Neurocognitive Functioning in Pediatric Human Immunodeficiency Virus Infection

Effects of Combined Therapy

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Objectives: To assess the impact of combination antiretroviral therapy on neurocognitive outcomes in perinatally human immunodeficiency virus (HIV)–infected patients and to determine if CD4 percentage and plasma HIV-1 RNA level (viral load) are predictive of future neurocognitive function.

Design: Retrospective cohort study.

Setting: An HIV-dedicated urban care center.

Participants: One hundred forty-six perinatally HIV-infected children born between June 1990 and May 2003 with at least 1 neurocognitive evaluation.

Main Outcome Measures: Neurocognitive standard testing scores as well as diagnosis of progressive encephalopathy, probable progressive encephalopathy, or static encephalopathy.

Results: The prevalence of progressive encephalopathy has decreased in children born prior to 1996 (period 1) compared with those born after 1996 (period 2) from 29.6% to 12.1% (P = .049). The prevalence of all progressive encephalopathy and static encephalopathy decreased from 40.7% to 18.2% in period 1 vs 2 (P = .02). For those diagnosed as neurocognitively healthy, neurocognitive scores remained stable over time with a mean (SD) standard score of 89.6 (11.8) at first evaluation compared with 91.9 (11.93) at most recent evaluation. The most recent mean (SD) standard score increased from 82.3 (18) to 87.2 (10.49) in period 1 vs period 2 (P = .001). A weak association was found between both the mean viral load (P = .06) and CD4 percentage (P < .001) and neurocognitive testing score 6 months later.

Conclusions: Since 1996, fewer children have been diagnosed with progressive encephalopathy, and neurocognitive functioning is preserved over time in those deemed neurocognitively healthy at entry. Viral load and CD4 percentage are marginally predictive of future changes in neurocognitive standard scores. These data support the observation that combination antiretroviral therapy is associated with improved neurocognitive outcomes in children with perinatally acquired HIV infection.

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INCE PERINATAL HUMAN IMMUNODEFICIENCY VIRUS (HIV) infection was first identified in the 1980s, HIV-related encephalopathy has been recognized as a common but unfortunate sequela of the disease.1-4 Progressive encephalopathy (PE) is the most severe and debilitating form of HIV-1–associated encephalopathy. Most children with PE are initially examined by 18 months of age and exhibit a decline in neurocognitive scores, loss of developmental milestones, acquired microcephaly, and/or acquired abnormalities in gross motor skills. Human immunodeficiency virus-1–related PE has been shown to result in early mortality, with an estimated survival of 12 to 24 months after diagnosis.5 In contrast to PE, patients with static encephalopathy (SE) exhibit a fixed, nonprogressive abnormality in either gross motor skills, learning abilities, or acquisition of developmental milestones. Before the widespread use of combination antiretroviral therapy in 1996, the prevalence of PE was estimated as between 30% and 50% of perinatally infected children with HIV and the prevalence of SE was estimated as high as 90%.6 Numerous studies have found impairment in cognitive development of perinatally HIV-infected infants even when controlling for confounders such as ethnicity, in utero drug exposure, maternal death, and other environmental factors.1,3,7-15

With the use of combination antiretroviral therapy, defined as a regimen with
at least 3 antiretroviral agents, children with HIV have experienced improved virologic control with immune reconstitution. Combination antiretroviral therapy has led to major improvements in survival and morbidity. In the HIV-infected adult population, patients treated with combination antiretroviral therapy have demonstrated improvements in neurocognitive abnormalities and performance. To our knowledge, to date, no study has investigated the long-term impact of combination antiretroviral therapy (≥3 drugs) on neurocognitive outcomes in children.

Several anti-HIV agents, such as zidovudine, efavirenz, stavudine, abacavir sulfate, indinavir sulfate, and nevirapine, have been shown to have better cerebrospinal fluid (CSF) penetration than other antiretrovirals. One study in adults showed no difference in neuropsychological testing among adults treated with a single vs multiple CSF-penetrating agents. However, no long-term investigations have been performed on the effect of CSF-penetrating agents on neurocognitive outcomes in children.

