Cerebrospinal Tau Levels Predict Early Disability in Multiple Sclerosis

Eleonora Virgilio (virgilioeleonora88@gmail.com)
University of Eastern Piedmont: Universita degli Studi del Piemonte Orientale Amedeo Avogadro
https://orcid.org/0000-0002-0045-3806
Domizia Vecchio
University of Eastern Piedmont: Universita degli Studi del Piemonte Orientale Amedeo Avogadro
Ilaria Crespi
University of Eastern Piedmont: Universita degli Studi del Piemonte Orientale Amedeo Avogadro
Roberto Serino
University of Eastern Piedmont: Universita degli Studi del Piemonte Orientale Amedeo Avogadro
Roberto Cantello
University of Eastern Piedmont: Universita degli Studi del Piemonte Orientale Amedeo Avogadro
Umberto Dianzani
University of Eastern Piedmont: Universita degli Studi del Piemonte Orientale Amedeo Avogadro
Cristoforo Comi
University of Eastern Piedmont: Universita degli Studi del Piemonte Orientale Amedeo Avogadro

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Abstract

Introduction: Multiple Sclerosis (MS) is a chronic autoimmune disease, displaying inflammation and neurodegeneration as neuropathological hallmarks. Nonetheless, the exact mechanisms underlying axonal and neuronal loss remain unclear. Several biomarkers have been investigated, with serum neurofilaments light chain (NFLs) being the most promising. Cerebrospinal fluid (CSF) levels of Tau and Beta-amyloid (Abeta) are currently used as biomarkers in other neurodegenerative diseases. Conversely in MS, investigation of CSF Tau and Abeta levels so far were reported to provide information on disease prognosis, but these results have not been replicated.

Aim of this work was to assess whether CSF Tau and Abeta levels could predict early disability accumulation in MS patients at diagnosis.

Methods: 100 MS patients underwent CSF analysis during their diagnostic work-up. Demographic, clinical, radiological features, and CSF were collected at baseline. MS severity score (MSSS) and age-related MSSS (ARMSS) were calculated at last follow-up. Statistical analysis was performed with the Mann–Whitney test for comparisons between groups, Spearman's coefficient and multiple regression analysis for significant predictors.

Results: Baseline CSF Tau levels correlated with MSSS (p=0.0001) and ARMSS (p=0.0176) after a mean two years follow-up. Predictors of early disability evaluated with MSSS and ARMSS were CSF Tau (p=0.009 and p=0.01), spinal cord involvement (p=0.029 and p=0.008), age at MS diagnosis (p=0.001), and high brain lesion load (p=0.02) at baseline.

Conclusion: CSF Tau levels showed a predictive value comparable to MRI features and age at diagnosis. We hypothesize that CSF Tau levels express chronic axonal damage, contributing to early MS disability.

Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS), displaying inflammation and neurodegeneration as neuropathological hallmarks [1–3]. The exact mechanisms underlying axonal and neuronal loss of MS still have to be completely elucidated [3, 4]. It is currently accepted that neurodegeneration can occur as a consequence of both inflammation (i.e., secondary neurodegeneration) [4] and an early and parallel mechanism independent from the inflammatory component [5–6]. MS is currently considered a "simultaneous two-component disease", in opposition with the previous concept of "two-stage disease" [2, 6]. The strong correlation between neurodegeneration and acquired disability, both in the motor and cognitive domains, is undisputed [7–8]. Several biomarkers of neuronal damage have been investigated, with serum neurofilaments light chain (NFLs) being the most promising, especially concerning acute axonal damage. Strong evidence shows that both serum and CSF NFLs levels identify disease activity and clinical relapses, and correlate with gadolinium (gd) enhancing lesions and new T2 WM lesions [9–11]. CSF baseline levels of NFLs have been associated also with short-term prognosis and conversion to secondary progressive (SP) MS, but conflicting results

