Poor Cognitive Functioning of School-Aged Children in Thailand with Perinatally Acquired HIV Infection Taking Antiretroviral Therapy

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Abstract

Neurocognitive outcome is an essential aspect of treatment for HIV-infected children. This study is aimed at assessing cognitive functioning in school-aged HIV-infected children and the change after receiving antiretroviral therapy (ART). We conducted a prospective cohort study of HIV-infected Thai children from 6–12 years of age compared with HIV-affected (children of HIV-positive mothers who were not infected with HIV), and normal control groups. Wechsler Intelligence Scale for Children-III (WISC-III) was administered at enrollment and 30 months of follow-up. Semistructured interviews of primary caregivers were performed. From April to October 2003, 121 children were enrolled; 39 HIV-infected, 40 HIV-affected, and 42 control children with a median age of 9.3 years. The HIV-infected group had a mean (standard deviation [SD]) CD4 percentage of 13.8% (5.3), 87% of whom had been receiving ART for a median of 35 weeks. At the first cognitive assessment, the mean (SD) of full-scale intelligence quotient (FSIQ) was 79 (13) and 88 (10) among HIV-infected and HIV-affected children, which was statistically lower than that of the control group at 96 (13; $p < 0.01$). The proportion of children with average intelligence level (FSIQ > 90) among 3 groups were 21%, 49%, and 76%, respectively ($p < 0.01$). At 30 months of follow-up, the HIV-infected group had a mean (SD) CD4 percentage of 25.6% (5.6); 77% had undetectable viral load. The mean (SD) FSIQ of children among three groups were 75 (12), 85 (12), and 91 (12), respectively. Compared with the baseline assessment, the verbal scale score significantly decreased in all groups, including the controls, whereas the performance scales did not change. In conclusion, school-aged HIV-infected children have lower cognitive function than HIV-affected and normal children. Cognitive function was not improved after receiving ART. Further study to address whether early ART can preserve cognitive functioning among HIV-infected children should be explored.

Introduction

CHILDREN WITH HIV infection are at high risk for developing neurodevelopment and cognitive impairments.¹ Several studies have demonstrated neurodevelopmental impairment among HIV-infected children as early as infancy.^{2–4} Data from Thai infants born to HIV-positive mothers showed that the neurodevelopment profile at 12 months of age using the Bayley Scales of Infant Development (BSID) test in HIV-infected infants was significantly lower than the noninfected group.² A study from Tanzania using the BSID test demonstrated 14.9 times higher risk of delayed mental functioning among HIV-infected infants compared with HIV negative

controls.³ A study from Rwanda also reported more frequent developmental delay in the gross motor domain among HIV-infected infants during the first 2 years of life.⁴ Few studies have demonstrated a neurocognitive deficit in HIV-infected preschool^{5,6} and school-aged children.^{7–11} Data from HIV-infected children aged from 4 months to 17 years in the United States showed lower cognitive function among the HIV-infected group compared to normal controls.⁸ Moreover, cognitive function was not improved after 48 weeks of antiretroviral therapy.⁸ The study among U.S. HIV-infected school-aged children and adolescents showed that one third of them had poor receptive language and word recognition skills, which lead to compromise in learning skills.¹¹ Children

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with abnormal structural brain findings such as cortical atrophy, poor immune function, or an AIDS-defining illness have more risk of poor cognitive function.^{9,12}

Most of the neurocognitive assessment studies of HIV-infected children have been performed in the United States and Europe where children have access to treatment earlier than children in resource-limited settings. Therefore, the magnitude of cognitive impairment might be worse in HIV-infected children in resource-limited settings. There are few data regarding neurocognitive outcome among HIV-infected school-aged children in Asia.¹³ This study is aimed at assessing cognitive functioning in Thai school-aged HIV-infected children. The secondary objective is to assess the change of neurocognitive function after receiving antiretroviral therapy (ART) among HIV-infected children.

Patients and Methods

Study population

This study was a prospective cohort study of school-aged children, which is defined as aged from 6 to 12 years. The study population included children in three groups: group I, perinatally HIV-infected children; group II, HIV-affected children (children of HIV-positive mothers who were not infected with HIV); and group III, normal control (children who had no chronic illness and were enrolled from a well-child clinic in the same hospital). The HIV-infected group was recruited by distributing study information to caregivers of HIV-infected children who attend the medical care services at Chiang Mai University Hospital and other provincial hospitals in Chiang Mai and Lamphun Provinces. The HIV-affected group was recruited from the children who had been followed up during infancy period at Chiang Mai University Hospital and also through the network of HIV-positive adults. The HIV-unexposed group was enrolled from the well-child clinic at Chiang Mai University Hospital.

Measurements

Primary caregivers were interviewed using a semi-structured questionnaire during a 20- to 30-min session by the study pediatricians. The topics of interview included demographic characteristics and social aspects of their children's lives. Demographic data were collected on biological parents and primary caregiver's age and education, family income, and child's school attendance. Laboratory values for CD4 and plasma HIV RNA levels, as well as Centers for Disease Control and Prevention (CDC) clinical category of HIV-infected children were extracted from medical records.