A meta-analysis of 5 Pediatric AIDS Clinical Trials Group studies demonstrated that viral loads, not CD4 counts, were predictive of cognitive decline in children older than 1 year. Unfortunately, the follow-up from these studies was only a median of 24 months. No other research linking biological markers of disease status with cognitive outcomes is available at this time.

The primary purpose of this descriptive study was to assess the cognitive function in a cohort of children followed up longitudinally at a single dedicated pediatric HIV care site and to assess the impact of combination antiretroviral therapy on cognitive function.

**METHODS**

The study design was a retrospective cohort study. The study site was an outpatient clinic in an academic children’s medical center that provides primary and specialty care to HIV-infected infants, children, and adolescents. The study population consisted of 146 perinatally HIV-1–infected children with at least 1 neurocognitive testing score.

For the study population, HIV infection was established by positive results on at least 2 HIV viral-specific tests: polymerase chain reaction DNA assay, quantitative HIV RNA assay, and/or HIV cocultures. As part of our standard HIV care protocol, a neurologic evaluation is completed at each clinic visit. In addition, all infected children receive a standardized measure of cognitive function soon after diagnosis of HIV infection or on enrollment into our clinic. Developmental and/or cognitive testing are repeated on a 12-month schedule and twice yearly for younger infants and children. Furthermore, children with perceived neurologic and/or cognitive deterioration are tested at the time of clinical detection of these changes. The type of neurocognitive test administered differs according to the age and functional abilities of the children (Table 1).

Data collected included the prenatal history, age at diagnosis, and any neurologic and/or psychiatric or HIV-related diagnosis. In addition, the age, CD4 counts (absolute and percentage), viral loads (absolute and log), antiretroviral regimen, use of psychostimulants, and number of CSF-penetrating agents at the time of each neurocognitive testing were recorded. Additional data extracted from the medical record included: patient’s demographic data, all documented Centers for Disease Control and Prevention category and immune status classifications, birth month and year, age at death, school environment, main caretaker, diagnosis of congenital infections, in utero substance exposure, and antiretroviral regimen of mother during pregnancy. Our institutional review board approved this study; patient consent was waived.

**DIAGNOSIS OF HIV ENCEPHALOPATHY**

Patients with abnormalities in neurocognitive testing, radiographic findings, and/or history of developmental and or neurologic dysfunction were categorized as having either PE or SE. We defined PE as a confirmed decrease in standard scores on cognitive testing of at least 15 points between 2 sequential visits or loss or plateau of developmental milestones and at least 1 of the following: combination antiretroviral therapy evidence of progressive atrophy, white matter changes, and/or basal ganglia calcifications; acquired microcephaly; and acquired abnormalities in gross motor skills. Since most children with PE are diagnosed between 18 and 36 months of age, the data were censored to compare children with exposure to combination antiretroviral therapy who were younger than 18 months by January 1996 with children born after January 1996. Children with a confirmed drop in standard scores of 15 points between 2 visits and no other clinical or radiographic abnormalities were diagnosed with probable PE.

We defined SE as the presence of nonprogressive cognitive or gross motor abnormalities. Patients with a standard score of less than 70 that changed less than 6 points (1 standard error) throughout follow-up were diagnosed with the cognitive definition of SE. Patients with nonprogressive gross motor abnormalities were diagnosed with the motor definition of SE.