were found for long-term prognosis [12–14]. Cerebrospinal fluid (CSF) levels of Tau and Beta-amyloid (Abeta) are currently used as diagnostic biomarkers of other neurodegenerative diseases, such as Alzheimer's disease (AD) [15, 16]. This condition is pathologically characterized by extracellular deposition of Abeta plaques and intracellular accumulation of hyperphosphorylated Tau inclusions (neurofibrillary tangles). Abeta is produced from proteolytic cleavage of the amyloid precursor protein (APP) and its physiological function remains unknown. Tau is a cytoskeletal protein belonging to the microtubule-associated-proteins family, which are highly expressed in neuronal cells [15] and localized predominantly in the axonal tracts of neurons where it exerts several functions, including promotion of microtubular assembly and stabilization, and regulation of axonal transport; recent evidence also supports a role in synaptic plasticity [16]. Following axonal injury, Tau is released in the extracellular fluid, thus resulting in increased levels in the CSF, whereas the accumulation of Abeta in extracellular plaques may cause a decrease of its levels in the CSF. High CSF Tau is the result of its release from neuronal cytoplasm following chronic axonal damage during the neurodegenerative process, whereas, after an abnormal cleavage and misfolding, CSF Abeta levels decline.

Previous studies addressing the role of Tau and Abeta yielded discrepant results in MS. Most reports found increased CSF Tau levels in MS patients [3, 17, 18] but normal or decreased levels were reported by others [19–21]. Similar inconsistency was found for CSF Abeta, where most studies detected decreased levels in MS [15, 19, 22]. Few evidence supports a role of Tau as a disease activity biomarker to track axonal loss during acute inflammation, correlating Tau CSF levels with T2 white matter lesion load (WMLL) [19], whereas most attention was focused on the role as indicator of chronic neurodegeneration tracking high clinical disability and bad prognosis [3, 15, 23–25], although an agreement is yet to be found.

Other markers of neurodegeneration are brain atrophy at MRI, which may be used for prognostic purposes but may not be universally available [7, 8, 26]. MRI features at MS presentation are well described prognostic factors, most notably spinal cord and infratentorial dissemination in early disease stages as well as high WMLL which are associated to a negative outcome [27, 28]. However, WMLL alone has a week predictive value without taking into consideration volume measurement [2].

Clinically, neurodegeneration in early disease stages has a relevant impact on patients' outcome and corresponds to the so-called “progression independent from activity” (PIRA) or “silent progression” (SI), noticeable even in patients efficiently responding to disease modifying treatment (DMTs), without evidence of inflammatory activity [5, 8, 29].

Expanded disability severity scale (EDSS), the current disability scale used in MS, has several limitations including the inability to detect variations for low scores below 3 particularly in the early-stage of relapsing-remitting (RR) MS [7, 26], and possible confounders as patient age and disease duration that are not considered in EDSS calculation. For this reason, alternative scores such as the MS severity score (MSSS), the age-related MSSS (ARMSS) have been introduced particularly in the research setting. MSSS combines EDSS with disease duration at the moment of evaluation; ARMSS associates also the age at

the moment of the evaluation [30, 31]. Previous studies evaluated a possible role of Tau and Abeta in tracking neurodegeneration correlating them with either EDSS or MSSS but, to our knowledge, no study is available correlating CSF Tau and Abeta levels at diagnosis with all two disease severity scales in a prospective study, which was the aim of the present study.

PATIENTS and METHODS

Study population and disability scores

We designed a longitudinal prospective study enrolling patients with newly-diagnosed MS, according to the 2010 and 2017 revised McDonald Criteria [32, 33]. A total of 100 subjects were consecutively recruited from 2015 to 2020. To be included in the final analysis, subjects needed at least one-year of disease follow-up from MS diagnosis. Clinical and imaging data were collected at diagnosis and last clinical follow-up. Patients underwent a standard MS diagnostic work-up including clinical evaluation, brain, and spinal cord MRI, and lumbar puncture (LP). We recorded the following clinical-demographic data: sex, age of onset, age at diagnosis, MS course, and EDSS. We also calculated normalized scores, such as MSSS, ARMSS. Baseline MRI scans were performed within 3 months from LP according to Italian diagnostic work-up recommendation for clinical practice [34]. We analyzed the following MRI variables: T2 WMLL, using an arbitrary cut-off of 10 lesions to define high and low WMLL [35], presence of spinal lesions (SL), presence of gd enhancing lesions. Exposition to DMTs during follow-up was also recorded. All patients signed an informed consent form for both diagnostic and research purposes at enrolment at the time of the LP. The study was approved by the ethical committee of the University Hospital of Novara (reference no : CE 190/19).