Overall cognitive functioning was assessed by the Full Scale Intelligence Quotient (FSIQ) of the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III; The Psychological Corporation, San Antonio, TX, 1991). The WISC was administered to each child by a trained psychologist who was blinded to the children's HIV status. The WISC-III in this study setting was translated into the Thai language and the examiners communicated with parents and children in Thai.

WISC-III is a standardized assessment of intelligence that provides three scores: verbal IQ (VIQ), performance IQ (PIQ), and full-scale score (FSIQ). The scores are standardized with a mean of 100 and a standard deviation (SD) of 15. The average

IQ score was defined as IQ 90–109 while IQ score of less than 70, 70–89, and greater than 110 were defined as retarded, dull/borderline, and superior. The verbal IQ score includes five subtests; comprehension, information, similarities, arithmetic, and vocabulary. The performance IQ score includes five subtests; picture completion, coding, picture arrangement, block design, and object assembly. The WISC-III was performed twice: the first assessment was performed at 6 months after enrollment and the second assessment was performed at the end of follow-up, 30 months later. After first assessment, the caregivers received a report of their children's cognitive abilities including information about education interventions, daily living skills, and problem-solving skills to help those children with below-average IQ.

The study was reviewed and approved by the Research Ethics Committee of Faculty of Medicine and Research Institute for Health Sciences, Chiang Mai University. Written informed consent was obtained from each child's parent or guardian prior to enrollment.

Statistical analysis

Data management and analysis was performed by using SPSS 11.0 for windows (SPSS Inc., Chicago, IL). A χ^2 test and an analysis of variance (ANOVA) were used to compare baseline characteristics of children among the three groups. Comparisons of intelligence score at baseline and subsequent follow-up were performed using paired *t* test. Association between poor cognitive function and potential risk factors including HIV status, age, gender, and family structure were analyzed using univariate logistic regression analysis. Factors with *p* value <0.25 in univariate analysis were included in the multivariate regression analysis model. Statistical significance was set at two-tailed *p* value <0.05.

Results

Demographic and clinical characteristics

In April 2003, 122 children were enrolled, including 40 HIV-infected, 40 HIV-affected, and 42 control children. Their median age was 9.3 years (interquartile range [IQR] 8.1–10.4). Sixty-four (53%) were male. One HIV-infected child died before neurocognitive assessment. Demographic characteristics of the patients are presented in Table 1. Of the 39 HIV-infected children, 34 (87%) had received antiretroviral therapy at study entry. Prior to initiation of ART, about half of the children (54%) were CDC clinical category B or C, the mean (SD) baseline CD4 lymphocyte percentage was 5.4 (5.8), and plasma HIV RNA level was 5.3 log₁₀ copies per milliliter (0.6). The first ART regimen used was a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). At the first cognitive measurement, the median duration on antiretroviral treatment was 35 weeks (IQR 29–53). The mean (SD) of CD4 percentage was 13.8 (5.3) and plasma HIV RNA was 2.2 log₁₀ copies per milliliter (SD1.0); 59% had viral suppression defined as plasma HIV RNA level less than 50 copies per milliliter.

Most of the HIV-infected children were under the care of their relatives or extended family members. Only 28% of HIV-infected group was cared for by one or both of their biological parents, which was significantly different from the other two

TABLE 1. DEMOGRAPHIC FEATURES OF SCHOOL-AGED CHILDREN BORN TO HIV-POSITIVE MOTHERS AND THE CONTROL GROUP

Features	HIV infected (n = 39)	HIV affected ^a (n = 40)	HIV unexposed (n = 42)	p Value
Male: no. (%)	23 (59)	19 (48)	22 (52)	0.59
Age at entry (yrs): mean (SD)	8.9 (1.8)	9.3 (1.4)	9.3 (1.3)	0.28
Primary caregiver: no. (%)				
Biological parents	11 (28)	29 (73)	41 (98)	<0.001
Grandparents	11 (28)	6 (15)	0 (0)	
Others relative	17 (44)	5 (12)	1 (2)	
Age (years), mean (SD)				
Father ^b	35.2 (6.3)	33.8 (6.1)	39.8 (5.3)	0.014
Mother ^b	31.7 (5.7)	35.1 (4.8)	37.3 (5.1)	0.005
Primary caregiver	45.6 (12.7)	39.3 (11.4)	38.0 (5.1)	0.002
Education higher than primary school: no (%)				
Father ^b	5 (50)	4 (80)	30 (75)	0.267
Mother ^b	2 (18)	8 (28)	25 (60)	0.003
Primary caregiver	8 (21)	11 (28)	24 (57)	0.001
Family incomes (baht/month), ^c mean (SD)	5274 (5885)	4044 (3098)	14971(9902)	<0.001
Child attend age-appropriate school grade: no (%)	31 (80)	39 (98)	42 (100)	<0.001

^aHIV-affected children defined as children born to HIV-positive mothers but not infected.

