19-21 GIUGNO ROMA
UNIVERSITA' CATTOLICA DEL SACRO CUORE
CENTRO CONGRESSI EUROPA
RESEARCH and CARE: FROM BENCH, TO BEDSIDE, TO COMMUNITY
Promosso da SIMIT
16° CONGRESSO NAZIONALE ICAR
Italian Conference on AIDS and Antiviral Research
P 77
POSTER 4 YOU ICAR 2024

The influence of blood brain barrier permeability on serum-to-CSF ratios of central nervous system biomarkers in people with HIV

J. Cusato, M. Antonucci, M. Trunfio, D. Imperiale, E. Vuaran, A. Palermiti, G. Di Perri, A. D'Avolio, S. Bonora, A. Calcagno

Introduction

- PWH can have central nervous system (CNS) comorbidities, including vascular disease, HIV-encephalopathy and neurodegenerative pathological changes, such as amyloid beta misfolding, taupathies and neuronal injury.
- Biomarkers can be a powerful tool for evaluating the outcome of CNS dysfunctions or treatment efficacy, other than for diagnosis of patients with an ongoing neuronal damage (ref.1).
- CSF sampling is a complex procedure, associated with discomfort and pain. Blood-based biomarkers may provide a non-invasive, cost-effective and scalable manner for detecting neurodegeneration, also in early disease stages. However, no data are available yet concerning the correlation between CSF and blood-based samples in the context of biomarkers in HIV.

Study Design

- This study aims at quantifying neurobiomarkers in different biological matrices (serum and CSF) in order to understand whether this non-invasive obtained sample could replace CSF. Different technical methods were also evaluated.
- Possible associations between neurobiomarkers, CSF-to-serum albumin ratio (CSAR) and altered blood-brain-barrier (BBB) were assessed.

Methods

- PWH were recruited in cross-sectional observational studies. They underwent lumbar puncture for clinical reasons or for research purposes.
- Available CSF and serum specimens were analysed through Single Molecule Array (SiMoA SR-X, Quanterix®) to evaluate ultrasensitive important neurology biomarkers with different kits.
- Following biomarkers were considered: tau, p-tau, Aβ1-40, Aβ1-42, neurofilament light chain (NfL), BDNF, UCHL1, PD-L1, GFAP.
- Reiber definition (normal BBB is present considering CSAR levels < 6.5 for patients aged < 40 years and < 8 for patients aged >=40 years).

Clinical features

Characteristics	Values
Patients, n	286
Age, years	42 (31-51)
Males, %	69%
CSAR	5,4 (3,9-7,3)
Abnormal BBB, %	66%

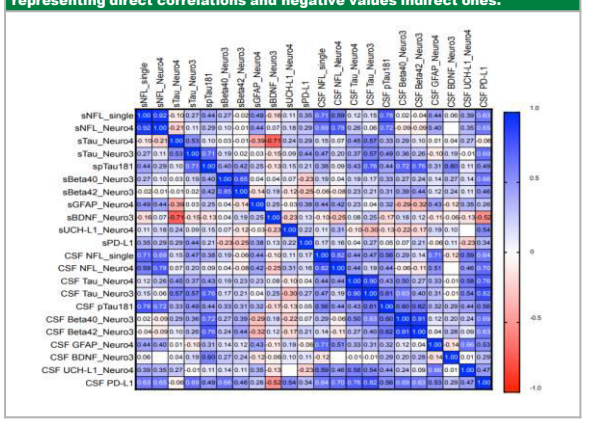
CSF and serum neurobiomarkers

- Biomarkers were analysed with different methods (Table 2).

