was defined as presence of at least one out of the three tests below the normality cut-off. Overall composite score was calculated as a mean of the single normalized scores

BVMT-R brief visuospatial memory revised test, *CVLT-II* California verbal learning test -II, *IPS* information processing speed, *SDMT* symbol digit modalities test, *SD* standard deviation, *NA* not available, *VM* verbal memory, *VSM* visuospatial memory

gender ($p = 0.4$), EDSS (1.3 ± 0.7 vs 1.6 ± 0.8 $p = 0.1$), age at onset (35.44 ± 8.8 vs 37.64 ± 11.33 years old $p = 0.7$), age at diagnosis (38.09 ± 10.89vs 40.46 ± 11.69 $p = 0.5$), and MRI characteristics (white matter lesion load $p = 0.7$, gd + lesions $p = 0.9$, spinal lesions $p = 0.8$). The only significant difference was noted in educational levels: patients with CI displayed a lower education than those without CI (11.8 ± 2.9 education years vs 13.8 ± 3.4, $p = 0.02$).

Cognition and CSF biomarkers

We compared the levels of the biomarkers displayed by patients with different cognitive statuses as reported in Table 3. Patients with impaired information processing speed and CI showed higher levels of CSF Tau than patients without impairment (178.6 pg/ml ± 52.8 vs 135.2 pg/ml ± 59.6 $p = 0.006$ and 162.1 pg/ml ± 52.96 vs 132.2 pg/ml ± 63.86 $p = 0.03$). Increased Tau levels were also associated with impaired composited *T* score (173.3 pg/ml ± 59.16 vs 139.7 pg/ml ± 59.79 $p = 0.049$) and a trend was also observed in patients with an increasingly progressive higher number of altered tests ($p = 0.09$). Conversely, no differences in terms of cognition impairment were observed for Abeta and NFLs. When stratifying patients according to the onset type and MRI characteristics, we found that NFLs were significantly higher in patients with at least one gd + lesion than in those without gd + lesions (3626 pg/ml ± 2886 vs 1379 pg/ml ± 1006 $p < 0.0001$). No other biomarkers differences were observed based on MRI.

Correlation analyses are reported in Table 4 and the significant correlations are represented in Fig. 1. We confirmed an inverse correlation between information processing speed *T* score, composite *T* score, and CSF Tau (respectively, $r = -0.29$ $p = 0.02$ and $r = -0.26$ $p = 0.04$) and a positive correlation between the number of the altered test (0, 1, 2 or 3) and CSF Tau levels ($r = 0.32$ $p = 001$). No other statistically significant correlations were observed. These findings also held after correction for EDSS and MRI status ($r - 0.29$ $p = 0.023$ and $r = -0.25$ $p = 0.049$).

We finally performed a linear regression analysis for the CSF biomarker that was more informative (Tau) and the cognitive domains that were significant at the univariate model (SDMT T scores and composite T score). Our model accounted for EDSS, MRI (spinal lesions, MRI T2 lesion load, Gd + lesion), and MS subtype and confirmed that only Tau is a predictor of information processing speed and cognitive impairment (see Table 5), even though our two models were not overall statistically significant (R^2: 0.133 $p = 0.2$ and R^2: 0.137 $p = 0.2$).

Discussion

This study confirms the high prevalence of CI and in particular information processing speed and verbal memory in MS patients at diagnosis and the feasibility of the BICAMS test battery; these findings are consistent with previous studies performed at diagnosis [1, 3, 8, 32]. Patients with CI were not dissimilar from patients without CI in terms of demographic (except for educational levels) and MRI characteristics, whereas we found significant differences for the CSF biomarkers, particularly for Tau. Few studies observed a relationship between literacy and CI in MS [33], but low education is a recognized risk factor for CI in other neurological diseases, such as Alzheimer's disease [34].

CI pathophysiology is still under study and there is currently a lack of fluid biomarkers for CI in MS. In our study, we explored the possible use of axonal damage (Tau and NFLs) and neurodegenerative (Abeta) biomarkers in tracking CI in early MS stages. While CSF Abeta and NFL failed, CSF Tau was significantly increased in CI patients and correlated with slowed IPS and overall CI. Regression analysis shows that CSF Tau may be a weak predictor of information processing speed, and prompt to confirm these results in a larger cohort. Slowed information processing speed in MS has been associated with dysfunction and disruption of cortico-subcortical networks [35, 36] and CSF Tau may increase proportionally with neuronal destruction.

