Introduction

HIV central nervous system (CNS) infection is associated with local inflammation that evolves over the course of systemic disease and impacts neurological function. To compare the evolution of CNS and systemic inflammation with disease progression, we assessed 10 inflammatory biomarkers in cerebrospinal fluid (CSF) and blood across a spectrum of subject groups.

Methods

This exploratory cross-sectional study measured 10 inflammatory biomarkers (TNF-α, MMP-9, CXCL10, iCD4, iCD163, αCAM, CCL2, IL-1, TNF-α, and neopterin) by ELISA in 9 subject groups: HIV-uninfected controls (HIV-20); primary HIV infection (PHI; 24); untreated neuroaidsymptomatic (NA) subjects in 4 blood CD4+ cell strata, ≥200, 200-349, 50-199 and ≤50 cells/L (NA, 20 each); untreated HIV-associated dementia (HAD, 12); treated, virus-suppressed (Rx, 19) and elite controllers (EC, 8). The Kruskal-Wallis test was used for overall comparisons across groups and in a priori defined between-group comparisons defined by pathological questions (MMP vs. HIV, over the 4 NA groups; HAD vs. combined groups with CD4≥200 cells/L, Rx and EC vs. HIV. Correlations among CSF and blood biomarkers in the entire sample were assessed by Spearman correlation. ANOVA with linear and quadratic orthogonal trends across the 4 NA groups were assessed 10 inflammatory biomarkers in cerebrospinal fluid (CSF) and blood across a spectrum of subject groups.

Results

Subject information is listed in Table 1 and the results of the analyses of the CSF and blood inflammatory markers are shown in Figure 1. Marker concentrations are shown in Figure 1. Marker concentrations are shown in Table 2. Increases in CSF and blood markers above HIV- levels were common in PHI implying early immun activation in both compartments.

In the four NA groups, the pattern differed in CSF and blood: with decreasing CD4 counts, increases in plasma biomarker concentrations were common and often linear (Table 2) while in CSF an inverted U pattern was seen in some of the biomarkers.

Inflammation in CSF and blood was reduced by treatment and was lower in elite controllers than viromics, but in both these groups inflammatory biomarker levels remained above those of the HIV-group.

Main findings and conclusions

- HIV infection is accompanied by a complex evolving inflammatory response in both CSF and blood.
- Changes in different inflammatory biomarkers diverged in the two sampled fluids indicating evolving compartmentalization of responses in the CNS.
- Primary infection is characterized by an early and broad CSF and blood inflammatory response which is largely (though not entirely) similar in the two compartments.
- Untreated systemic disease progression defined by blood CD4+ T cell loss across the four non-HAD NA groups shows important divergence of inflammatory response:
  - Blood showed variable progressive increase in most of the inflammatory biomarkers.
  - MMP-9 was a conspicuous exception with progressive decrease.
  - By contrast, CSF showed two patterns of change.
    1. An inverted U with initial rise and then fall, e.g., TNF-α, MMP-9, CXCL10.
    2. Progressive increase, e.g., sCD163, CCL2.
  - We hypothesize that these indicate predominantly lymphocytic (1) and macrophage (2) responses in CSF, respectively.
- HAD was characterized by compartmentalized increase in all CSF inflammatory biomarkers.
  - High, often highest, levels of all CSF biomarkers were noted in HAD group.
  - This was not mirrored in blood concentrations of these biomarkers.
- CSF inflammation, like that in blood, was markedly attenuated by treatment-induced and endogenous viral suppression (elites).
  - Though, concentrations remained higher than HIV-controls, indicating residual systemic and CNS immunomodulation in these subjects.

Table 2. Trend analysis across NA groups. Linear and quadratic trends in the biomarker levels with increasing CD4 counts were assessed in the four NA groups. A four-way interaction was common in blood (except MMP-9). An inverted U (quadratic) trend was seen in several CSF markers like TNF-α. We hypothesize that in CSF a linear fit designates lymphocyte-predominant inflammation and a quadratic fit indicates lymphocyte-macrophage-predominant inflammation. Intensity of red fit designates level of significance: dark red shows full Bonferroni correction, lighter red p<0.01 and very light red p<0.05.

Figure 1. CSF and blood inflammatory biomarker concentrations.

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