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RESEARCH

Serum but not cerebrospinal fluid biomarkers are associated with domain-specific cognitive performance in PWH

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Abstract

Introduction Blood biomarkers would be the ideal tool in routine practice in early identifying People With HIV (PWH) with low cognitive performance (LNP). We aimed to assess the diagnostic performance of neurodegeneration and brain injury biomarkers in cerebrospinal fluid (CSF) and serum to detect global and domain-specific cognitive performance in PWH.

Methods Retrospective cross-sectional study. Serum and CSF Tau, NFL, GFAP, UCH-L1, BDNF, AB40 and AB42, and CSF SNAP25 concentrations were measured by Single Molecule Assay (SiMoA) in treated PWH without neurological confounders. Global Deficit Score (GDS) was calculated assessing 6 cognitive domains; LNP defined as GDS $\geq$0.5. Correlations, AUROC, and diagnostic accuracy metrics were used to study the relationships between GDS, domain impairment, and biomarkers.

Results 74 adult PWH on suppressive antiretroviral therapy were included (53% male, age 56$\pm$9.8 years, median CD4+T-cells 542/µL); 50% had LNP. Despite moderate-to-strong correlations between CSF and serum biomarkers, only serum GFAP was associated with LNP (AUROC 0.67, $p=0.007$, sensitivity 67.6%, specificity 64.9%). Serum Tau was associated with impairment in memory (AUROC 0.66, $p=0.031$, sensitivity 85.0%, specificity 42.9%), processing speed (AUROC 0.71, $p=0.002$, sensitivity 46.0%, specificity 99.5%), and motor functions (AUROC 0.74, $p<0.001$, sensitivity 55.6% specificity 88.5%); serum NFL with executive dysfunction (AUROC 0.66, $p=0.024$, sensitivity 80.8%, specificity 50.0%). Variably combining serum GFAP, Tau, and NFL did not improve accuracy in detecting LNP.

Conclusions We observed very selective relationships between specific serum biomarkers and cognitive phenotypes, suggesting heterogeneity of the mechanisms underlying LNP in PWH, which may limit the diagnostic power of biomarker-based strategies.

Keywords Neurocognitive impairment · SIMOA · Neuroinflammation · Neurodegeneration · Phenotypes · Biotypes

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Introduction

Human Immunodeficiency Virus (HIV) enters the central nervous system (CNS) as early as 8 days after infection (Valcour et al. 2012). The persistence of chronic inflammation under antiretroviral therapy (ART), also within the CNS, and incidental brain injury during untreated infection (legacy effect) (Qu et al. 2022) can explain why 30–50% of people living with HIV (PWH) still suffer from different degrees of HIV-associated neurocognitive impairment (Caligaris et al. 2021; Heaton et al. 2010; Trunfio et al. 2018; Zenebe et al. 2022). With earlier initiation of ART and its world-scale implementation, HIV-associated dementia (HAD) has become far less frequent, while asymptomatic neurocognitive impairment (ANI) has become prevalent (Saloner and Cysique 2017). The fact that such a large proportion of PWH suffers from mild forms of neurocognitive impairment represents a therapeutic and diagnostic challenge. Sensitive biomarkers to reliably and feasibly detect and monitor neurocognitive functions in clinical settings would be of great support also to provide further insights into HIV neuropathology and inform targeted interventions specific to the CNS. In fact, ANI is a risk factor for further and more severe cognitive decline (Grant et al. 2014), and the aging population of PWH is coping with an unprecedented incidence rate of dementia compared to age-matched elderly without HIV infection (Bobrow et al. 2020; Lam et al. 2021; Yu et al. 2023). Identifying PWH with low cognitive performance (LNP) may allow for early diagnosis and, if available, appropriate treatment (such as cognitive rehabilitation) (Cysique et al. 2024; Nightingale et al. 2023; Nweke et al. 2022).

