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Original article

CSF β-amyloid predicts early cerebellar atrophy and is associated with a poor prognosis in multiple sclerosis

Anna M. Pietroboni[a,b,c,1,*], Francesca Schiano di Cola[d,1], Annalisa Colombi[b,c], Tiziana Carandini[b,c], Chiara Fenoglio[b,c], Laura Ghezzi[a,b,c], Milena A. De Riz[a,b,c], Fabio Triulzi[e], Elio Scarpini[a,b,c], Alessandro Padovani[d], Daniela Galimberti[a,b,c]

[a] Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy
[b] University of Milan, Milan, Italy
[c] Dino Ferrari Center, Milan, Italy
[d] Neurology Clinic, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[e] Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Neuroradiology Unit, Milan, Italy

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ABSTRACT

Background: Neurodegeneration is present from the earliest stages of multiple sclerosis (MS) and is critically involved in MS related clinical disability. Aim of the present study was to assess the connection between amyloid burden and early cerebellar grey matter (GM) atrophy compared to early brain GM atrophy in MS patients.
Methods: Forty newly diagnosed relapsing-remitting (RR-) MS patients were recruited. β-amyloid1-42 (Aβ) levels were determined in cerebrospinal fluid (CSF) samples from all subjects. All participants underwent neurological examination and brain magnetic resonance imaging (MRI) at baseline. Twenty-nine out of 40 patients repeated a brain MRI at 1-year follow-up. T1-weighted scans were segmented using the Voxel-Based Morphometry (VBM) protocol and the Spatially Unbiased Infratentorial Toolbox (SUIT) from Statistical Parametric Mapping (SPM12).
Results: Between-group comparison of cerebellar parenchymal fraction (GM + WM/total cerebellar volume%) showed significant differences between $A\beta^{high}$ and $A\beta^{low}$ at baseline ($p < 0.0001$) and follow-up ($p = 0.02$). Similarly, a between-group comparison of cerebellar GM fraction (GMF) showed significant differences between $A\beta^{high}$ and $A\beta^{low}$ at baseline ($p = 0.002$) and follow-up ($p = 0.04$). The multiple regression analysis showed CSF Aβ concentration as the best predictor of GMF both at baseline and over time ($\beta = 0.505$, $\beta = 0.377$; $p < 0.05$). No significant results were found regarding global brain atrophy and CSF Aβ concentration.
Conclusions: Early cerebellar atrophy seems to be crucial in predicting a poor prognosis in MS, more than early global brain atrophy.

1. Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the central nervous system (CNS) (Reich et al., 2018). Although its pathologic hallmark is myelin loss, the neurodegenerative component is now considered remarkably relevant, particularly as it is related to long-term disability (Filippi et al., 2013). Histological studies have demonstrated that neurodegeneration is reflected by imaging-derived grey matter (GM) atrophy, as assessed by magnetic resonance imaging (MRI) (Filippi et al., 2012). As expected, global GM atrophy develops at a faster rate in patients with MS than healthy control subjects. Interestingly, GM atrophy is not uniform across the brain, and some regions are more susceptible than others (Steenwijk et al., 2016; Preziosa et al., 2017), suggesting that it occurs largely in a nonrandom manner and develops according to distinct anatomical patterns. At present, however, the biological mechanisms underlying GM atrophy in MS are still largely unknown. Consequently, evaluating neurodegeneration using novel MRI techniques, and its possible link with predictive biomarkers, has become a crucial area of research in MS (Pietroboni et al., 2017, 2018).

Cerebellar impairment is frequent in MS and traditionally considered predictive of a negative outcome (Weinshenker et al., 1991).

* Corresponding author at: Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122 Milan, Italy.
E-mail address: pb.anna@libero.it (A.M. Pietroboni).
[1] These Authors contributed equally to this work

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The cerebellum is, in fact, a predilection site for lesion development and both GM and WM demyelination are observed (Parmar et al., 2018). In contrast to late stage disease (Kutzelnigg et al., 2007), cerebellar cortical demyelination in early MS has been described as sporadic, whereas cerebellar atrophy has been detected earlier in patients with relapse-onset disease compared to patients with primary-progressive MS (Eshaghi et al., 2018).