At the last clinical follow-up, 62 patients (62%) were under low efficacy DMTs (interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, azathioprine), and 26 patients (26%) under high efficacy treatments (fingolimod, natalizumab, alemtuzumab, cladribine, ocrelizumab). Among the latter group, 13/26 (50%) patients were escalated from a low efficacy DMT, and 13/26 (50%) started from diagnosis with a high efficacy DMTs (induction therapy). Twelve patients did not start any DMT during follow-up; 9 of them were followed for only one year after MS diagnosis in our MS Centre and were then lost at follow-up, but still included in our final analysis for an early disability evaluation.

CSF collection and biomarkers identification

CSF samples were obtained by LP, performed in the L3/L4 or L4/L5 interspace, at diagnosis. CSF samples were centrifuged at 8000r/min for 10 minutes. The supernatants were aliquoted in polypropylene tubes and stored at − 80°C until use. Every patient was tested for cell counts, glucose, and protein CSF concentration. Oligoclonal bands were detected using isoelectrofocusing on agarose gel (Hydragel9 CSF Isofocusing; Sebia, Bagno a Ripoli, FI, Italia) followed by immunofixation with peroxidase, conjugated with anti-IgG antibodies on an electrophoresis system (Sebia Hydrasys). As part of the diagnostic MS procedure using nephelometry, we calculated albumin, IgG Index, and kappa free light chain index [36–38]. CSF total Tau and Abeta were measured using, respectively, two commercially

available sandwich enzyme-linked immunosorbent assay (ELISA) kits. The INNOTEST® hTAU antigen kit (Fujirebio Diagnostics, Ghent, Belgium) measures the six isoforms from 352 to 441 amino acids. The kit has a low detection limit (LLoQ) of 34 pg/ml and calibrator range (CR) of 50- 2500 pg/ml. CSF Tau over 300pg/ml are considered pathological in subjects under 50 years old. The INNOTEST® beta-AMYLOID 1–42 kit (Fujirebio Diagnostics, Ghent, Belgium) for Abeta detection, has a CR between 62,5-4000 pg/mL and LLoQ of 65pg/ml. CSF Abeta under 500pg/ml are considered pathological independently from age. Duplicates testing requiring 25 ml x 2 were performed for both kits. CSF samples were analyzed by board-certified laboratory technicians, blinded to clinical data.

Statistical analyses

Statistical analyses were performed using SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA) and Graphpad Prism 9 for Windows (Graphpad Software, La Jolla, CA, USA). Continuous data are presented with mean and standard deviation (SD), categorical data with median, range, and interquartile range (IQR), and proportions as numbers with the corresponding percentage. Normal distribution of data was preliminarily assessed with Kolmogorov-Smirnov Test. Unpaired T-test with Welch's test and Mann–Whitney U test were used for comparison between groups, and Spearman's rank correlation coefficient test was used for the correlation between continuous variables. Multiple regression analyses including CSF Abeta and Tau levels, gender, age, MRI characteristics, and EDSS score at baseline as independent variables and MSSS, ARMSS as dependent variables were run to identify the best predictors of disease early progression. In all these analyses we considered $p < 0,005$ as statistically significant.

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Results

CSF Abeta and total Tau concentrations: group comparisons

Among our 100 newly diagnosed MS patients (65 females), 97 (97%) had RR and 3 (3%) with primary progressive (PP) MS course. Main demographic and clinical features of patients are summarized in Table 1. None of them was under DMTs or corticosteroids at sampling time. Mean CSF Tau and Abeta concentration were 132,51±68,56pg/ml, and 621,48±252,21pg/ml, respectively. Biomarker comparisons of patients stratified by MRI and clinical (gender and MS phenotype) features are shown in Table 2. We found no statistically significant differences when comparing biomarkers of patients according to either WMLL (high versus low; Tau: 131.91±70.75 pg/ml versus 133.15±66.85 pg/ml p=0.9; Abeta 580.86±233.89 pg/ml versus 665.48±266.11 pg/ml p=0.09); or spinal cord involvement (yes-no, Tau: 139.2±71.11 pg/ml versus 112.50±56.95 pg/ml p=0.1; Abeta: 643.5±260.6 pg/ml versus 555.5±216.8 pg/ml p=0.1); or contrast enhancement (yes-no, Tau: 133.30±57.02 pg/ml versus 131.90±76.03 pg/ml p=0.5; Abeta: 627.50±225.80 pg/ml versus 617.30±270.90 pg/ml p=0.6).