Blood biomarkers would be the ideal tool in routine practice due to the minimal invasiveness of sample collection (e.g., compared to CSF), but their ability to detect CNS processes may be limited and strong correlations between CSF and serum biomarkers of phenomena occurring in the CNS have been described only for a few (e.g., NFL (Alagaratnam et al. 2022) and GFAP (Stukas et al. 2023). Especially at the extremes of the detection range, traditional immune-enzymatic assays have limited power of quantification, rendering a granular stratification of PWH across the wide span of degree of cognitive performance hard to attain. More recently, the advent of single molecule arrays such as Single Molecule Assay (SiMoA) and Olink® multiplexed assays have improved the sensitivity in quantifying ultra-low concentrations of multiple biomarkers at a time and has allowed a more sensitive detection of inflammation and neurodegeneration in PWH on suppressive ART (Alagaratnam et al. 2024; Azzoni et al. 2022; Kuhle et al. 2016; van der Post et al. 2022). For instance, NFL serum levels measured by SIMOA have been recently proven to be sensitive to LNP in PWH (Cooley et al. 2024), while previous studies using standard immune-enzymatic assays reported negative findings (Hakkers et al. 2020).

Therefore, the aim of this study was (A) to evaluate the CSF–blood correlation of 8 biomarkers of brain injury and neurodegeneration measured through SiMoA; (B) to evaluate the accuracy of the serum and CSF levels of these biomarkers in detecting global and domain-specific LNP in a cohort of PWH on suppressive ART.

Methods

Study design

We performed a retrospective cross-sectional study to describe the serum and CSF concentrations of an extensive panel of biomarkers of inflammation and neurodegeneration measured through the ultrasensitive SiMoA SR-X (Quanterix, Billerica, MA, USA) and their accuracy in detecting both global LNP and domain-specific impairment among adult PWH on suppressive ART.

SiMoA SR-X uses an ultrasensitive bead-based technology that enables to quantify biomarkers at concentrations below the lower limit of quantification of immunoassays based on other methodology (e.g., ELISA, Luminex) commonly used for clinical and research purposes. The main difference with other technologies resides in its capability to separate single immunocomplexes in microwells holding one paramagnetic bead bound to one protein each, allowing for digital automatic reading that reaches up to 1000-fold greater sensitivity than standard immunoassays. The technology is validated on multiple samples, including plasma, serum, and CSF (Bayoumy et al. 2021; Kuhle et al. 2016; Li and Mielke 2019; Nilsson et al. 2022).

Biomarkers were measured in 74 paired serum-CSF samples stored (-80 °C) after being collected from PWH participating in prospective studies on HIV infection of the CNS performed at the Unit of Infectious Diseases, Amedeo di Savoia Hospital (Turin, Italy) between 2010 and 2020. As sampling could affect concentration of protein in CSF, we used the same standard procedure of CSF collection for all participants. Specifically, samples were collected within the same morning time window to minimize circadian fluctuations in CSF composition. The last tube of each collection was used to reduce the risk of blood contamination, further excluded by the absence of red blood cells in the chemical-physical analysis. Samples were immediately stored at −80 °C without centrifugation.

Participants were enrolled for research purposes; none had clinical indications for LP (e.g., infections or disorders of the CNS), nor contraindication to it. Exclusion criteria

were major confounding factors for the neurocognitive evaluation (e.g., active substance and alcohol abuse, CNS disorders), conditions able to affect CSF and serum levels of the assessed biomarkers (e.g., active infection, neuropathy by any cause), being on ART since less than 6 months, and detectable plasma HIV RNA > 200 cp/mL.

Demographic, clinical, and immunovirological data were collected at the LP (e.g., ART regimen, CD4 + T cell count and nadir). HIV RNA was quantified in blood and CSF by the Roche Amplicor assay v2.0 (Hoffman–LaRoche, Basel, Switzerland; lower limit of quantification 20 copies/mL).

The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Inter-Department Ethics Committee of San Luigi Hospital, Orbassano, IT (PRODIN study protocol n.0011279). Informed consent was obtained from all participants.

CSF and blood biomarkers

Total tau (Tau), neurofilament light chain (NFL), glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1), brain-derived neurotrophic factor (BDNF), fragments 1–40 and 1–42 of amyloid beta (AB40 and AB42) in blood and CSF and synaptosomal-associated protein 25 kDa (SNAP25) in CSF were measured.