Several structural and functional imaging techniques have been applied to investigate the extent of cerebellar involvement in MS and its contribution to the clinical manifestations of the disease (Parmar et al., 2018). Macro- and microscopic alterations in the cerebellar GM and WM were already found early in the disease course and even in absence of focal lesions (Deppe et al., 2016).

Cerebellar volume loss has not been the primary focus of MRI research for a long time, partly due to technical challenges concerning correct segmentation of the thin cerebellar gyri, sulci and cerebellar nuclei, and extraction of cerebellar tissue from adjacent infratentorial structures (Parmar et al., 2018). Only recently, automated segmentation tools focusing on the cerebellum were developed (Diedrichsen et al., 2009), even if results seem heterogeneous.

β-amyloid$_{1–42}$ (Aβ) has been recently thouroughly investigated as a putative biomarker of neurodegeneration in MS disability. Amyloid precursor protein (APP) has been detected in MS plaques with a higher APP immunoreactivity in actively demyelinating compared to chronic lesions, thus indicating a modification of APP metabolism across disease stages (Gehrmann et al., 1995). Reduced cerebrospinal fluid (CSF) Aβ levels have also been reported in MS patients (Pietroboni et al., 2017; Augutis et al., 2013) although the interpretation of these findings is still partially unclear (Gentile et al., 2015). In addition, two recent studies revealed that lower baseline levels of CSF Aβ are predictive of a more severe disease progression over a 3–5 years follow-up (Pietroboni et al., 2017, 2018). Moreover, reduced florbetapir uptake, using amyloid-PET imaging, has been found in WM lesions compared to normal appearing white matter in all clinical phenotypes of MS (Matías-Guiu et al., 2015). In fact, amyloid tracers used in PET imaging bind extensively to WM and uptake decreases significantly with demyelination.

In this scenario, we aimed to investigate how early cerebellar volume loss interacts with cerebrospinal fluid (CSF) Aβ levels in patients with MS in order to better understand the relationship between poor prognosis in MS patients, early cerebellar damage and amyloid pathology.

2. Materials and methods

2.1. Subjects

Forty patients with a new diagnosis of relapsing-remitting (RR-) MS, according to the 2010 revised McDonald criteria (Polman et al., 2011) have been recruited from January 2015 to January 2018. All patients underwent clinical assessment, brain MRI and lumbar puncture (LP) at baseline. LP was always performed in the acute phase of the disease (i.e. clinical relapse or the presence of new and/or gadolinium enhancement lesions at MRI) and before starting any treatment, including corticosteroids.

According to a previous study (Pietroboni et al., 2018), MS patients were split into two groups based on CSF Aβ levels (Aβ^{low} under 813 pg/ml and Aβ^{high} over 813 pg/ml).

Twenty-nine out of 40 patients underwent extra MRI scan at 1-year follow-up.

The main demographic and clinical characteristics of all subjects are summarized in Tables 1 and 2.

The current study was approved by the Institutional Review Board of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan, Italy). All MS patients gave their written informed consent for this research before entering the study.

Table 1
Subjects' demographic, laboratory, and clinical characteristics.

Variable	SM-RR (n = 40)
Age at LP, years (mean, SD)	37 ± 12.38
Sex, female% (n)	65% (26)
Disease duration at LP, years (mean, SD)	1.9 ± 4.3
EDSS baseline, total score (median; IQ1-IQ3)	2.0;2.0–3.0
Aβ, pg/mL (mean, SD)	799 ± 266
Intrathecal IgG synthesis% (n)	67.5% (27)

Table 2
Subjects' demographic, laboratory, and clinical characteristics classified according to their CSF Aβ levels (high: > 813 pg/ml; low: < 813 pg/ml).