Multiple regression and correlation analysis

Disability scores at last clinical follow-up are provided in Table 3. Patients were followed for at least one year. The mean follow-up duration was 2 years (SD ±1,5) ranging from 1 to 6 years. Median and mean EDSS were unchanged from baseline to last clinical follow-up, in line with the low disability scores (90% of patients with EDSS<3 at last clinical follow up); EDSS was evaluated at least 1 month after a relapse. Mean MSSS and ARMSS at last clinical follow-up were respectively 3.17 ±2.28 (mean±SD) and 2.84 ±1.88). According to a univariate model, age at diagnosis showed a positive correlation with MSSS at last clinical follow-up (r=0.214 p=0.03). Patients with spinal cord lesions at baseline, developed significantly higher MSSS and ARMSS at last clinical follow-up (respectively 3.308 ±2.038 versus 2.279 ±2.303, p=0.009 and 2.994 ±1.830 versus 2.077 ±1.648, p=0.01). ARMSS was also significantly higher in patients with high WMLL at baseline (2.365 ±1.934) than in those with low WMLL (3.127 ±1.643, p=0.006).

According to a univariate model, baseline CSF Tau levels correlated with MSSS (r=0.372; 95% CI 0.1838–0.5340; p=0.0001 – Figure 1) and ARMSS (r=0.237; 95% CI 0.03664–0.4190, p=0.0176 – Figure 2) at last clinical follow up.

Then, we performed a multiple regression analysis, using MSSS and ARMSS as a dependent factor and CSF Abeta and Tau levels, gender, age, MRI characteristics, and EDSS score at baseline as independent variables. This analysis confirmed CSF Tau level as predictor of early disability evaluated with both MSSS (Beta:0.258; R2:0.24; 95% CI 0.02-0.14; p=0.009) and ARMSS (Beta:0.252; R2:0.22; 95% CI 0.002-0.12; p=0.01). Spinal cord involvement (Beta:0.196; p=0.029) and age at MS diagnosis (Beta:0.286 p=0.001) also were predictor of high MSSS in the multivariate model; whereas spinal cord involvement (Beta:0,240 p=0,008) and high brain LL (Beta:0,207 p=0,02) were predictors of high ARMSS.

On the contrary, Abeta was not a predictor of early disability, since it did not show any significant correlation in either the univariate (r=0.128; p=0.1 for MSSS and r=0.11 p=0.2 for ARMSS) or multivariate models.

Tau results were confirmed in the RR subgroup. Spearman correlation analysis found a positive correlation with MSSS (r=0.41 p<0.0001) and ARMSS (r=0.26 0.009); and multiple regression analysis confirmed Tau as a predictor of disability for MSSS (Beta:0.294; R2:0.21; 95% CI 0.003- 0.016; p=0.006) and ARMSS (Beta:0.244; R2:0.277; 95% CI 0.001-0.012; p=0.016).

Discussion

Our longitudinal study demonstrates that CSF Tau levels at MS diagnosis predict the accumulation of disability in the next two years, measured with both MSSS and ARMSS. CSF Tau levels at diagnosis showed a predictive value comparable to MRI and age at diagnosis.

Tau is a structural protein of the neuronal microtubule, which is released in the CSF upon cell disruption. Tau can therefore be detected in individuals with neurodegenerative diseases, but also in healthy individuals of different ages without any apparent CNS pathology [39,40], as a result of physiological aging. Tau clearance from the CSF most probably occurs spontaneously [25], with Tau concentrations resulting lower in serum than in CSF [41]. Consistently, in patients with AD, total Tau is constantly released into the CSF following neuronal loss, and pathologically phosphorylated Tau protein forms neurofibrillary tangles that can be detected in the CSF [42]. In other neurodegenerative diseases, such as Creutzfeldt–Jakob disease (CJD), extensive neuronal damage causes high CSF Tau levels with no increase in hyperphosphorylated Tau [43]; therefore Tau may represent a biomarker of axonal loss also in other neurological conditions. In MS, axonal damage and neuronal loss have been demonstrated starting from the early disease stages and can be ascribed only partially to demyelination [2,5,7,8]. Accordingly, Tau CSF levels seem to reflect chronic axonal damage in our MS population. As a result, both MS and other neurodegenerative diseases display a progressive decrease of brain volume and accumulation of disability. No data are available so far on brain atrophy over time and CSF Tau in RR MS population. On the other hand, Pietroboni et al. detected a positive correlation between CSF Tau levels and MRI T2 LL [19]. The same group did not find a relation to disability at three years measured by EDSS [19]. This result is comparable to ours, but including MSSS and ARMSS, we identified, through CSF Tau levels, disability accumulation when EDSS is stable from baseline. To our knowledge, previously published studies used solely EDSS or rarely EDSS and MSSS to explore the prognostic value of biomarkers of neurodegeneration. ARMSS has the additional advantage of age correction, which is particularly relevant dealing with neurodegeneration.