Tau is a microtubule-associated protein released from injured axons in neurodegenerative disorders such as Alzheimer's Disease (AD) (Nam et al. 2020). NFL is a cytoskeletal protein expressed in neurons; it's a marker of axonal damage in blood and CSF (Delaby et al. 2022). GFAP is a cytoskeletal protein expressed in astrocytes, released in reaction to a variety of CNS injuries (Zheng et al. 2024). UCH-L1 regulates the ubiquitin pathways and oxidative stress primarily in neurons (Mi and Graham 2023). BDNF is a neurotrophic factor regulating neuronal plasticity with a protective role in neurodegenerative disorders (Colucci-D'Amato et al. 2020). Amyloid-β proteins (Aβ; fragments 1–40 and 1–42) are implicated in AD pathogenesis through their accumulation as extracellular plaques (Drabik et al. 2020). Lastly, SNAP25 is involved in cortical maturation and axonal development; (Batista et al. 2017) its levels decrease in diseases such AD (Jia et al. 2021).

The limit of detection and lower limit of quantification for each biomarker are reported in Suppl. Table 1. No biomarkers' cut-off has been validated for SiMoA in people with and without HIV infection; however, for serum NFL, we evaluated the age-adjusted cut-off proposed by Simrén et al. (Simrén et al. 2022) in healthy people without HIV infection.

Reibergrams were used to calculate Tourtellotte, IgG, and Tibbling Index as markers of intrathecal synthesis, as previously described (Reiber 1995). Blood-brain barrier (BBB) integrity was evaluated through CSF-to-serum albumin ratio (CSAR; CSF albumin mg/L/serum albumin g/L), as previously detailed (Caligaris et al. 2021). Age-adjusted cut-offs for BBB impairment were > 6.5 in people aged < 40 years and > 8.0 in people > 40 years.

Neurocognitive assessment

Participants underwent a neurocognitive battery of 16 tests assessing 6 cognitive domains: attention/working memory (Digit Span forward and backward tests, Digit Symbol test); executive functions/language (Trail Making Test B, Stroop Color test, phonemic verbal fluency); long- and short-term memory (Corsi block tapping test, Disyllabic words serial repetition, Free and Cued Selective Reminding Test); processing speed (Trail Making test A); sensory-perceptual skills (Copy of the Rey-Osterrieth complex figure); motor functions (Groove Pegboard Test for dominant/non-dominant hand). Raw test scores were converted into demographically adjusted (by age, sex, ethnicity, and education) T-scores based on published reference manuals, as previously detailed (Trunfio et al. 2022). T-scores were then converted into deficit scores, that were used to calculate domain-specific deficit scores and the Global Deficit Score (GDS), as previously described (Blackstone et al. 2012). A GDS ≥ 0.5 was used to define the presence of LNP, as previously suggested (Blackstone et al. 2012).

Statistical analysis

Normality was assessed with the Shapiro Wilk test, and all biomarker values were log10-transformed to minimize skewness. Either Student's t test or Wilcoxon rank sum test were used to compare continuous variables. False Discovery Rate was applied to address multiple testing when comparing biomarkers between groups defined by cognitive performance. Pearson's correlations were performed between variables. Areas under the operating curve (AUROC) were calculated for each biomarker against either cognitive impairment or impairment in each domain. The best performing cut-off was identified based on Youden index (JI), and the corresponding sensitivity and specificity were reported. Significant biomarkers were then combined to assess whether the diagnostic accuracy improved compared to the one of each single biomarker. To do so, biomarkers values were converted into categorical variables by the identified cut-offs at AUROC analysis; for the biomarkers with more than one cut-off (e.g., serum Tau) all of them were assessed alternatively. Comparisons between AUROCs were based on Z statistics (DeLong). The following combinations were

evaluated: all the biomarkers above the cut-off, at least one above, or at least two above. SPSS v29 (IBM Statistics, NY, USA) and Prism v10.3 (GraphPad, Boston, MA, USA) were used for the analyses.

