Neurocognitive Dysfunction in HIV+ Youth: Investigating the Relationship to Immune Activation

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Abstract

Background: HIV+ individuals are at an increased risk of developing neurocognitive impairment compared to the general population. It is postulated that ongoing viral replication causes immune activation that results in neural damage. Few studies have investigated this phenomenon in the pediatric and young adult HIV+ population.

Methods: This was a pilot, cross-sectional study enrolling a cohort of HIV+ youth and matched healthy controls. Neurocognitive performance was assessed by WAIS-IV intelligence scale and markers of lymphocyte and monocyte activation assessed via flow cytometry in plasma and PBMC samples. Analyses used parametric and non-parametric tests. Spearman coefficients, as well as multiple linear regression.

Results: Eighty subjects (47 HIV+: 57% male, 89% black, mean age 17 years) were enrolled. Mean scores were low-average for 4 of 5 testing domains for the HIV+ subjects and average for all 5 in the controls. Working memory was the only statistically significant factor in HIV+ compared to healthy, matched controls.

Conclusions: Primary objective: to determine the relationship between neurocognitive performance and markers of lymphocyte and monocyte activation among HIV+ youth.

Secondary objective: to investigate differences in associations between immune activation and neurocognitive performance in HIV+ youth compared to healthy, matched controls.

Methods

STUDY DESIGN

Prospective, cross-sectional evaluation of a cohort of HIV+ youth aged 8-26 years with immune activation assessed by CD38 and HLA-DR. HIV+ activation was higher in the HIV+ subjects compared to the controls, but proportions of inflammatory (CD4+CD16+) and protective monocytes (CD14dimCD16+) were similar between groups. In the HIV+ group, plasma levels of soluble CD14 and sCD16 were similar to controls.

Inclusion criteria for controls: absence of HIV, 8-26 years of age, good overall health, no chronic medical conditions, no current psychiatric disorder, no substance use disorder, no recent acute illness. Inclusion criteria for HIV-infected group: HIV-1 infection, age 8-26 years, cumulative ARV duration ≥6 months, current ARV regimen controlled for CD4+ and HIV RNA level ≤5,000 copies/mL.

Exclusion criteria for controls: absence of HIV, 8-26 years of age, presence of chronic medical condition, malignancy, medication use which could lead to changes in cognitive performance, working memory and full-scale intelligence quotient. Malaria was seen as a confounder as it is associated with working memory and processing speed. Multivariable regression analyses were conducted with working memory. HIV duration was the only statistically significant factor in the HIV+ group (P = 0.05).

Conclusion: HIV+ youth have evidence of immune activation and increased immune activation compared to matched healthy controls. This relationship appears to be an important factor in this study.

Background

HIV+ individuals are at an increased risk of developing HIV- associated neurocognitive disorders (HAND). While ART has reduced the incidence of severe HAND, the prevalence of milder forms of neurocognitive dysfunction has increased in the post-ART era. HAND is proposed to be due to, in part, to immune activation from viral replication which causes neural damage despite ART. Immune activation assessed via CD38 and HLA-DR (phenotype) as well as increased plasma levels of sCD14 and sCD16 are associated with impaired neurocognitive performance in adults. Few studies have assessed neurocognitive impairment and immune activation in HIV+ youth.

Objectives

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Summary of Results

➢ HIV+ youth have evidence of neurocognitive impairment and increased immune activation compared to matched healthy controls.

➢ Mean neurocognitive scores were below average for 4 of 5 testing domains for HIV+ subjects and average for all 5 in controls.

➢ Markers of CD4+ and CD8+ T-cell and monocyte activation were higher in HIV+ subjects compared to controls, but proportions were similar between groups.

➢ After multivariate analysis, HIV duration was the only statistically significant factor associated with working memory.

Limitations

➢ Cross-sectional design, small sample size

➢ Performance on neurocognitive testing in HIV+ youth may be confounded by environmental factors but subjects were well-matched to controls with regard to socioeconomic status.

Conclusions

➢ HIV+ youth with virologic suppression perform below average on neurocognitive tests and have higher levels of peripheral immune activation compared to controls.

➢ HIV duration may play a significant role in the spectrum of neurocognitive deficits seen in HIV+ youth in the post-ART era.

➢ Ramifications of uncontrolled HAND could be immense given that youth comprise the fastest-growing population of newly infected HIV+ individuals.

➢ Targeting this population offers an opportunity to identify those at risk for poor outcomes and develop strategies to mitigate damage while neurodevelopment is still occurring.

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References

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