Variable	Aβ^{high}	Aβ^{low}	p
Subjects (n)	20	20	ns[a]
Age at LP, years (mean, SD)	33 ± 11.3	40 ± 12.5	ns[a]
Disease duration at LP, years (mean, SD)	2.3 ± 5.03	1.5 ± 3.5	ns[a]
EDSS baseline, total score (median; IQ1-IQ3)	2.0; 2.0–2.5	2.0; 2.0–3.5	ns[b]
EDSS follow-up, total score (median; IQ1-IQ3)	1.0; 1.0–1.0	2.0; 2.0–3.0	0.02[b]
Aβ, pg/mL (mean, SD)	1021 ± 136	576 ± 149	< 0.0001[a]
Cerebellar GMF baseline (mean, SD)	65.06 ± 2.03	62.06 ± 3.4	0.002[a]
Cerebellar GMF follow-up (mean, SD)	64.65 ± 2.1	62.50 ± 3.4	0.04[a]
Cerebellar WMF baseline (mean, SD)	33.92 ± 1.7	33.43 ± 3.1	ns[a]
Cerebellar WMF follow-up (mean, SD)	33.60 ± 2.3	32.70 ± 3.0	ns[a]

[a] Mann–Whitney U test.
[b] Median test.

2.2. CSF collection and Aβ determination

CSF samples were collected by LP in the L3/L4 or L4/L5 interspace. The LP was performed between 8 and 10 a.m. after one-night fasting. Then, CSF samples were centrifuged in 8000 rpm for 10 min. The supernatants were aliquoted in polypropylene tubes and stored at −80 °C until use. Volume of the aliquots produced for the analyses was 500 µl. CSF cell counts, glucose, and proteins were determined. CSF Aβ levels were measured using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit (Fujirebio, Ghent, Belgium).

2.3. MRI acquisition

All patients underwent an MRI examination on Achieva 3T scanner (Philips, The Netherlands) at baseline. Twenty-nine out of 40 patients repeated an MRI scan at 1-year follow-up.

The acquisition protocol included: 1) a 3D T1-weighted scan (TR 9.90 ms; TE 4.61 ms; Flip angle 8°; slices thickness 1 mm; gap 0); 2) a T2-weighted scan (TR 2492 ms; TE 78 ms; Flip angle 90°; slices thickness 4 mm; gap 0); 3) a Fluid attenuated inversion recovery (FLAIR) scan (TR 11,000 ms; TE 125 ms; Flip angle 90°; slices thickness 2 mm; gap 0); 4) a double inversion recovery (DIR) scan (TR 14,109 ms; TE 25 ms; Flip angle 90°; slices thickness 3 mm; gap 0).

2.3.1. Cerebellar volumetrics

All 3D T1-weighted scans (n = 69) were first visually inspected to exclude the presence of macroscopic artefacts. Then, all MRI scans were preprocessed using the Spatially Unbiased Infratentorial Atlas Template (SUIT) toolbox (Diedrichsen, 2006), implemented in the Statistical Parametric Mapping toolbox version 12 (SPM12; http://www.fil.ion.ucl.ac.uk/spm/). Images were then segmented into GM, white WM, and CSF using the unified segmentation algorithm (Ashburner and Friston, 2005). For each scan, GM and WM fractions (GMF and WMF) were calculated, respectively, as the ratio of total WM and GM volume

to the total cerebellar volume (TCV). Additionally, longitudinal changes were assessed for each patient (Δ = 1-year follow-up minus baseline volume/TCV%).

2.3.2. Brain volumetrics

All 3D T1-weighted scans ($n = 69$) were first visually inspected to exclude the presence of macroscopic artefacts. Then, all MRI scans were processed using an optimized voxel-based morphometry (VBM) protocol in SPM 12 (Wellcome Department of Imaging Neuroscience; www.fil.ion.ucl.ac.uk/spm/). Segmentation and normalization produced a GM probability map (Ashburner and Friston, 2005) in Montreal Neurological Institute (MNI) coordinates. To compensate for compression or expansion during warping of images to match the template, GM maps were modulated by multiplying the intensity of each voxel by the local value derived from the deformation field (Ashburner and Friston, 2001). All data were smoothed using a 8-mm full width half maximum (FWHM) Gaussian kernel.

We derived for each scan the WMF and GMF fractions, which were calculated, respectively, as the ratio of total WM and GM volume to the total intracranial volume (TIV). Additionally, longitudinal changes were assessed for each patient (Δ = 1-year follow-up minus baseline volume/TIV%).

2.4. . Statistical analyses

All statistical analyses were performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Due to the non-normal distribution of data, all between-group comparisons were tested by non-parametric inferential statistical analyses (Median test and unpaired Mann–Whitney U test).