Results

Study population

Seventy-four PWH were included, the majority being white (95.9%) males (71.6%), with a mean age of 56 years. The estimated duration of HIV infection was 13 years, and despite a high prevalence of AIDS in their medical history (71.6%), the CD4+T cell count was 542 cells/µL. Among participants with detectable plasma viremia ($n=11$), the median HIV RNA was 36 (IQR 31–63) cp/mL; 21.6% had detectable CSF HIV RNA with a median value of 80 (IQR 45–129) cp/mL. Fourteen participants (18.9%) had CSF viral escape (defined as a difference between CSF and plasma HIV RNA≥0.5 log10 cp/mL (Trunfio et al. 2019). The demographic, clinical, and immunovirological characteristics of the participants are shown in Table 1.

Participants underwent neurocognitive assessment within a median time of 3 (IQR 1–6) months from the LP. According to GDS, half ($n=37$) had LNP. Participants without LNP were similar to the LNP group except that they were younger (52.5 vs. 60.0 years, $p<0.001$), received longer education (11.0 vs. 9.0 years, $p=0.002$), and were more commonly prescribed with NNRTI-including regimes (45.1% vs. 10.8%, $p=0.013$; Table 1).

CSF and serum biomarkers

Between compartments, we observed moderate-to-strong correlations between CSF and serum levels of Tau (rho=0.606, $p<0.001$), NFL (rho=0.628, $p=0.001$), GFAP (rho=0.544, $p=0.001$), and AB42 (rho=0.361, $p=0.007$). UCH-L1 (rho=-0.263, $p=0.041$) and AB40 (rho=0.171, $p=0.010$) mildly correlated between compartments, while BDNF levels in CSF showed no significant correlation (rho=-0.044, $p=0.747$).

Among biomarkers, we found moderate-to-strong correlations only between NFL and GFAP levels: serum NFL-serum GFAP (rho=0.485, $p<0.001$), serum NFL-CSF GFAP (rho=0.416, $p<0.001$), CSF NFL-CSF GFAP (rho=0.480, $p<0.001$), and CSF NFL-serum GFAP (rho=0.740, $p<0.001$). The correlations between biomarkers and clinical and viro-immunological parameters are shown in Fig. 1. Few weak associations were observed with HIV-related parameters: CSF and serum NFL and serum UCH-L1 levels were all negatively associated with CD4+T cell nadir (rho=-0.271, $p=0.021$; rho=-0.294, $p=0.012$; rho=-0.365, $p=0.004$, respectively), and serum UCH-L1 was also inversely correlated with CD4+T cell count (rho=-0.409, $p=0.001$).

Table 1 Demographic, clinical, and Immunovirological characteristics of the study participants in the whole population and stratified by cognitive performance

	N = 74	NNP (n=37)	LNP (n=37)	p
Male, n (%)	53 (71.6)	28 (75.7)	25 (67.6)	0.439
White, n (%)	71 (95.9)	36 (97.3)	35 (94.6)	0.556
HIV acquisition route, n (%)				0.126
MSM	33 (44.6)	19 (51.4)	14 (37.8)	
Heterosexual	22 (29.7)	7 (18.9)	15 (40.5)	
IVDU	19 (25.7)	11 (29.7)	8 (21.6)	
Age, mean (SD)	56.0 (9.8)	52.5 (9.4)	60.0 (8.8)	**<0.001**
Education years, mean (SD)	10 (4)	11 (4)	9 (4)	**0.002**
HCV Ab+, n (%)	14 (18.9)	10 (27)	4 (10.8)	0.075
Est. duration of HIV infection, years median (IQR)	13.9 (3.8–18.1)	15.1 (3.5–19.2)	13.3 (3.8–17.8)	0.551
Plasma HIV RNA <LLOQ, n (%)	63 (85.1)	31 (83.8)	32 (86.5)	0.744
Plasma HIV RNA, Log10 cp/mL median (IQR)°	1.6 (1.5–1.7)	1.5 (1.5–1.6)	1.8 (1.6–1.9)	**0.030**
CSF HIV RNA <LLOQ, n (%)	58 (78.4)	28 (75.7)	30 (81.1)	0.572
CSF HIV RNA, Log10 cp/mL median (IQR)°	1.7 (1.5–5.2)	1.9 (1.8–5.2)	1.5 (1.4 – 1.7)	0.308
CSF escape, n (%)	14 (18.9)	7 (18.9)	7 (18.9)	1.000
CD4+ T cell count, cells/µL, median (IQR)	542 (380–786)	551 (307–821)	534 (428–759)	0.479
CD4+ T cell nadir, cells/ µL median (IQR)	119 (68–330)	185 (66–400)	118 (72–255)	0.551
ART regimen, n (%)				
PI-including	35 (47.3)	18 (48.6)	17 (45.9)	0.816
INSTI-including	38 (51.4)	15 (40.5)	23 (62.2)	0.063
NNRTI-including	17 (23)	13 (45.1)	4 (10.8)	**0.013**
MVC-including	11 (14.9)	8 (21.6)	3 (8.1)	0.102
GDS, median (IQR)	0.6 (0.2–1.2)	0.2 (0.0–0.3)	1.2 (0.8–1.6)	-

