High Plasma GFAP in older PWH with Low Nadir CD4 Support Legacy Brain Injury and Reactive Gliosis

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BACKGROUND

Measuring cerebrospinal or plasma levels of brain-derived markers may provide useful information on **HIV neuropathogenesis** and help characterize cognitive impairment in PWH.

With the aim to evaluate whether HIV infection past history may influence plasma levels of brain-derived markers, we measured these markers in PWH ≥ 50 years and compared to plasma levels in people without HIV (PWoH) ≥ 50 years, to history of HIV, and to mental and physical performance.

PARTICIPANTS

- 102 ART-treated PWH ≥ 50 years
- 44 PWoH ≥ 50 years

Asymptomatic, no previous neurological disease

Table 1, 2. Characteristics of Participants

	PWH (n=102)	PWoH (n=44)
Male sex nr.	72 (73%)	21 (48%)
Age	60 (57-63)	57 (52-62)
Smoking (nr)		
- Active	41 (40%)	10 (23%)
- Ex	24 (24%)	11 (25%)
- Never	37 (36%)	23 (52%)
Drug use (nr)		
- Active	8 (8%)	1 (2%)
- Ex	22 (22%)	3 (7%)
- Never	72 (70%)	40 (91%)

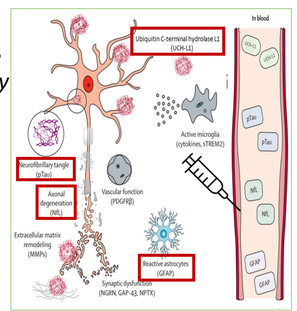
	PWH (n=102)
Years of infection	35 (19-33)
Nadir CD4+/µL	250 (150-362)
CD4+/µL	790 (582-971)
CD4+/CD8+	0,88 (0-52)
VL >50 c/mL (nr, %)	5 (5%)
cART (nr, %)	
- PI+NRTI	5 (5%)
- INSTI+NRTI	57 (56%)
- NNRTI+NRTI	22 (21,5%)
- Others	18 (17,6%)

Note: Values indicate median (IQR range) if not otherwise indicated

METHODS

Plasma Levels of Brain-Derived Markers (*Single Molecule Array Human Neurology Plex*):

- Neurofilament Light Chain (NfL)
- Glial Fibrillar Acid Protein (GFAP)
- Tau protein
- Ubiquitin carboxy-terminal hydrolase L1 (UHC-L1)



Cognitive and Functional Evaluations

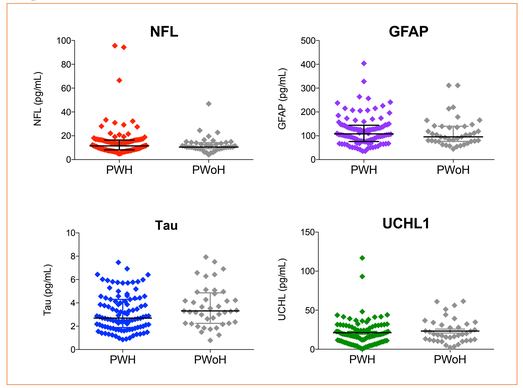
- Neurocognitive performance (*TMT-A, TMT-B, Digit Symbol)*
- Depression and anxiety (*HADS)*
- Muscle strength (*Handgrip test, Chair Stand test)*
- Balance (*Mini-BESTest)*

102 ART-treated PWH ≥50 years were prospectively assessed for **plasma brain derived markers** (*NfL, GFAP, t-tau* and *UHCL-1*) and for **functional** and **cognitive performance**, **depression and anxiety.**

✓ Higher NfL and GFAP level correlated to *age*, as expected.
✓ High GFAP level correlated to *low nadir CD4+ and long infection duration*, suggesting **legacy brain injury** with **reactive gliosis.**
✓ *Low functional performance* correlated to high GFAP and NfL level, providing useful for **characterization of global mental-physical status**

