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Original Article

HIV-Related Cognitive Impairment of Orphans in Myanmar With Vertically Transmitted HIV Taking Antiretroviral Therapy

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ABSTRACT

OBJECTIVE: We determined the effect of perinatally acquired HIV on neurocognition in Myanmar children treated with antiretroviral therapy by comparison to demographically matched seronegative children. **BACKGROUND:** Myanmar has one of the highest HIV-1 prevalence rates in Southeast Asia. Studies from other resource-poor countries have shown that HIV-infected children differ in socioeconomic, nutritional and caregiver status compared to normal controls. Some vertically infected orphans in Myanmar reside separately from HIV-uninfected children in separate orphanages, thus the demographic variables of interest are naturally controlled. This study provides a unique evaluation of the neurocognitive effects of HIV in children, with control over key demographic variables. We hypothesized that HIV-infected orphans would perform significantly worse on cognitive indices compared with HIV-negative orphans. **DESIGN/METHODS:** A battery of cognitive tests sensitive to HIV-associated impairments in children was administered to 28 perinatally acquired HIV-positive children and 31 HIV-negative children from two orphanages in Myanmar; 21 children from each cohort underwent testing at baseline and again after 12 months. **RESULTS:** Baseline comparison of the two groups indicated that the HIV-infected children performed poorly across all tests, with significant group differences in executive function, visuospatial reasoning, fine motor dexterity, and visual motor integration. On subsequent testing, both cohorts of children showed improvements across multiple domains, with no significant effect of age at treatment initiation. **CONCLUSIONS:** Our results demonstrate a strong effect of HIV infection on specific neurocognitive deficits in vertically infected children. Understanding viral and host determinants and timing and choice of antiretroviral therapy on cognition will be critical to preventing cognitive impairment of children with HIV.

Keywords: HIV, neurocognitive, children, social confounders

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Introduction

Worldwide there are approximately 35 million people living with HIV, including 3.2 million children younger than age 15 years. Each year, an estimated 240,000 children are diagnosed with HIV, the overwhelming majority from vertical transmission.[1] Outside of sub-Saharan Africa, Asia has the highest number of individuals living with HIV at approximately 5.0 million.[2]

The negative impact of HIV infection on neurocognitive function is well-established for both adults and children.[3-6] Neurocognitive outcomes in vertically acquired HIV before the advent of antiretroviral medications were quite poor. Deficits ranged from static to progressive encephalopathy with variable severity. Since the initiation of combination antiretroviral therapy (cART), children have experienced

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dramatically improved morbidity, mortality, and neurocognitive outcomes, but children with HIV infection still lag behind uninfected peers.[7] Subtle, but quantifiable deficits in language, processing speed, executive function, motor function and working memory, and behavioral disturbances remain in children with HIV relative to uninfected children.[8]

The reason for this gap is still unclear. HIV infection itself may irreparably alter brain development in the setting of vertically acquired infection.[9,10] cART may cause neurotoxic effects on the developing brain,[11] although studies otherwise suggest benefit from these medications.[12,13] Further, the socioeconomic status of children with HIV, particularly in developing countries, influences cognitive outcomes.[9] Most studies of HIV-infected children in both resource-rich and resource-poor settings report results compared with normative data from the standardization of the instrument, rather than a matched control group, which can exaggerate cognitive deficits. Existing studies of pediatric HIV and neurocognitive function are limited by inadequate control populations for comparison.[14-16] Although many studies have characterized the pattern of deficits among adults with HIV and children living with HIV, relatively few have controlled for socioeconomic confounders. Our study uniquely controlled for differences in environment and biases in interpretation that limit previous studies.

We compared children in two orphanages in Myanmar. Neurocognition was assessed in children with vertically acquired HIV compared with HIV-negative children with identical nutrition, caregiver status, education, and access to services. In doing so, we could control for important stressors that are likely to confound neurocognitive outcomes, such as illness, loss of caregivers, obligations to care for family, malnutrition, and limited access to education because of economic constraints. Moreover, to eliminate the effect of insufficient HIV treatment, the children in the present study were supervised when taking their daily medications and adherence to their treatment was nearly 100%.