Hierarchical multiple regressions analyses between cerebellum and brain volumes as dependent variables and CSF Aβ levels and EDSS scores as explanatory variables were performed using SPSS. The regression model was adjusted in order to control for the potential effect of age, gender and disease duration.

Spearman correlation coefficient between CSF Aβ levels and EDSS scores was assessed in all patients.

For all statistical analyses the significance threshold was set to $p \leq 0.05$.

3. Results

3.1. Clinical variables and CSF biomarkers

CSF Aβ levels correlated with the EDSS score at baseline ($r = -0.443$, $p = 0.004$) and at 1-year follow-up ($r = -0.371$, $p = 0.01$).

3.2. Cerebellar volumes

Between-group comparison of cerebellar parenchymal fraction (GM + WM/TCV%) showed significant differences between $A\beta^{high}$ and $A\beta^{low}$ at baseline (98.98 ± 1.63 vs 95.5 ± 3.48; $p < 0.0001$; Fig. 1) and follow-up (98.26 ± 3.19 vs 95.22 ± 3.49; $p = 0.02$; Fig. 1).

Similarly, a between-group comparison of cerebellar GMF showed significant differences between $A\beta^{high}$ and $A\beta^{low}$ at baseline (65.06 ± 2.03 vs 62.06 ± 3.04; $p = 0.002$; Fig. 1) and follow-up (64.6 ± 2.1 vs 62.5 ± 3.4; $p = 0.04$; Fig. 1).

Then, a multiple regression analysis (adjusted for the potential effect of age and gender) was conducted to test whether CSF Aβ baseline concentration could predict cerebellar GMF and WMF at baseline. CSF Aβ concentration significantly predicted cerebellar GMF at baseline ($\beta = 0.505$, $p = 0.001$; Fig. 2), but not cerebellar WMF.

Lastly, a multiple regression analysis was conducted to test whether cerebellar volumes (GMF, WMF, ΔGMF, Δ WMF, parenchymal fraction) could predict patients' EDSS latest score (mean disease duration 1.9 years ± 4.3). EDSS was found to be significantly predicted by baseline cerebellar parenchymal fraction ($\beta = -0.406$, $p = 0.025$). Moreover, subjects were divided into two subgroups according to their EDSS score (≥ or < 3) at follow-up. We then performed a MANOVA analysis and found a statistically significant difference in cerebellar parenchymal fraction at follow-up based on EDSS score at follow-up. In particular, the subgroup with the highest EDSS score (EDSS ≥ 3) displayed lower overall cerebellar parenchymal fraction, $F(9, 17) = 3.960$, $p = 0.05$; Wilk's $\Lambda = 0.377$, partial $\eta 2 = 0.623$.

3.3. Brain volumes

A multiple regression analysis (adjusted for the potential effect of age and gender) was conducted to test whether CSF Aβ baseline concentrations could predict global brain volumes at baseline and at 1-year imaging follow-up. This analysis did not show any statistically significant result ($p > 0.05$).

4. Discussion

To explore the contribution of early cerebellar damage to disease progression in MS, we first compared cerebellar volumes between $A\beta^{high}$ and $A\beta^{low}$ patients, divided accordingly to their risk of progression based on CSF Aβ levels. As reduced CSF Aβ concentrations have been recently suggested as a prognostic biomarker in MS (Pietroboni et al., 2017, 2018; Pietroboni et al., 2018; Mattsson et al., 2009; Matías-Guiu et al., 2016), we decided to focus on this topic.

To the best of our knowledge, there is no other study evaluating early cerebellar GM atrophy related to amyloid burden in MS.

The $A\beta^{low}$ subgroup displayed higher EDSS score at follow-up and had significantly lower cerebellar GMF both at baseline and at follow-up compared to the $A\beta^{high}$ subgroup. Moreover, CSF Aβ levels proved to be a significant predictor of cerebellar GMF already at the very early stages of the disease. Interestingly, cerebellar atrophy seems to be an earlier predictor of disease activity than global brain atrophy, which appears to occur at a relatively later stage.