Table 3 Group comparison. Differences in biomarkers levels, MRI, clinical and cognitive performances

		TAU		Abeta		NFL	
		Mean ± SD	*p*-value	Mean SD	*p*-value	Mean SD	*p*-value
IPS	Impaired (*N*:15)	178.6 ± 52.8	***0.006***	711.1 ± 282.0	0.3	2963 ± 3010	0.2
	Not impaired	135.2 ± 59.6		619.8 ± 255.4		1821 ± 1878	
VM	Impaired (*N*:15)	168.3 ± 61.9	0.1	630.7 ± 273.5	0.8	1824 ± 816.6	0.6
	Not impaired	138.5 ± 59.0		653.3 ± 289.3		2384 ± 2513	
VSM	Impaired (*N*:11)	155.4 ± 45.11	0.3	747.9 ± 413.8	0.5	2901 ± 3370	0.9
	Not impaired	143.6 ± 63.61		626.3 ± 247.3		2108 ± 1919	
CI*	Impaired (*N*:28)	162.1 ± 52.96	***0.03***	705.8 ± 348.7	0.2	2704 ± 2655	0.1
	Not impaired	132.2 ± 63.86		600.1 ± 209.6		1874 ± 1763	
C. Score**	Impaired (*N*:11)	173.3 ± 59.16	***0.049***	639.2 ± 220.7	0.9	2280 ± 2596	0.9
	Not impaired	139.7 ± 59.79		649.7 ± 297.2		2242 ± 2172	
N° of ≠ test***	0 test ≠ (*N*:34)	132.2 ± 63.84		600.1 ± 209.6		1874 ± 1763	
	1/3 ≠ (*N*:16)	150.1 ± 50.81		724.2 ± 418.1		2565 ± 2349	
	2/3 ≠ (*N*:10)	176.0 ± 59.37		625.8 ± 197.9		2734 ± 2965	
	3/3 ≠ (*N*:2)	205.5 ± 65.69	0.09	747.1 ± 418.5	0.7	1176 ± 110.3	0.3
Gd + lesion	Present	150.5 ± 50.54	0.3	653.3 ± 222.1	0.4	3626 ± 2886	***< 0.0001***
	Absent	147.2 ± 66.64		644.4 ± 319.1		1379 ± 1006	
SL	Present	147.1 ± 62.54	0.9	667.9 ± 305.3	0.4	2481 ± 2561	0.6
	Absent	142.6 ± 57.45		602.4 ± 227.6		1723 ± 1060	
WMLL	High	142.5 ± 59.81	0.6	603.7 ± 250.2	0.1	2608 ± 2549	0.1
	low	152.0 ± 63.08		734.1 ± 329.0		1548 ± 1182	
Onset	S/P	149.2 ± 70.24		610.7 ± 234.2		1786 ± 1793	
	C/B	134.9 ± 39.78		618.2 ± 254.7		2573 ± 2690	
	Visual	140.7 ± 68.40		686.5 ± 452.1		2295 ± 2039	
	Spinal	169.4 ± 52.56		792.9 ± 252.7		3053 ± 2658	
	Progressive	139.7 ± 134.6	0.6	582.9 ± 54.59	0.4	1046 ± 747.2	0.2

P-value in bold are *p* statistically significant

*Cognitive impairment is defined as at least one test with a normalized score under the cut-off

** Composite Score defined as the mean of the three single normalized scores of the patient

***Number of impaired BICAMS tests ranging from 0 to all 3 tests with a normalized score below the cut-off

Abeta beta amyloid, *C/B* cerebellar and brainstem onset, *CI* cognitive impairment, *C. score* composite score, *Gd+* gadolinium enhancing, *IPS* information processing speed, *N°* number, *NFL* neurofilament light chain, *RR* relapsing remitting, *SD* standard deviation, *SL* spinal cord lesion, *S/P* sensory and pyramidal onset, *VM* verbal memory, *VSM* visuospatial memory, *WMLL* white matter lesion load; ≠ :impaired

Furthermore, we also observed that CSF Tau track not only information processing speed but also overall cognition (CI and composite score), strengthening the idea that information processing speed is one of the main components of CI in MS [4].