°Among participants with detectable HIV RNA in blood and CSF, respectively. *NNP* normal neurocognitive performance; *LNP* low neurocognitive performance; *MSM* men having sex with men; *IVDU* intravenous drug users; *HCV* Hepatitis C virus; *Ab* antibodies; *CSF* cerebrospinal fluid; *LLOQ* lower limit of quantification; *ART* antiretroviral therapy. *PI* protease inhibitors; *INSTI* integrase inhibitors; *NNRTI* non-nucleoside reverse transcriptase inhibitors; *MVC* Maraviroc; *GDS* global deficit score

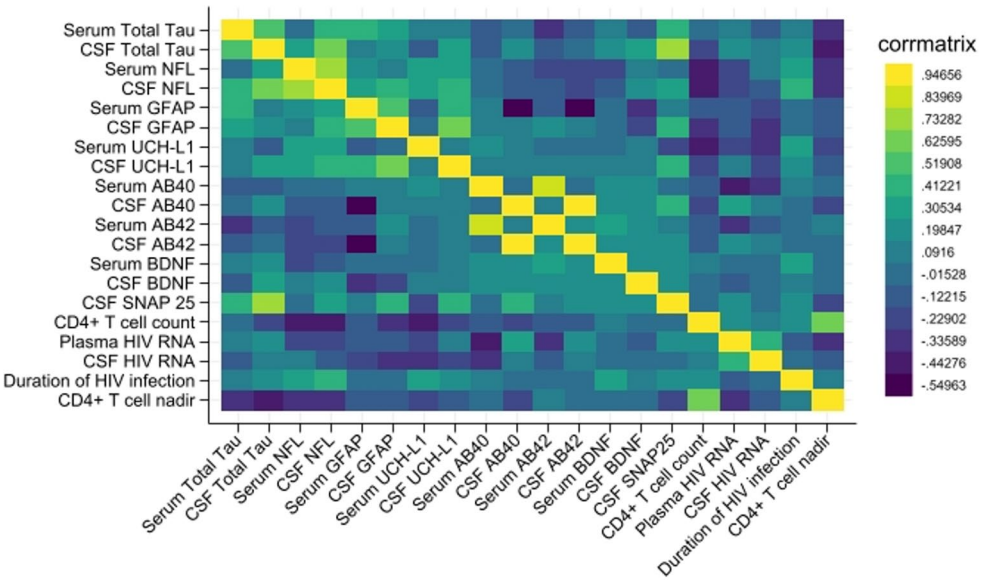

Fig. 1 The heatmap shows the correlation between serum and CSF biomarkers and between biomarkers and immunovirological features. Abbreviations. CSF: Cerebrospinal fluid. NFL: Neurofilament Light. GFAP: Glial Fibrillary Acid Protein. UCH-L1: Ubiquitin Carboxyl-terminal Hydrolase L1; AB40: Amyloid Beta fragment 1-40; AB42: Amyloid Beta fragment 1-42; BDNF: Brain Derived Neurotropic Factor; SNAP 25: Synaptosomal-Associated Protein 25 kDa