In the present study, we could not find any significant association between baseline global brain volumes and CSF Aβ concentration nor EDSS. It could be argued that cerebellum atrophy might precede altogether cerebral atrophy. Being CSF Aβ levels associated with neurodegeneration and inflammation and being the cerebellum particularly susceptible to both GM and WM demyelination, this could explain why CSF Aβ concentrations were able to predict cerebellar volumes very early.

The role of inflammation as a major contributor to cerebellar GM damage is usually accepted and, traditionally, the cerebellum is considered to be particularly susceptible to inflammatory damage from the CSF (Parmar et al., 2018). Therefore, in the cerebellum, overlying inflammation may play a role and amplify other pathological mechanisms, such as retrograde neurodegeneration secondary to WM lesions (Gilmore et al., 2009). The presence of cerebellar volume loss from the very early stages of the disease, together with an increased risk of disease progression, might be explained by a more inflammatory milieu (Eshaghi et al., 2018). However, histopathological studies showing significant widespread axonal degeneration suggest that cerebellar pathology in MS is at least in part independent of global cerebellar lesion load (Pomeroy et al., 2010). Hence, there is a pressing need to identify reliable biomarkers of early cerebellar GM atrophy.

Concerning β-amyloid and MS, the real issue is: why do CSF Aβ levels decrease in patients with early progressing disability? As already speculated (Pietroboni et al., 2017), lower CSF Aβ levels may be associated with the activation of more aggressive pathogenic mechanisms that are already in place since the early stages of disease. By referring only to the cerebellum, we argue that a precocious more inflammatory milieu could explain the strong association between CSF Aβ levels and early cerebellar volume loss in patients with higher disability.

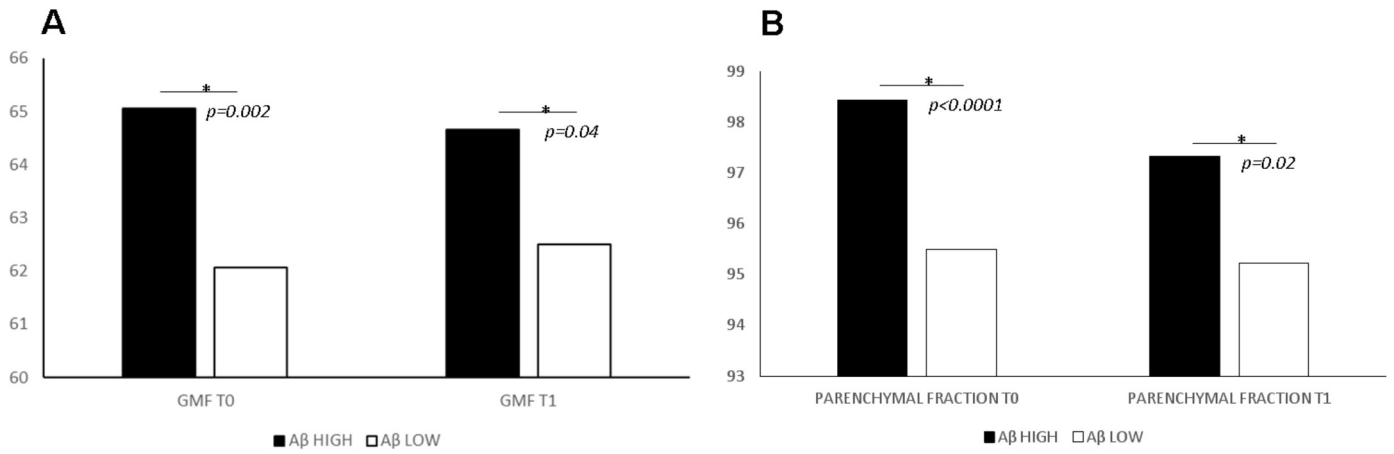

Fig. 1. (A) Mean grey matter fraction (GMF) at baseline (T0) and follow-up (T1) in the $A\beta^{high}$ and $A\beta^{low}$ subgroups. (B) Mean cerebellar parenchymal fraction at baseline (T0) and follow-up (T1) in the $A\beta^{high}$ and $A\beta^{low}$ subgroups. [$A\beta^{high}$: > 813 pg/ml; $A\beta^{low}$: ≤813 pg/ml].