Stratification of patients according to prognostic factors at diagnosis (spinal cord involvement, lesion load, gd enhancing lesions) did not detect significant differences in CSF biomarkers levels. In previous studies the most relevant correlation between prognostic factors at diagnosis and biomarkers of neuronal damage was found for NFLs, particularly regarding the correlation between NFLs levels and gd enhancing lesions [9,10]. We may speculate that CSF Tau reflects chronic axonal damage, less sensitive to acute inflammation, as opposed to NFLs, particularly serum levels, which are highly sensitive to acute inflammation and, therefore, under investigation as a surrogate marker of relapse [9,17].

In our patients, CSF Tau and Abeta levels were similar to those reported by other authors [17,19-25, 44]. As regards to MS progression phenotypes, we included only three patients with PP MS and for this reason, no reliable comparison with RR patients could be performed, similarly to the study by Guimaraes et al. [44]. Other studies specifically addressing this question showed contrasting results. Kapaci et al found higher CSF Tau levels in progressive (both PP and SP MS) than in RR MS and ascribed this difference to the higher neurodegeneration of progressive forms [17]. By contrast, Jaworsky et al showed lower CSF Tau levels in SP than RRMS [25], and Terzi et al. found no differences [24]. Jaworsky et al suggested that, in SP, the decrease of neuronal density results in loss of Tau resources [25]. Future studies are necessary to clarify this issue, taking into consideration the different demographic features of progressive MS, such as older age at onset than RRMS, since a linear age-associated increase in CSF Tau has been detected in both healthy subjects and AD patients. Therefore age-adjusted reference values are used in clinical practice for AD patients [42], but it is currently unknown whether the reference values for AD may apply to the MS population. To note, only two patients in our population showed Tau values above the AD reference values.

Few data were previously published on the possible prognostic role of Abeta in MS population. [13,16]. Levels of APP immunoreactivity were high in actively demyelinating MS lesions but not chronic MS lesions, perhaps indicating modifications of APP metabolism across disease stages [45-46]. However, incidence of AD was not increased in aged MS patients and evidence from PET-based studies showed that MS patients had significantly lower cortical beta-amyloid deposition than their matched controls, suggesting that inflammation and, in particular, microglial activation may have a protective role against Abeta pathology in early MS stages [47]. Morevover, Pietroboni et al. reported a significant decrease of CSF Abeta levels in MS patients, predicting increased disability at 3 years follow-up in terms of levels achievement of EDSS $\geq$ 3 [19]. On the contrary, Stampanoni Bassi et al and Martinez et al found no correlation between CSF Abeta levels and EDSS or disease activity [48,49]. Our study failed to detect a predictive value for Abeta in disease progression evaluated with either MSSS or ARMSS. We found lower CSF Abeta levels in patients with high versus low brain WMLL, but this difference was not statistically significant; however, we did not perform a volumetric analysis of MRI studies, which might have provided further relevant information. To our knowledge, no previous study compared CSF Abeta in RR versus and PP MS, and this aspect should be assessed in future studies. Age did not significantly influence Abeta CSF concentrations in our population. The relationship between age and CSF Abeta in healthy and AD populations is still under study, but current findings indicate a non-linear correlation and most laboratories do not currently use an age correction for AD diagnosis [40,42].

In conclusion, our study suggests that CSF Tau levels may help in early identifying MS patients who will develop high disability after two years, and may help to identify patients with aggressive disease who may benefit from high efficacy DMTs.

Declarations

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Conflicts of interest: we declare no CI for all authors

Availability of data and material: The data that support the findings of this study are available from the corresponding author, E. V, upon reasonable request.