CSF and serum biomarkers by global and domain cognitive impairment

Participants with normal and low neurocognitive performance did not differ by BBB impairment and intrathecal synthesis, nor by any other CSF parameter (Suppl. Table 2). Among the biomarkers, only serum GFAP significantly differed between groups: participants with LNP had higher serum levels compared to participants without LNP (120.3 vs. 92.6 pg/mL, $p=0.012$; Suppl. Fig. 2a, Suppl. Table 2). GDS positively correlated with serum but not CSF levels of GFAP (rho = 0.230, $p=0.049$). However, after FDR adjustment, a significant difference in serum GFAP was not retained (Suppl. Fig. 2b). Among the biomarkers, serum GFAP showed the highest AUROC to detect global LNP: 0.67 (95%CI 0.55–0.80), $p=0.007$. The best-performing cut-off based on a JI of 0.32 was 109.65 pg/mL (sensitivity 67.6%, specificity 64.9%; Suppl. Figure 2a).

When the accuracy in detecting global LNP was assessed for serum NFL, neither the best cut-off identified within the study population (≥11.5 pg/mL, JI 0.22) nor the age-adjusted cut-off of serum NFL proposed by Simrén et al. (Simrén et al. 2022) showed sufficient performance: sensitivity 62.2%, specificity 59.5%, AUROC 0.61 (95%CI 0.49–0.72), $p=0.101$, and sensitivity 30%, specificity 27%, AUROC 0.54 (95%CI 0.41–0.67), $p=0.547$, respectively. The inter-rater agreement between the two cut-offs was lower than expected by chance (Cohen's K -0.130, see Suppl.

Table 3).

Worse scores at memory were associated with higher serum (rho = 0.242, $p=0.038$) and CSF levels of GFAP (rho = 0.254, $p=0.029$). Worse scores at executive functions were associated with higher serum NFL levels (rho = 0.286, $p=0.014$). Worse scores at processing speed were associated with higher serum tau levels (rho = 0.263, $p=0.033$). Worse scores at motor functions were associated with higher Tau (rho = 0.379, $p=0.005$) and higher GFAP levels in serum (rho = 0.388, $p=0.004$). The performance in the domains of attention/working memory and sensory/perception was not associated with any biomarker. When participants were grouped by impairment of single domains, significant domain-biomarker-specific associations were retained with the same pattern described by the previous correlations (Suppl. Figure 2).

Serum Tau had the best AUROC to detect memory impairment (0.66 [95%CI 0.51–0.80], $p=0.031$): at the cut-off of ≥1.09 pg/mL (JI 0.279) sensitivity and specificity were 85.0% and 42.9% (Suppl. Figure 2b). Serum Tau was also the best performing biomarker to detect impairment in processing speed (AUROC 0.71, 95%CI 0.58–0.84, $p=0.002$; Suppl. Figure 2c), although the sensitivity at the cut-off of ≥0.74 pg/mL (JI 0.398) was low (46.0%; specificity 99.5%), and motor functions (AUROC 0.74, 95%CI 0.60–0.88, $p<0.001$, Suppl. Figure 2d; sensitivity and specificity of 55.6% and 88.5%, respectively, at the cut-off of ≥0.89 pg/mL, JI 0.440).

Serum NFL showed the best performance to detect executive dysfunction: AUROC 0.66 (95%CI 0.52–0.80; $p=0.024$), best-performing cut-off of ≥16.60 pg/mL (JI 0.308, sensitivity 80.8%, specificity 50.0% Suppl. Figure 3). Exploratively, we also assessed the performance of the age-adjusted cut-off proposed by Simrén for executive dysfunction: AUROC 0.50 (95%CI 0.38–0.62, $p=0.994$), sensitivity 31.8%, and specificity 69.2% (DeLong's $p=0.019$ for AUROCs comparison).