Methods

Study design

This was a cross-sectional study of school-aged children from 6 to 16 years of age, with a longitudinal component for a subset of the cohort. This study was approved by Myanmar Ministry of Health according to set protocols and guidelines for human studies in Myanmar as well as by the Institutional Review Boards at Washington University and the University of Missouri, St. Louis.

Setting

Children were recruited from two large orphanages in Yangon, Myanmar: one orphanage for HIV-infected children and the other orphanage for HIV-negative children. Each orphanage holds more than 150 children. The orphanages are well-staffed and run by nongovernmental organizations. All children speak Myanmar as the primary and current language, go to school, and receive formal education. All the HIV-infected children are on cART according to national guidelines, which are adopted from World Health Organization guidelines.[17] cART is provided by the National AIDS Program, international and local nongovernmental organizations in Myanmar using the national protocol "Guidelines for the clinical management of HIV infection in children." Most HIV-infected children in the orphanages we studied were on the same cART regimen, with at least one central nervous system–penetrating agent, according to the national protocol. Compliance is effectively 100%.

Participants and study size

The study population included 28 HIV-infected and 31 HIV-negative children. Twenty-one of the children from each group were tested twice, at 1-year intervals. The participants were selected by orphanage staff to have a similar distribution of age, sex, and education level. We excluded children with known neurodevelopmental disorders or other chronic medical conditions unrelated to the complications of HIV, but that might affect cognition. Additionally, children were excluded if they had an acute illness; coinfection with hepatitis C, tuberculosis, or other opportunistic infections; were not on cART; were unable to understand the assent process because of severe cognitive impairment; or if they were malnourished.

Consent was obtained from the caretakers and each child provided consent. All testing data were deidentified before analysis.

Variables

We collected demographic data including age, education level, current CD4 count, and treatment duration.

A battery of cognitive tests (Supplementary Table 1) sensitive to deficits associated with HIV in children was administered to all subjects. The battery comprised tests that captured performance on (1) executive function, (2) visuospatial skills, (3) attention span, (4) learning and memory, (5) visual motor integration, (6) and fine motor dexterity and speed. This battery provides breadth of coverage to adequately define the neuropsychological signature associated with HIV. As such, our selection of tests for the battery balances both HIV specificity and overall breadth to ensure adequate coverage across domains. These tests have been used in other pediatric studies of HIV[8] and were selected based on ease of cultural application and feasibility of translation, test administration, and scoring. All measures were translated into the Myanmar language and back translated to English to ensure accuracy. Additionally, letters on the Trails A test were replaced with corresponding Burmese symbols, and semantic category words on the verbal learning task were replaced with culturally relevant terms (see test descriptions in the following section).

Data sources/measurement

Demographic information, current CD4 counts, and treatment duration were obtained from each child's medical chart. Educational level was provided by orphanage staff.

All tests were administered according to standard procedures by trained pediatricians fluent in the Myanmar language. The dependent variables included time to completion for Trail Making and Pegs, and total correct for Digit Span, design fluency, and Object Assembly. Verbal learning was tested with the Hopkins Verbal Learning Test–Revised.[18] The test consists of a word list presented to the participant on three successive learning trials. These words were carefully chosen to make sure that the children in the testing age groups would be familiar with them and to ensure cultural relevance (e.g., we replaced gemstones with fruits and vegetables). Participants were required to recall as many words as possible on each learning trial and then again after a 20-minute delay. A recognition trial was administered after the delay, but the primary dependent variable included total recall across the learning trials. Visual motor learning was examined with Visual Motor Integration (Beery VMI)[19] and fine motor dexterity with the Grooved Pegboard.[20] The total time for test administration is approximately 50 minutes. The test administration was sequenced to avoid fluency confounds during verbal recall on the memory test.

Statistical methods

Preliminary group analyses were conducted using independent means *t* tests for age and education variables to assess the need to include these as covariates in subsequent analyses. Both the HIV-positive