**DATA/STATISTICAL ANALYSIS**

The initial analysis was to describe the distribution of data. We characterized the population of perinatally HIV-infected children by all potential risk factors including demographic variables and use of combination antiretroviral therapy. Categorical variables were summarized by frequencies, while continuous variables were summarized by using mean, median, standard deviation, and range. Our primary analysis was to evaluate the effect of combination antiretroviral therapy on the neurocognitive outcomes of perinatally HIV-infected children over time, as measured by developmental quotient and prevalence of HIV encephalopa-
The prevalence of children evaluated as neurocognitively healthy or diagnosed with PE, probable PE, the cognitive definition of SE, or the motor definition of SE is presented in Table 2. Of the children developing PE during the study period, the median age of diagnosis was 1.75 years (range, 0.33-9.33 years), with 74.3% of events occurring prior to the age of 3 years. As presented in Table 3, there was a statistically significant decrease in the prevalence of PE, the combined prevalence of PE and SE, and the prevalence of SE in children born in period 1 (pre–combination antiretroviral therapy era) vs period 2 (post–combination antiretroviral therapy era). No change was detected in the prevalence of children with the cognitive definition of SE or the motor definition of SE born in period 1 vs period 2.

NEUROCOGNITIVE TESTING RESULTS

The median age of the children at initial neurocognitive testing was 21.5 months and at most recent testing, 8.3 years. As presented in Table 4, there was stability in mean neurocognitive scores for all subjects over time. Additionally, there was a significant increase in most recent mean neurocognitive scores between children born in period 1 vs period 2. The mean of the most recent neurocognitive score for all neurocognitively healthy children was 91.9, as shown in the bell curve in the Figure. The mean score for most recent test of all children also fell below the standardized mean (100) for the developmental tests (Figure).

### STUDY POPULATION

Between June 1990 and March 2003, 207 children with perinatally acquired HIV infection enrolled at the Special Immunology Clinic at the Children’s Hospital of Philadelphia in Pennsylvania. Of these, 61 children never received cognitive testing (21 died prior to first cognitive testing, and 40 children moved out of the area or their families refused testing). Of the 21 that died prior to testing, 20 were born prior to May 1996.

One hundred forty-six children underwent neurocognitive testing. The demographic characteristics of these 146 children are shown in Table 1. Fifteen children (10.3%) with at least 1 documented cognitive evaluation had died by April 2003. All 15 children were born in the pre–combination antiretroviral therapy era (prior to January 1996). Of the 33 children born in the post–combination antiretroviral therapy era, 97% (32/33) were receiving combination therapy by the time of their first neurocognitive testing.

The median number of neurocognitive evaluations per child was 4 (range, 1-15). The median age of the children at the time of initial testing was 21.5 months (range, 3-170 months), and the median follow-up from the time of the first testing was 4.75 years (range, 1 day-12.5 years). The median age at the most recent evaluation was 8.1 years (range, 0.34-22.8 years).

### PREVALENCE OF HIV-1–ASSOCIATED ENCEPHALOPATHY

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No association was found between the mean initial neurocognitive scores and maternal history of substance abuse, in utero exposure to antiretroviral agents, caregiver status, or ethnicity (data not shown).

**PREDICTIVE FACTORS**

Viral load log was marginally associated with neurocognitive scores (n=123; number of observations=369; P=.06), such that a 1-log unit decrease in viral load log was associated with an increase in overall neurocognitive standard score of 0.88 points. The mean CD4 percentage during the 6 months prior to testing was also associated with neurocognitive scores (n=141; number of observations=685; P<.001), such that a 1-unit log increase in CD4 percentage was associated with an increase in full-scale neurocognitive score of 0.25 points.

**CSF-PENETRATING AGENTS**

After stratifying patients according to the number of CSF-penetrating agents incorporated in their antiretroviral therapy regimen in the 6 months prior to testing, the number of CSF-penetrating agents was not associated with neurocognitive scores (n=146; number of observations=715; P=.51).

Our study further highlights the importance of neurocognitive testing in detecting and monitoring children's neurodevelopmental progress. Although individual cognitive scores were stable over time in the group as a whole, notable individual variation was seen among some patients. In addition, the population mean scores were negatively skewed compared with those expected in the general population (with a mean score of 100). A similar distribution has been described by a recent study of cocaine-exposed and unexposed children living in Philadelphia. In the study, 95% (141/149) of the children with a similar demographic profile as our study population, regardless of prenatal and/or natal exposures, had Wechsler Preschool and Primary Scales of Intelligence-Revised full-scale standardized neurocognitive scores lower than 100 at age 4 years. Furthermore, in this study, home environment and caregiver-child interaction were associated with higher full-scale cognitive indexes, providing possible targets for early intervention among this socioeconomic group. Poverty and low socioeconomic status have been repeatedly linked to poor outcomes on neurocognitive testing. Whether the negative skew in the scores for our population is indicative of the impact of HIV infection or a reflection of the interaction between psychosocial and/or socioeconomic factors and neurocognitive outcomes is concerning and in need of further study and, ultimately, effective interventions.

