CSF Complement is Correlated to Immune Activation in Untreated but not Treated HIV

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Different patterns were seen in CSF complement factor concentrations in PLWHA vs. HIV-negative

Correlation to CSF immune activation was seen only in untreated HIV but not in PLWHA on ART

Background

Antiretroviral therapy (ART) has substantially reduced the risk for serious central nervous system (CNS) complications in chronic HIV infection, but milder forms of neurocognitive impairment have been described in people living with HIV/AIDS (PLWHA) using ART. Intrathecal immune activation is a key component in HIV-associated CNS injury in advanced untreated infection, while the importance of the residual, low grade CNS inflammation seen during ART is less clear. The immune activation is initiated by the virus, but secondary immunological mechanisms may contribute to the inflammatory process.

The complement system is involved in the pathogenesis of other inflammatory CNS conditions, but the importance in HIV-associated CNS infection, as well as the potential impact of ART is less well characterized. The aim of this study was to explore evidence of complement activation in CSF in untreated HIV infection and in PLWHA on ART.

Methods

Design: retrospective cross-sectional study including PLWHA on (HIV-ART) or off (HIV-untreated) ART monitored in a standardized CSF sampling protocol, and HIV-negative patient controls (no evidence of CNS infection in clinical diagnostic lumbar puncture).

Biomarker analyses: commercial ELISA was used for quantification of CFB, C1q, C3a, C4b2a, C5, C5a (Cloud-Clone Corp.) and C3b (Cusabio Biotech). Neopterin was measured using a commercial immunoassay (BRAHMS). The light subunit of the neurofilament protein (NfL) was measured using an in house sandwich ELISA. Concentrations are reported as the age 65 equivalent NfL(65).

Statistical methods: group differences of $\log_{10}$ biomarker concentrations were estimated using ANOVA (LSD post-hoc test). Correlations were calculated using Pearson correlation

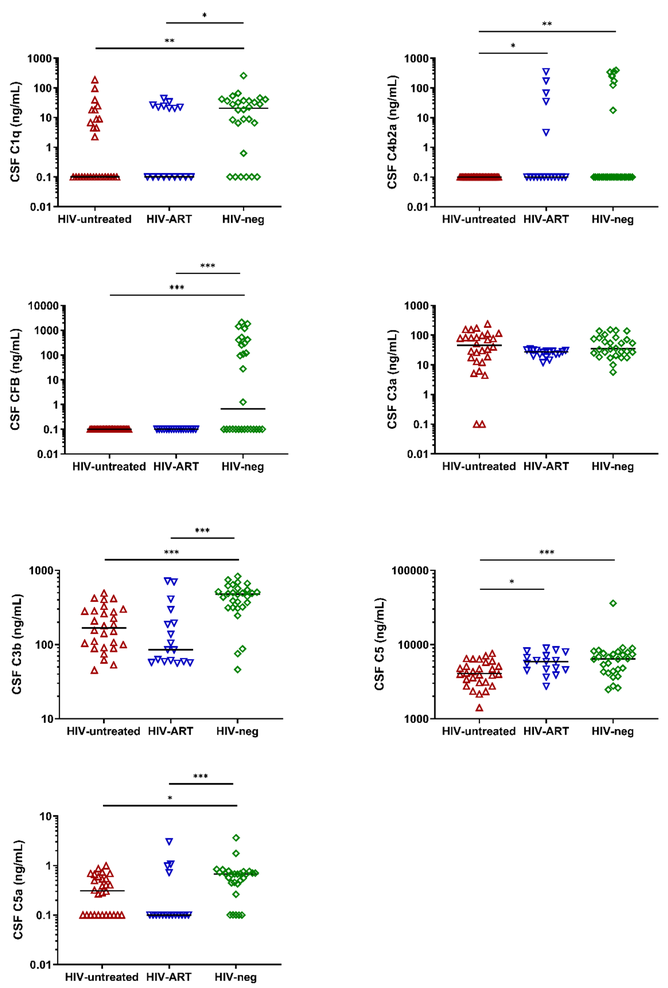

Figure 1. CSF Complement Factor Concentrations

Significant differences in CSF complement concentrations were seen ***between HIV-untreated and controls*** in C1q (p=.004), C4b2a (p=.003), CFB (p=< .001), C3b (p=< .001), C5 (p=.001) and C5a (p=.02), but not C3a (p=.3), ***between HIV-ART and controls*** for C1q (p=.05), CFB (p=< .001), C3b (p=< .001) and C5a (p=< .001), and ***between HIV-untreated and HIV-ART*** for C4b2a (p=.03), C5 (p=.02).

Table 1. Baseline characteristics and CSF biomarker concentrations

Group	HIV-ART (n=17)	HIV-untreated (n=28)	HIV-neg (n=28)
Baseline characteristic			
Gender (female), number (%)	8 (47%)	11 (39%)	9 (32%)
Age (years)	38 (30-47)	41 (32-50)	44 (37-55)
CD4+ T-cells (cells /µL)	600 (488-815)	270 (100-445)	–
Time on ART (months)	39 (19-84)	–	–
HIV-RNA, plasma ($\log_{10}$ c/mL)	0	4,49 (4,14-5,04)	–
HIV-RNA, CSF (log10 c/mL)	0 (0-1,52)	3,8 (2,77-4,5)	–
CSF biomarkers			
CSF WBC (cells)	0 (0-2)	9 (3-16)	–
CSF neopterin (nmol/L)	5,0 (4,6-5,9)	16,5 (10,5-23,5)	–
CSF NfL (age-adjusted), (ng/L)	332 (191-442)	395 (274-495)	–
CSF complement factors (ng/mL)			
C1q	0 (0-23)	0 (0-9)	20 (2.1-36.9)
C4b2a	0 (0-19)	0	0 (0-97.3)
CFB	0	0	0.7 (0-378.5)
C3a	27,3 (21,2-31)	45,9 (14,2-93,9)	35.3 (21.7-79.4)
C3b	85 (59-245)	167 (93-283)	480 (316-563)
C5	5911 (4523-7546)	4063 (3087-5612)	6403 (4310-7765)
C5a	0 (0-0,41)	0,31 (0-0,58)	0.7 (0.4-0.7)

All values are median (IQR) unless otherwize stated

Biomarker correlations: In the **HIV-untreated group only**, significant correlations were seen between CSF neopterin and complement factors C1q (r=.63; p< .001), C3b (r=.47; p=.01), C5 (r=.56; p=.002); CSF neopterin and CD4+ T-cell count (r=-0.53; p<0.01) and NfL(65) (r=0.46; p=0.01); CD4+ T-cell count and complement factors C3a (.45; p=0.16); C5 (-.65; p<.001).

Conclusions

Different patterns were found in PLWHA compared to controls in CSF complement activity for all activation pathways (classic, alternative, lectin) as well as the terminal cascade. Correlation to macrophage/microglial activation was seem only in untreated PLWHA.

ART appeared to reduce, but not eliminate, complement activity in CSF. Although the clinical significance of residual intrathecal immune activation needs further study, complement activity may potentially contribute to the CNS pathogenesis in HIV.

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