Previously published data on Tau and cognition in MS are very limited. In MS, CSF Tau has been mainly investigated as a prognostic factor for severe disability over time [37–41]. We previously demonstrated that Tau may be a marker of future disability in early MS stages, but we did not explore cognition at the time [13]. Mori et al. evaluated cognition with the RBRB in 21 MS patients and found decreased CSF Abeta levels in patients with overall CI and a positive correlation with IPS and Abeta. No significant results were reported for Tau and either MRI findings or cognitive parameters [14]. Javorsky et al. observed that Tau may reflect brain atrophy in 48 MS patients (RR and SP) but cognition was not assessed [39]. In our patients, no significant results were found for Abeta and cognition.

Conflicting data were reported on NFL and cognition (evaluated with heterogeneous test batteries), whereas NFL is now considered the most promising disease activity and treatment response biomarker in MS [15]. A correlation of CSF and serum NFL with information processing speed was described in several works [16, 18, 22, 42]. A significant correlation with verbal fluency scores was reported by Quintana et al. [17] and it was confirmed by Gaetani et al. [16]. Kalatha et al. observed an association between BICAMS z scores and CSF NFL in progressive MS [19]. Conversely, several studies on CSF and serum NFL did not observe any

Table 4 Correlation analysis between CSF biomarkers and cognition

Biomarker	Test (*T* score)	*R*	*P* value
Tau	SDMT	−0.29	***0.02***
	CVLT	−0.22	0.07
	BVMTR	−0.10	0.4
	Composite *T* score	−0.26	***0.04***
	N° impaired test	0.32	***0.01***
Abeta	SDMT	−0.11	0.3
	CVLT	−0.05	0.6
	BVMTR	0.09	0.4
	Composite *T* score	−0.03	0.7
	N° impaired test	0.14	0.2
NFL	SDMT	0.04	0.7
	CVLT	−0.15	0.2
	BVMTR	−0.09	0.4
	Composite *T* score	−0.09	0.4
	N° impaired test	0.15	0.2

P-value in bold are *p* statistically significant

correlation with cognition [11, 21]. Similarly, we did not observe any correlation between BICAMS and CSF NFL but we observed higher levels of NFL in patients with at least one gd + lesion as previously reported [15].

White matter accounts for a part of CI pathophysiology, whereas global brain and regional atrophy are involved in cognitive decline in MS [6, 9]. In our study, patients with CI had similar MRI characteristics at diagnosis and MRI was not a significant predictor of information processing speed and overall cognition in the regression analysis, but we did not perform atrophy quantification. Despite this limitation, we confirm that information processing speed and CI may be present at diagnosis independently from white matter lesion load in conventional MRI sequences. Lumbar puncture was not performed under steroids, but we cannot exclude that disease activity might influence CSF Tau levels, even though we found no differences in CSF levels in patients with or without Gd + lesions. Lastly, we included in our study a relatively small number of patients, but overall we suggest that Tau may be a surrogate biomarker of axonal loss reflecting a chronic neuronal loss independent from acute inflammation (gd + lesions) or white matter lesion load.