Code availability: not applicable

Authors' contributions: Conceptualization: Eleonora Virgilio, Domizia Vecchio, Cristoforo Comi; Methodology: Cristoforo Comi; Data curation: Eleonora Virgilio, Domizia Vecchio, Ilaria Crespi, Formal analysis: Eleonora Virgilio, Ilaria Crespi; Visualization: Eleonora Virgilio; Writing-original draft: Eleonora Virgilio; Investigation: Domizia Vecchio , Ilaria Crespi, Roberto Serino; Writing-review & editing: Domizia Vecchio , Umberto Dianzani, Cristoforo Comi; Supervision: Roberto Cantello, Umberto Dianzani, Cristoforo Comi, Resources: Cristoforo Comi

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Ethics approval: The study was approved by the ethical committee of the University Hospital of Novara (reference no : CE 190/19).

Consent to participate: All patients signed an informed consent form for both diagnostic and research purposes at enrolment at the time of the LP

Consent for publication: The corresponding author ensures that all authors have seen and approved the final version of the paper and all are aware of the submission of the paper. The corresponding author is solely responsible for maintaining a proper communication with the journal and between co-authors, before and after publication.

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Tables

Table 1. Demographic, clinical features and biomarkers values at baseline. (N=100)

Gender	Female n,(%)	65 (65%)
Age	Onset (mean ± SD - year)	35.29 ± 10.50
	Diagnosis (mean ± SD - year)	36.98 ± 10.79
	-Relapsing Remitting	36.60 ±10.64
	-Primary Progressive	49.33 ±12.85
EDSS	At diagnosis (median, range, IQR)	1.5 , 0-4, 1-2
Type	Relapsing Remitting n,(%)	97 (97%)
	Primary Progressive n,(%)	3 (3%)
Brain WM lesion load (LL)	High LL (≥10) n,(%)	52 (52%)
	Low LL (<10) n,(%)	48 (48%)
Contrast enhancement	Absent n,(%)	59 (59%)
	Present n,(%)	41 (41%)
Spinal lesions (SL)	Absent n,(%)	25 (25%)
	Present n,(%)	75 (75%)
CSF Tau	Mean ± SD (pg/ml)	132.51 ± 68.56
CSF Abeta	Mean ± SD (pg/ml)	621.48 ± 252.21

Abbreviations: SD, standard deviation; EDSS; Expanded Disability Status Scale; IQR, interquartile range; CSF, cerebrospinal fluid; Abeta, beta-amyloid

Table 2. Biomarker comparisons of patients stratified by MRI, demographic features and MS features. (N=100)

Table 2		TAU		ABETA	
		(mean±SD)	P-value *	(mean±SD)	P-value *
Brain WM lesion load	High LL (≥10)	131.91 ± 70.75	0.9	580.86 ± 233.89	0.09
	Low LL (<10)	133.15 ± 66.85		665.48 ± 266.11	
Spinal lesions (SL)	Present	139.20 ± 71.11	0.1	643.50 ± 260.60	0.1
	Absent	112.50 ± 56.95		555.50 ± 216.80	
Contrast enhancement	Present	133.30 ± 57.02	0.5	627.50 ± 225.80	0.6
	Absent	131.90 ± 76.03		617.30 ± 270.90	
MS phenotype	Primary Progressive	150.43 ± 39.71	0.4	754.76 ± 246.95	0.2
	Relapsing Remitting	131.95 ± 69.31		617.35 ± 252.49	
Sex	Male	128.79 ± 55.03	0.8	618.87 ± 215.79	0.9
	Female	134.50 ± 75.17		622.88 ± 271.42	

* calculated with Mann–Whitney U test for comparison between groups

Abbreviations: Abeta, beta-amyloid; SD, standard deviation; LL, lesion load; MS, Multiple Sclerosis;

Table 3. Disability scores at last clinical follow-up. (N=100)

Table 3		
All patients (N=100)	mean (SD)	Median (range; IQR)
EDSS	1.5 (±1.21)	1.5 (0-6.5; 1-2)
MSSS	3.17 (±2.28)	2.52 (0.05-9.35; 1.32-4.30).
ARMSS	2.84 (±1.88)	2.90 (0.22-7.98; 1.15-4.30)
RR MS (N=97)		
EDSS	1.4 (± 0.9)	1.5 (0-4; 1-2)
MSSS	3.04 (± 2.14)	2.4 (0.05-9.09; 1.28-4.30)
ARMSS	2.8 (± 1.8)	2.76 (0.22-6.96; 1.11-3.89)
Progressive MS (N=3)		
EDSS	3.8 (± 1.9)	3.5 (0-6.5)
MSSS	5.2 (± 2.1)	9.08 (4.10-9.35)
ARMSS	4.1 (± 2.2)	4.82 (4.11-7.89)