No biomarker had an AUROC > 0.50 in detecting impairment in attention/working memory and sensory/perception. Considering the domain-specific relationships observed between cognition and biomarkers, we proceeded to assess the diagnostic accuracy of the combination of serum Tau, serum NFL, and serum GFAP in detecting global LNP. None of the combinations had an equal or better performance compared to the AUROC of serum GFAP alone (see Suppl. Table 4).

Discussion

In a small but well-characterized convenient sample of 74 adult PWH on effective ART, we observed significant correlations between CSF and serum levels of Tau, NFL, GFAP, UCH-L1, AB1-40, and AB1-42. This finding endorses the opportunity of measuring these biomarkers in serum to describe CNS processes, avoiding invasive CSF collection. However, only serum Tau, NFL, and GFAP levels were sensitive to clinically relevant correlates (cognitive impairment). More surprisingly, none of the biomarkers measured in CSF was associated with neither global LNP nor domain-specific cognitive impairment. Lastly, we observed that the biomarkers had better performance in detecting impairment of specific cognitive domains compared to their sensitivity to a measure of global LNP, showing consistent biomarker-domain relationship across different types of analyses: serum NFL with executive functions, serum Tau with memory, processing speed, and motor functions, and serum GFAP variably with the formers.

We found the blood compartment to be quite representative of the CSF, with moderate-to-strong correlation of every biomarker in the two compartments except for BDNF. This neurotropic factor can be independently produced by different cells in both CNS and peripheral tissues, such as megakaryocytes and skeletal muscle, and several factors contribute in influencing its levels: e.g., physical exercise (Delezie and Handschin 2018), thyroid hormones (Kamyshna et al. 2021) and antidepressants (Colucci-D'Amato et al. 2020). Of note, BDNF was undetectable in 36 CSF samples, while quantifiable in all the serum samples, compatibly with the idea that its levels may follow independent processes in the two compartments.

Despite moderate-to-strong correlation of biomarkers between the two compartments, only serum levels of NFL, Tau, and GFAP had associations with either global or domain-specific LNP. This finding may be explained by differences in the physiology underlying the production and clearance of the biomarkers: for example, greater stability over time in blood compared to CSF could render snapshot measurements in blood more representative of chronic processes, while greater fluctuations in biomarker levels may occur in CSF due to protein turnover, different kinetics of CSF clearance, or higher sensitivity to non-specific triggers (Wang and Holtzman 2020). For instance, NFL has a very long half-life in serum, continuing to increase in the two weeks following brain injuries and persisting elevated for up to one year (Thelin et al. 2017). For comparison with the other biomarkers not associated with any of our outcomes, UCH-L1 serum half-life is only 6–10 h (Thelin et al. 2017), making it a less suitable candidate for cross-sectional evaluations compared to more stable biomarkers. GFAP expression mainly occurs in astrocytes branches, which are in direct contact with the blood vessels forming the BBB, where it may be primarily released (Abdelhak et al. 2018; Hicks et al. 2022), making blood a representative sample. Tau is released in interstitial fluid from injured neurons and then rapidly increases in blood with a clearance from the CNS that occurs within minutes through caveolin1-mediated transcytosis and other efflux mechanisms along the BBB (Eisenbaum et al. 2021; Ojo et al. 2021; Pase et al. 2019; Yanamandra et al., 2017). In our population, Tau levels in serum were much lower than in CSF. This could be explained by saturation of such mechanisms or alternative clearance systems, such as the glymphatic system (Iliff et al. 2014) and protein degradation. Of note, all the biomarkers but BDNF showed levels in serum much lower than in CSF, without overlap between compartments. This may allow for a "floor effect" for which CSF levels exceeded by far the serum thresholds for LNP, making more challenging their diagnostic application. Longitudinal studies confirming chronically increased levels of these biomarkers able to saturate mechanisms of CSF clearance are warranted to confirm our findings. We furthermore cannot exclude the effect on the CNS of peripheral changes operated during and after systemic viral infections, as lately demonstrated for Long Covid (Wong et al. 2023).

