Cerebrospinal Fluid Viral Blips and Persistent Escape in HIV-Infected Patients On ART

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Background: Cerebrospinal fluid (CSF) viral escape, where HIV-1 RNA is increased in CSF while suppressed in plasma, has previously been shown to occur infrequently in subjects responding well to antiretroviral therapy (ART). It is unclear if CSF viral escape represents a continuous low-grade CNS infection in some patients, and may constitute a risk for future neuronal damage. The light subunit of the neurofilament protein (NFL) is a component of myelinated axons, and elevated concentrations in CSF are a sensitive marker of ongoing axonal injury in HIV-associated dementia (HAD). To investigate the frequency of CSF viral escape in relation to neuronal damage, we analyzed NFL in a longitudinal cohort of subjects responding well to ART.

Methodology: Subjects on effective ART ≥6 months with plasma HIV-1 RNA <50 c/ml at inclusion, followed with ≥2 lumbar punctures for CSF analysis were identified from a longitudinal study. Subjects with CNS opportunistic infections or other significant CNS disease were excluded from the analysis. Transient low increases in plasma viral load ("blips") during the study period were allowed. HIV-1 RNA was analyzed with real-time PCR (Cobas TaqMan, Roche). CSF concentrations of NFL were measured by an enzymatic 2-site quantitative immunoassay (UmanDiagnostics, Umea, Sweden). CSF neopterin was measured by ELISA. The relationship between CSF NFL levels and age were analyzed with a linear mixed effects model. Mann Whitney U-test was used for group wise comparison.

Results: Seventy-five (52 male, 23 female) patients with multiple CSF analyses (median 5, range 2-14) were included in the analysis. 26 (35%) had CSF RNA above quantification limit (20 c/ml) on at least one time point (median 50; IQR 32-78 c/ml); 6 (8%) subjects had increased CSF RNA in consecutive samples. 40 (53%) patients had ≥1 (range 0-6) transient plasma HIV-1 RNA >20 c/ml (median 44; IQR 29-71 c/ml). In 8 samples, RNA was >20 c/ml in both CSF and plasma. Of all 373 tested samples, 38 (10%) and 74 (20%) were >20 c/ml in CSF and plasma, respectively. CSF neopterin was higher in samples with increased (median 7.3, IQR 6.4-11 nmol/l) than with undetectable (median 6.4, IQR 5.1-7.7 nmol/l) CSF HIV-1 RNA (p<0.05). No similar difference was found in CSF NFL.

Conclusions: In this longitudinal analysis we found that occasional increased CSF HIV-1 RNA was not uncommon in patients on effective ART, although less frequent than in plasma. A minority of subjects had persistently increased CSF virus which may represent CSF viral escape. Increased CSF HIV-1 RNA was related to a higher level of intrathecal immune activation. However, we found no correlation between CSF HIV-1 RNA and NFL, suggesting that increased CSF virus and immune activation does not result in CNS axonal injury in patients on ART, at least not in the short term.