Biomarker (pg/mL)	Method	Median (IQR)
CSF Aβ1-40	Simoa Human N3PA kit	6131.7 (3798.1;9499.2)
Serum Aβ1-40	Simoa Human N3PA kit	144.0 (0.7;192.2)
CSF Aβ1-42	Simoa Human N3PA kit	409.0 (269.5;649.2)
Serum Aβ1-42	Simoa Human N3PA kit	7.6 (1.2;10.0)
CSF Aβ1-42/ Aβ1-40 ratio	Simoa Human N3PA kit	0.07 (0.06;0.08)
Serum Aβ1-42/ Aβ1-40 ratio	Simoa Human N3PA kit	0.05 (0.04;0.06)
CSF tau	Simoa™ N4PA Advantage Kit SR-X	81.3 (33.4;141.2)
	Simoa Human N3PA kit	88.5 (49.34;149.7)
	Simoa all kits	81.1 (31.8;141.0)
Serum tau	Simoa™ N4PA Advantage Kit SR-X	1.9 (0.9;4.7)
	Simoa Human N3PA kit	0.64 (0.02;1.08)
	Simoa all kits	1.9 (0.9;4.59)
CSF Ptau	Simoa® pTau-181 Advantage V2 Kit	288.5 (168.9;688.9)
Serum Ptau	Simoa® pTau-181 Advantage V2 Kit	6.33 (4.61;9.04)
CSF NfL	Simoa™ N4PA Advantage Kit SR-X	634.2 (421.5;1322.9)
	Simoa® NF-light™ Advantage (SR-X) Kit	654.5 (387.7;1055.7)
	Simoa all kits kit	631.1 (421.1;1316.0)
Serum NfL	Simoa™ N4PA Advantage Kit SR-X	10.4 (7.0;16.7)
	Simoa® NF-light™ Advantage (SR-X) Kit	8.7 (6.2;16.3)
	Simoa all kits kit	10.4 (7.0;16.7)
CSF GFAP	Simoa™ N4PA Advantage Kit SR-X	6591.0 (4405.5;10253.9)
Serum GFAP	Simoa™ N4PA Advantage Kit SR-X	753.0 (46.3;115.6)
CSF UCHL1	Simoa™ N4PA Advantage Kit SR-X	1486.0 (1055.2;2034.5)
Serum UCHL1	Simoa™ N4PA Advantage Kit SR-X	22.2 (16.8;30.8)
CSF PDL-1	Simoa™ PD-L1 Discovery Kit	1.3 (0.9;2.1)
Serum PDL-1	Simoa™ PD-L1 Discovery Kit	1.7 (1.4;1.9)
CSF BDNF	Simoa™ BDNF Discovery Kit	0.03 (0.01;0.17)
Serum BDNF	Simoa™ BDNF Discovery Kit	54809 (2646;19561)

- Correlations between serum and CSF biomarkers were investigated according to the different used kits: significant correlations between serum and CSF biomarkers were observed for NfL, tau, p-tau, Aβ1-40, Aβ1-42 and GFAP (Figure 1).

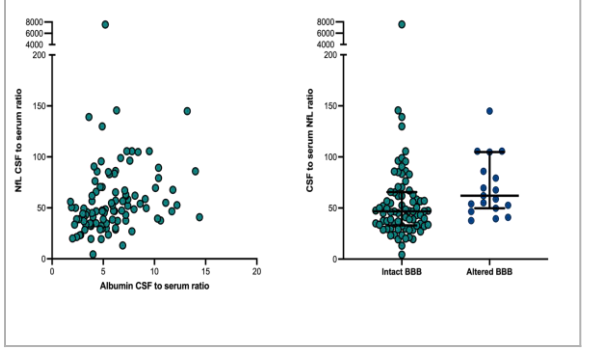
Figure 1 **A heatmap representing the correlation matrix between serum and cerebrospinal fluid biomarkers according to the different used methods. Spearman's tho values are reported and depicted with positive values representing direct correlations and negative values indirect ones.**



Biomarkers, CSAR and BBB impairment

- Associations between biomarkers CSF-to-serum ratios, CSAR levels and altered BBB were assessed. Higher CSAR were associated with higher CSF levels of NfL Neuro 4 kit (p>0,001; P=0.416) and with higher CSF levels of NfL all SIMOA KITS (p>0,001; P=0.416).
- When considering CSF-to-serum ratio only NfL had a statistically significant association with impaired BBB, according to Reiber definition: higher CSF-to-serum ratios of NfL was associated with altered BBB (p>0.001; 34 vs 65), as depicted in Figure 2.

Figure 2. NfL CSF to serum ratio according to albumin CSF to serum ratio (a) and altered blood brain barrier (b, BBB).



Conclusion

- A statistically significant correlation between serum and CSF levels of biomarkers of neuronal damage (NfL, tau), Alzheimer's disease pathogenesis (p-tau, Beta-42, Beta-40) and astrocyte damage/inflammation (GFAP) was observed. These findings support their use a peripherally collected biomarkers of CNS involvement.
- We also showed that blood brain barrier permeability may slightly modify the observed correlation suggesting to consider this not uncommon feature in PWH.
- Finally, the influence of different kits and methods on the biomarkers results and correlation warrant caution when comparing studies with methodological differences.

Reference

1. Blood-Brain Barrier Impairment in Patients Living with HIV: Predictors and Associated Biomarkers, Caligaris et al., Diagnostics, 2021