Astrocytes are key regulators of the brain's inflammatory response. Astrogliosis occurs when astrocytes respond to injuries to the CNS by undergoing a spectrum of molecular and morphological changes. The impact of reactive astrogliosis in diseases is complex, and so for MS: reactive astrocytes can be both harmful and beneficial to surrounding cells and may worsen or resolve the initial CNS injury. Several studies have demonstrated that astrocytes express β-secretase (BACE1) at sufficient levels to generate Aβ, and that expression can be increased by inflammation (Zhao et al., 2011; Jin et al., 2012). Specifically, proinflammatory cytokines upregulate BACE1 activity (Sastre et al., 2003). Astrocytic expression of APP has also been demonstrated. Additionally, inflammation can upregulate APP expression and, therefore, Aβ secretion (Frost and Li, 2017). Aβ itself can be considered a proinflammatory mediator due to its ability to induce inflammation (Maezawa et al., 2011). Additionally, Aβ can stimulate proinflammatory cytokine release from astrocytes (Craft et al., 2004).

In line with these findings and hypotheses, the correlation we describe between CSF Aβ concentration and early cerebellar volume loss suggests the cerebellum may represent a site particularly susceptible both to inflammation and neurodegeneration, and seems to confirm the prognostic role of amyloid in MS.

Some limitations should be considered. First, this represents an exploratory study and a larger cohort of patients will be needed to confirm our findings. Second, it would be necessary to prolong the follow-up time to clarify cerebellar impairment, also in terms of WM volume loss and possible clinical manifestations. Third, our analysis refers to global cerebellar volume loss, but it would be interesting to extend our speculations investigating the cerebellum in its anatomical components, i.e. lobules and deep nuclei.

5. Conclusion

In conclusion, this study emphasizes the predictive role of CSF Aβ levels in MS, particularly in relation to early cerebellar involvement, and may allow an early prognosis in MS patients.

Informed consent

Informed consent was obtained from all individual participants included in the study.

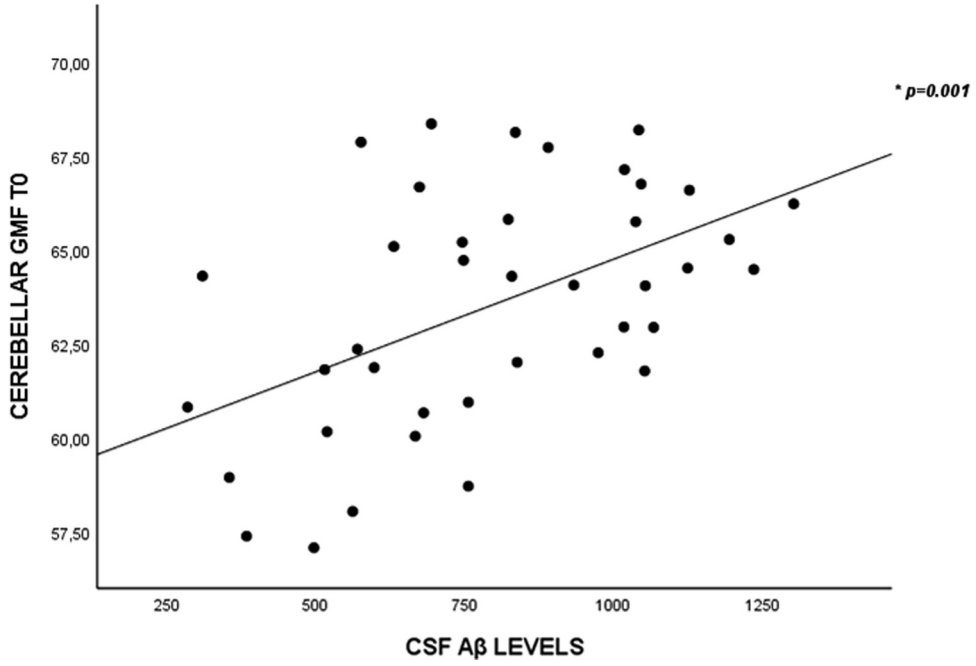

Fig. 2. Scatter plot of multiple regression analysis of GMF at baseline (T0) in function of CSF Aβ levels.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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