In agreement with the biotypes framework recently proposed - highlighting the large heterogeneity within PWH suffering from LNP in terms of cognitive domains, symptoms, and also associated biomarkers and underlying mechanisms (Joseph et al. 2023; Sundermann et al. 2024; Tang et al. 2024) - we found that rather than detecting LNP as a whole (one size fits all), each biomarker was sensitive to impairment of selective cognitive domains, possibly reflecting different processes. As an example, NFL is a marker of axonal damage; its levels have been correlated with a decreased expression of presynaptic putaminal dopamine transporters, reflecting nigrostriatal degeneration (Buhmann et al. 2023; Diekämper et al. 2021). This process is common in HIV-related neuropathology (Nosheny et al. 2006) and nigrostriatal circuits are involved in executive functions (Ilardi et al. 2023), potentially explaining our selective association.

Similarly, Tau pathology has been associated with both memory impairment (Pelgrim et al. 2021) and motoneuron damage in general population (Süssmuth et al. 2010; Tang et al. 2019); herein, we observed a selective association between Tau and both memory and motor functions.

Impairment in attention/working memory and sensory/perception was not associated with any biomarkers. Every domain was assessed with a different number of tests, and the evaluation of sensory/perception domain relied on a single test, which may have not been sufficient or sensitive enough in discriminating among participants. Furthermore, we also acknowledge that the "one test-one domain-one outcome" has limitations (Kronemer et al. 2017), as every test requires the involvement of multiple abilities and brain areas simultaneously. It is therefore important to confirm the specificity of our biomarker-domain associations with different batteries of cognitive tests, explore more biomarkers, and replicate our findings in different populations. In this regard, none of the biomarkers was strongly associated with any of the HIV-related parameters (e.g., CD4+T cell count and nadir). This can probably be ascribed to the overall good immunovirological status of our sample, which better represents modern cohorts of PWH; different findings could be observed in PWH experiencing viral replication or poor immune recovery (Calcagno et al. 2024).

The milder levels of ongoing neuroinflammation persisting in nonviremic PWH is another reason in support of the use of sensitive technologies such as SiMoA when studying the etiopathogenesis of HIV-associated LNP: previous research may have underestimated the prevalence and impact of neuroinflammation in nonviremic PWH due to sensitivity limitations of measurement tools, while providing a more nuanced range of values may help characterize different biotypes.

As a secondary finding, we exploratively assessed the performance of the age-adjusted cut-off of serum NFL proposed to detect global LNP in the general population (Simrén et al. 2022). Since our sample presented a limited variability in age (56.0±9.8 years), we could not perform age-adjusted analyses. We found poor accordance between ours and Simrén cut-off possibly because those thresholds do not account for the "brain-age gap" previously described in people living with HIV (Petersen et al. 2021): Indeed, the median serum NFL of our participants (11.6 pg/mL, IQR 7.9–17.6) was closer to the one reported in the age group 61–70 in Simrén's paper (12 pg/mL, SD 5.2).

Among other limitations of this study, the small sample size, the cross-sectional design, the lack of previously validated cut-offs for the biomarkers, and the time gap between the lumbar puncture and the neurocognitive assessment (median 3 months) which may have biased the sensitivity of the biomarkers to the examined outcomes in favors of those biomarkers with longer half-life. On the other hand, despite the small sample, significant associations were retained even after adjusting for multiple testing, suggesting strong relationships; furthermore, all the lumbar punctures were performed within the same range of morning hours to limit the variability of measurements due to circadian fluctuations in CSF concentrations.

Conclusions

Biomarkers in serum, and surprisingly not in CSF, showed specific associations with distinct cognitive domains and weaker or no ability to detect global LNP: NFL was sensitive to executive dysfunction, Tau to impairment in memory, processing speed, and motor functions, and GFAP variably with all the above. These results suggest the complexity and heterogeneity in mechanisms and associated markers underlying cognitive impairment in PWH, endorse a more tailored approach to investigate HIV neuropathology such as the identification of cognitive phenotypes, and reinforce the possibility to identify less invasive and reliable biomarkers in blood.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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