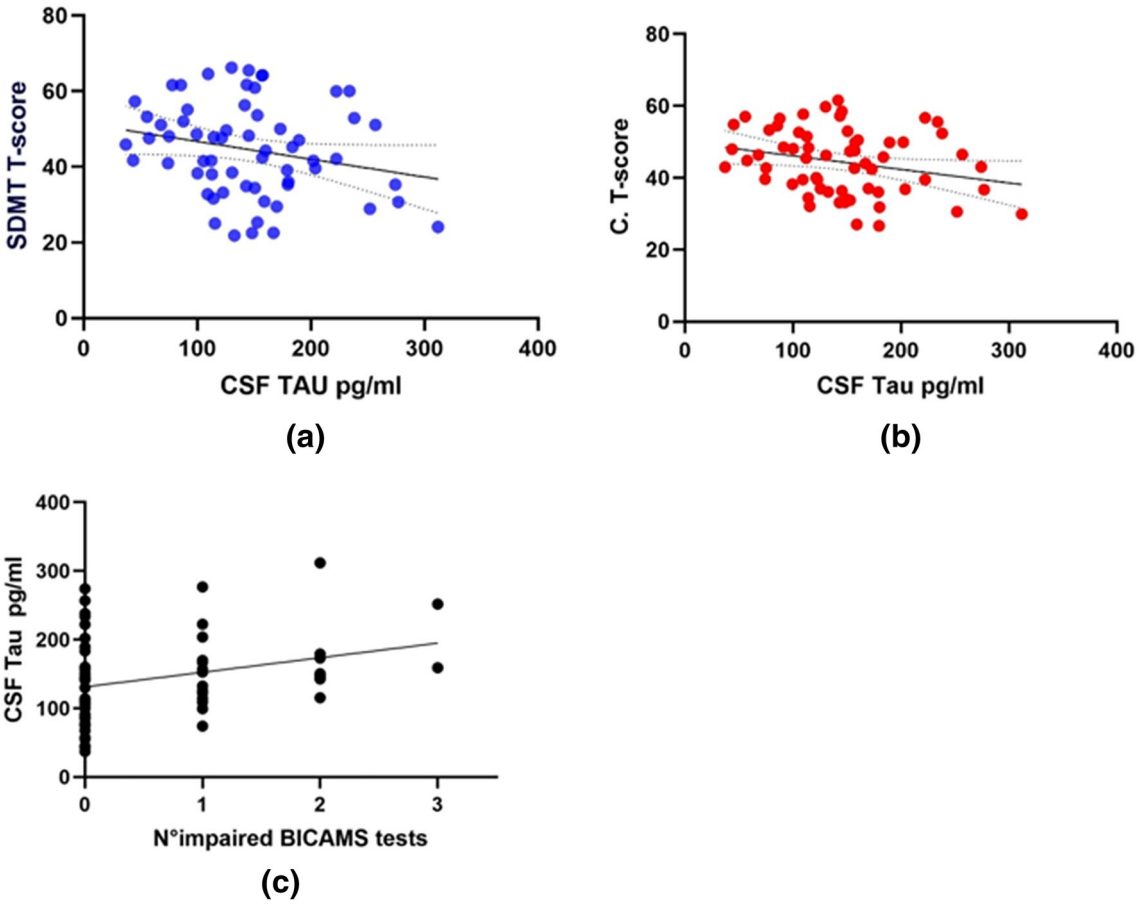

Fig. 1 Correlations between CSF Tau and information processing speed ($r = -29$ $p = 0.02$) (**a**), composite *T* score ($r = -0.26$ $p = 0.04$) (**b**) and number of impaired test ($r = 0.31$ $p = 0.01$) (**c**). *C.* composite, *CSF* cerebrospinal fluid, *N°* number, *SDMT* symbol digit modalities score

Table 5 Predictive factors at Ms diagnosis for slowed information processing speed (Model 1) and overall cognition (Model 2). *N*:62

		Beta	95% CI	P value
Model 1*	Tau	−0.300	−0.104–0–008	**0.02**
	EDSS	−0.010	−3.833–3.551	0.9
	Gd+	0.195	−1.551–10.489	0.1
	SL	0.088	−4.066—8.342	0.4
	WMLL	−0.149	−9.634–2.633	0.2
	Ms subtype	0.019	−15.332–17.767	0.8
Model 2**	Tau	−0.254	−0.076–0.001	**0.05**
	EDSS	−0.101	−4.030–1.853	0.4
	Gd+	0.113	−2.727–6.866	0.3
	SL	0.08	−3.354–6.531	0.5
	WMLL	−0.221	−9.041–0.732	0.09
	Ms subtype	−0.075	−16.959–9.412	0.5

P-value in bold are *p* statistically significant

*Model 1 considering SDMT T score as dependent variable and Tau, EDSS, MRI, and Ms subtype as the independent variable. T-scores are normalized for age, gender, and educational level

** Model 2 considers composite T score as dependent variable and Tau, EDSS, MRI, and Ms subtype as the independent variable. Composite Score is defined as the mean of the three single normalized scores of the patient

EDSS expanded disability status score, *Gd+* gadolinium enhancing, *Ms* Multiple sclerosis, *SL* spinal cord lesion, *WMLL* white matter lesion load;

Conclusions

CSF Tau at diagnosis is associated with impaired information processing speed and CI in the MS, and, as a measure of ongoing axonal damage, may be particularly sensitive in tracking information processing speed and overall CI, independently from potential confounders.

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Data availability statement Data are available upon reasonable request.

Declarations

Conflicts of interest The authors declare no conflict of interest.

Institutional review board statement The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of AOU Ospedale Maggiore della Carità di Novara (reference no: CE 190/19).

Informed consent statement Informed consent was obtained from all subjects involved in the study.

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