Additionally, we evaluated whether the incorporation of CSF-penetrating agents could confer additional neuroprotective benefit. We were unable to demonstrate any superiority of incorporating antiretrovirals with higher central nervous system penetration into the treatment of perinatally HIV–infected patients with relative improvements in neurocognitive functioning. It may be that our sample size was too small to note such an association or that the individual drug differences in central nervous system penetration were not enough to result in added benefit. Finally, we noted that CD4 percentage and viral load in the 6 months prior to testing were weakly associated with future neurocognitive scores. The limitations of this study include the necessary use of different testing instruments over time in following up individual patients. In addition, 21 of the patients died prior to the first neurocognitive testing (95.2% were born in the pre–combination antiretroviral therapy era). This would bias our results toward a less significant improvement in neurocognitive outcome because the most immunocompromised, and arguably more neurocognitively compromised, children died prior to testing.

A final limitation on the generalizability of our results is that the study population was a mostly urban, African American population receiving care in a single center with multiple ancillary services including nutritional, social, and psychiatric support. Results may vary because the population and available services differ between HIV care sites.

Our study was able to show an improvement in cognitive status and a decrease in the prevalence of HIV-1–associated encephalopathy since the use of combination antiretroviral therapy began in 1996. Although this is promising, there is still a significant percentage of chil-

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**Table 4. Neurocognitive Testing Results**

<table>
<thead>
<tr>
<th>Age at testing, median</th>
<th>Score of all subjects, mean (SD)*</th>
<th>Score of healthy children, mean</th>
<th>Score of children with cognitive definition of SE, mean</th>
<th>Score of children born in period 1, mean (SD)†</th>
<th>Score of children born in period 2, mean (SD)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Test</td>
<td>Med 21.5 mo</td>
<td>86.2 (18.7)</td>
<td>89.6</td>
<td>82.3 (18)</td>
<td>87.2 (10.49)</td>
</tr>
<tr>
<td>Most Recent Test</td>
<td>8.3 y</td>
<td>83.4 (16.7)</td>
<td>91.9</td>
<td>P=.001</td>
<td></td>
</tr>
<tr>
<td>Comment</td>
<td>Median follow-up, 4.75 y</td>
<td>No significant change per patient over time</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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*Median of 4 tests per patient (range, 1-15).
†Period 1 is before January 1996; period 2 is after January 1996.
dren with HIV receiving combined antiretroviral therapy who continue to have neurocognitive delay. A recent study by Tamula et al30 documented 4 children who, despite virologic suppression, continued to experience neurocognitive decline. Recent evidence suggests that there is a discordant pattern found in the evolution of antiretroviral resistance between the central nervous system and plasma in HIV-infected children.41 The neurocognitive decline seen in HIV-infected patients receiving combination antiretroviral therapy may be due to both a disparate relationship between the systemic and CSF viral load and suboptimal CSF penetration of the antiretroviral agents. Antiretroviral CSF penetration should remain a vital consideration in the design and investigation of optimal therapeutic regimens for neurocognitively impaired HIV-infected children.

Neurocognitive testing remains critical in detecting subtle cognitive deficits and monitoring the neurocognitive progress of HIV-infected children. More research needs to be directed at evaluating risk factors for neurocognitive decline and the appropriate social, clinical, and scholastic interventions that may aid HIV-infected children who already have neurocognitive delay. In the study of antiretroviral regimens, the importance of CSF penetration should remain a focus of further investigation.

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REFERENCES