Abbreviations: SD, standard deviation; IQR, interquartile range; EDSS, Expanded Disability Status Scale; MSSS, Multiple Sclerosis Severity Score; ARMSS, Age-related MSSS

Figures

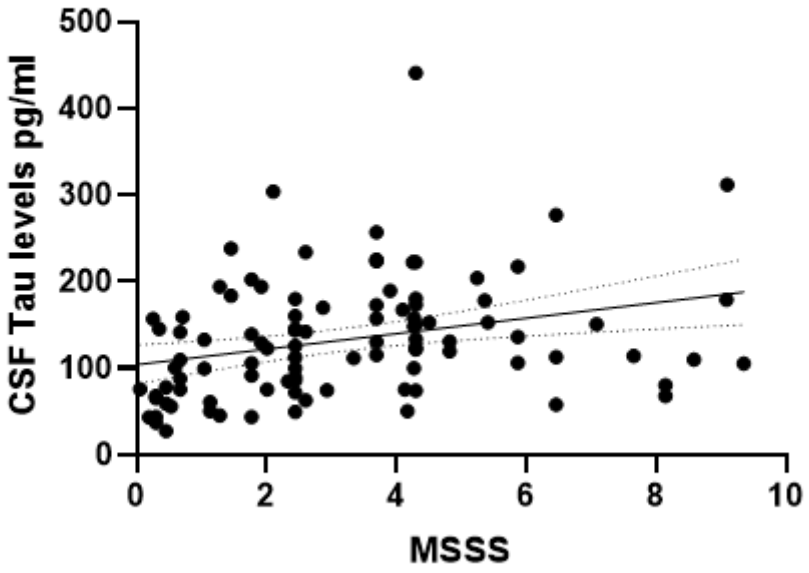

Figure 1

Correlation between CSF Tau concentrations in newly diagnosed MS patients and MSSS at last clinical follow-up. Correlation between CSF Tau concentrations and MSSS at last clinical follow-up r: 0.372 (95% CI 0.1838–0.5340, p=0.0001), Abbreviations: CSF, cerebrospinal fluid; MSSS, Multiple Sclerosis Severity Score

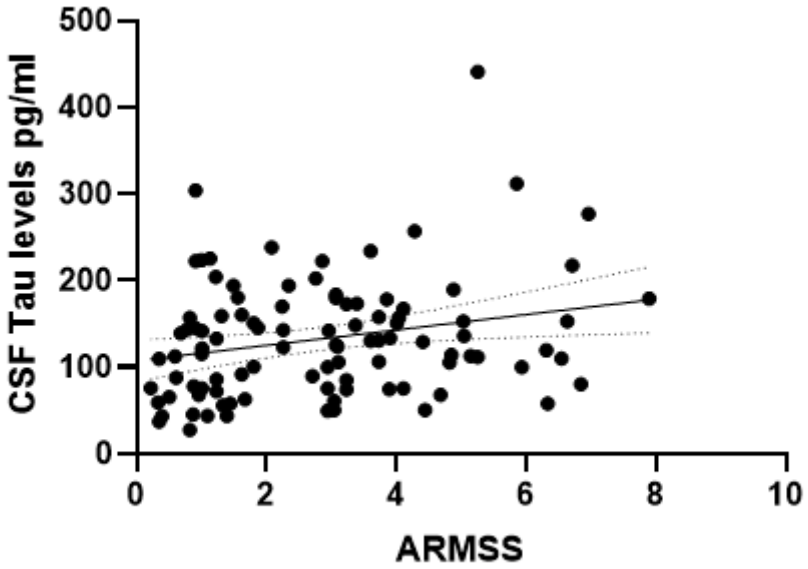

Figure 2

Correlation between CSF Tau concentrations in newly diagnosed MS patients and ARMSS at last clinical follow-up. Correlation between CSF Tau concentrations and ARMSS at last clinical follow-up r:0,2370 (95% CI 0.03664–0.4190 , p=0.0176), Abbreviations: CSF, cerebrospinal fluid; ARMSS, Age-related Multiple Sclerosis Severity Score