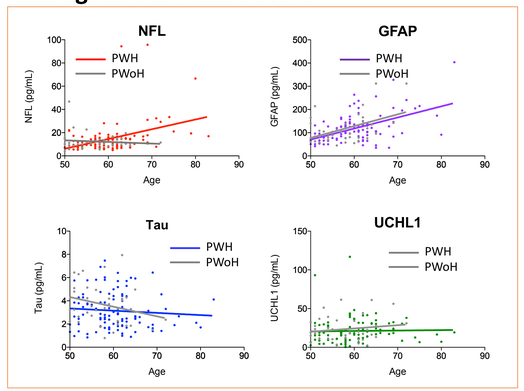
RESULTS

Fig.1: Plasma markers level in PWH vs PWoH



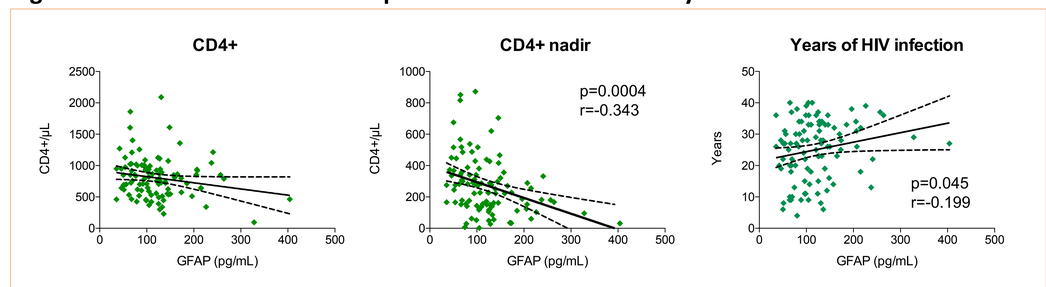
For ***none*** of the brain-derived markers, plasma level **differ significantly between PWH and PWoH** (Mann-Whitney test, fig.1).

Fig.2: Correlations of plasma markers level and age in PWH and PWoH



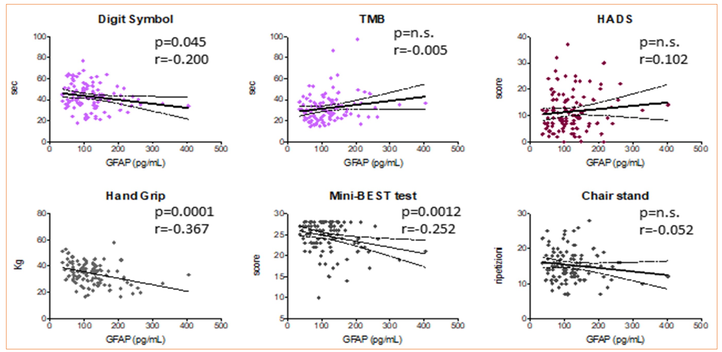
NfL and **GFAP** level directly ***correlate in PWH***; **age** correlate to ***GFAP*** in both groups, and with ***NfL*** *only in PWH* (Linear regression, fig.2).

Fig.3: Correlations between GFAP plasma level and HIV history variables



Higher **GFAP** level correlate to ***lower nadir CD4+ cell count*** and ***longer duration of infection***, but not to current CD4+ cell counts (Linear regression and Spearman's correlation, fig.3)

Fig.4: Correlations of plasma GFAP level to performance at functional tests in PWH



Higher **NfL** level correlated to ***lower performance at mini-BESTest***, and higher **GFAP** at ***DS***, ***handgrip*** and ***mini-BESTest*** (Linear regression and Spearman's correlation, fig. 4).

No association was observed between level of any marker and measures of cognitive impairment and depression/anxiety.

Table 3. Multivariate analysis of the variables associated with high NfL and GFAP level

	NfL		GFAP	
Variable	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Female gender	-3.30 (-9.10, 2.51)	0.26	26.28 (2.90, 49.66)	**0.03**
Age (years)	0.63 (0.16, 1.09)	**0.008**	4.44 (2.57, 6.31)	**<0.001**
DS (score)	0.06 (-0.18, 0.29)	0.64	-0.54 (-1.50, 0.41)	0.26
Mini-BEST test (score)	-0.88 (-1.76, 0.017)	**0.05**	1.49 (-2.10, 5.08)	0.41
Nadir CD4+/µL	0.0006 (-0.014, 0.015)	0.92	-0.07 (-0.13, -0.01)	**0.017**

Higher NFL level was independently associated with *older age* and *lower Mini-BESTest performance*; **higher GFAP** with *older age, being female* and *low nadir CD4+* (Logistic regression, Tab. 3)

CONCLUSIONS

- The association of *high GFAP level* with *low nadir CD4+ counts* and *long infection duration* may reflect a **legacy injury** with **reactive gliosis**, **of a previous untreated CNS HIV infection**.
- In conjunction with plasma levels of brain-derived markers, *functional assessment* may help characterize *the global mental and physical status in PWH.*

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