No association between plasma homocysteine and amyloid metabolism in people living with HIV

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Background

Advancement in antiretroviral therapy (ART) have significantly improved the quality of life for people living with HIV (PLWH), yet the intersection of HIV with neurocognitive functions remains a complex area of study. Disruptions in amyloid metabolism are central to the pathophysiology of Alzheimer's disease (AD), but PLWH also exhibit altered patterns regarding amyloid proteins and other cerebrospinal fluid (CSF) biomarkers. Homocysteine has been linked to the development of AD and correlates with markers of axonal degeneration in PLWH. The aim of this study was to examine the potential correlation between plasma homocysteine and signs of disrupted CSF amyloid metabolism in PLWH.

Methods

This cross-sectional study included archived samples from 139 PLWH receiving care at the Department of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg, Sweden. Participants were divided into groups based on ART use. Plasma homocysteine and CSF biomarkers including neopterin, Amyloid β1-42 (Aβ1-42), soluble amyloid precursor proteins (sAPP) α and β, and neurofilament light chain protein (NfL) were analysed.

Table 1. Background information on subjects divided by treatment status.

Groups	N	Gender M/F	Age (years)	Log plasma HIV RNA (copies/mL)	Log CSF HIV RNA (copies/mL)	Blood CD4+ count/mL
ART	75	47/28	45.0 (37.0 – 59.5)	<1.7	<1.7	530 (375 – 690)
Untreated	64	45/19	36.0 (31.0 – 43.0)	5.04 (4.24–5.63)	3.64 (2.67 – 4.40)	210 (63 - 458)

Abbreviations: ART, antiretroviral treatment; CSF, cerebrospinal fluid

Results

Levels of plasma homocysteine were similar among untreated participants compared with participants receiving ART. Even if there was evidence of possible disruption in amyloid metabolism among the untreated subjects, no significant correlation was found between plasma homocysteine and CD4+ T-cell count nor any of the amyloid proteins. A positive correlation was observed between homocysteine levels and CSF NfL ($r = 0.44$, $p < 0.001$).

Table 2. Median and interquartile ranges of analyzed biomarkers in the two groups. As age varied significantly between the groups, age-matched ratios of the biomarker levels (95% CI) were also calculated, ART group constitutes baseline.

Biomarkers Median (IQR)	ART	Untreated	Ratio	p-value
CSF sAPPα (ng/L)	402 (290–519)	500 (378–709)	1.38 (1.19–1.58)	< 0.001
CSF sAPPβ (ng/L)	265 (195–374)	270 (207–315)	0.88 (0.78–1.00)	0.042
CSF Aβ42 (ng/L)	990 (805–1178)	762 (626–867)	0.78 (0.72–0.85)	< 0.001
CSF neopterin (nmol/L)	7.10 (4.65–9.00)	16.85 (9.45–30.60)	2.70 (2.19–3.32)	< 0.001
CSF NfL (ng/L)	526 (324–773)	484 (276–953)	1.61 (1.27–2.03)	< 0.001
Plasma homocysteine (µmol/mL)	11.69 (9.43–16.18)	12.58 (10.12–15.35)	1.05 (0.97–1.15)	0.220

Abbreviations: Aβ42, Amyloid β42; ART, antiretroviral treatment; sAPP, soluble amyloid protein; NFL, neurofilament light chain.

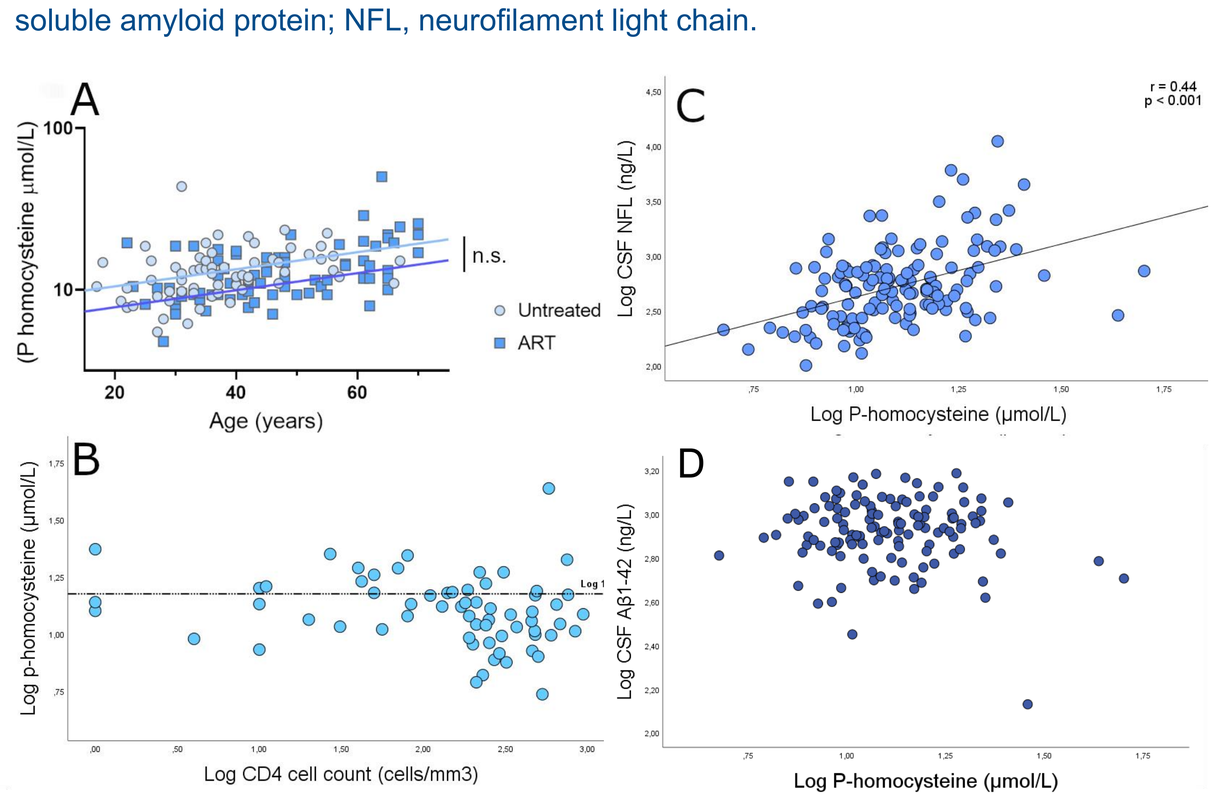

Figure 1. **A:** Distribution of plasma homocysteine in untreated and ART groups with age taken into consideration. **B:** No significant correlation between plasma homocysteine (p-homocysteine) and $CD4^+$ cell count in the untreated group. The horizontal line marks log 15, the upper reference value for p-homocysteine. **C:** Correlation between p-homocysteine and CSF NfL. **D:** No correlation between p-homocysteine and CSF Amyloid β42. Similarly, there was no correlation between p-homocysteine and the soluble amyloid precursor proteins α and β (not pictured). Abbreviations: NfL, neurofilament light chain; P-homocysteine, plasma homocysteine; n.s., non-significant

Conclusion

This study confirms the association between plasma homocysteine levels and neurofilament light chain (NfL) in people living with HIV (PLWH), as observed in our previous research. While we found no significant link between plasma homocysteine levels and amyloid metabolism in PLWH, the consistent correlation with NfL suggests a potential connection to B12 and folate deficiencies and their role in subcortical neuronal injury in this population. It is important to note, however, that these findings do not establish a direct causal relationship between homocysteine levels and increased NfL. Further investigation is required to fully understand these interactions and their implications for the neurological health of PLWH.