^bOnly for those with living father ($n = 10, 5, 40$) and/or mother ($n = 11, 29, 42$).

^cThe gross domestic product (GDP) per capita of Thailand in 2003 was \$2258.95 per year, which was equal to 7,810 baht/month (exchange rate 41.49) www.nationmaster.com.

Data presented as number (%) or mean (SD).

SD, standard deviation.

groups where 73% of affected and 98% of normal children were under care of their father and/or mother. Parental education, age, and family income were lower in children of parents with HIV infection than those in control group.

Cognitive function of children

The cognitive function test results are shown in Table 2. At the first cognitive assessment, the mean (SD) of FSIQ was 79 (13) and 88 (10) among HIV-infected and HIV affected children, which was statistically lower than that of the control group at 96 (13; $p < 0.01$). The baseline IQ test results stratified by level of intelligence are shown in Figure 1. At study entry only 21% of HIV-infected children had average IQ or above (≥ 90) compared to 49% and 76% of HIV-affected and control group, respectively ($p < 0.01$). In the follow-up assessment, the performance IQ scores were not different from baseline; however, verbal IQ scores significantly decreased among all three groups of children.

Among the HIV-infected group, 34 (87%) had received antiretroviral therapy prior to study entry, while 2 initiated ART after first assessment. The median time of ART was 35 weeks (IQR 29–53) and 160 weeks (IQR 155–177) at the time of first and second cognitive assessment. At the second cognitive assessment, the mean (SD) of CD4 percentage was 25.6% (5.6), and 77% had plasma HIV RNA less 50 copies per milliliter. There was a significant decrease in verbal IQ score ($p = 0.004$) at the second measurement, but not in performance IQ score ($p = 0.90$; Table 2).

Regarding school performance, all children attended regular schools, but 20% of HIV-infected children attended lower than age-appropriate grade, compared to 2% of HIV-affected children, and none in the control group ($p < 0.01$).

Predictors of poor cognitive function

In the univariate logistic regression analysis, HIV-infection was significantly associated with poor cognitive function, defined as FSIQ score less than 90 (odds ratio [OR] 6.06,

TABLE 2. INTELLIGENCE SCALE SCORES MEASURED BY WISC-III AMONG SCHOOL-AGED CHILDREN

	HIV infected (n = 39)	HIV affected (n = 40)	HIV unexposed (n = 42)	p Value ^a
<i>Baseline</i>				
Number of children	38 ^b	40	42	
Verbal IQ	79 (13)	86 (10)	93 (13)	<0.01
Performance IQ	83 (16)	92 (13)	100 (14)	<0.01
Full-scale IQ	79 (13)	88 (10)	96 (13)	<0.01
<i>Second measurement</i>				
Number of children	39	40	40 ^b	
Verbal IQ	73 (11)	82 (11)	86 (13)	<0.01
Performance IQ	82 (15)	90 (19)	100 (13)	<0.01
Full-scale IQ	75 (12)	85 (12)	91 (12)	<0.01
<i>Comparison between baseline and second measurement^c</i>				
Verbal IQ	0.004	0.019	<0.001	
Performance IQ	0.901	0.887	0.465	
Full-scale IQ	0.072	0.052	0.003	

^aBy ANOVA.

^bOne HIV-infected child was not tested for IQ at baseline due to hospitalization and 2 children in control group were lost to follow-up.

^cBy paired *t*-test.

WISC-III, the Wechsler Intelligence Tests for Children, 3rd edition, IQ; intelligence quotient; ANOVA, analysis of variance.

FIG. 1. The cognitive function of school-aged HIV-infected children assessed by the Wechsler Intelligence Scale for Children, 3rd edition.

$p < 0.01$). Family structure, including living with caregivers other than biological parents, lower education of caregiver, and lower family income, were associated with higher risk of poor cognitive function (Table 3). In the multivariate logistic regression, after adjusting for the family structure factor, the HIV-infected children had a significantly higher risk of poor cognitive outcome (OR 6.20, $p < 0.01$).

Among HIV-infected children, gender, age at the time of ART initiation, baseline CD4, HIV RNA level, duration on ART, and living with biological parents were not found to be significant predictors of poor cognitive function (data not shown).

Discussion

Our study demonstrated that school-aged HIV-infected children have low cognitive function, with 79% having below normal intelligence quotient. We found that HIV-infected children had lower cognitive function compared to age-matched HIV-affected and normal children. After receiving antiretroviral treatment for average of 3 years, there was no improvement in cognitive function.

Several reports have shown low cognitive function among school-aged HIV-infected children.^{8,11,13} The mean IQ among HIV-infected Thai school-aged children in this study is 79 (SD 13), which is slightly lower than report from a large study

among U.S. children with a mean IQ of 84 (SD 15).⁸ However, in the U.S. study, the children had better immunologic status with average CD4 of approximately 690 cells. The study among U.S. HIV-infected and HIV-affected school-aged children focused on the receptive language ability, which is highly correlated with IQ score, found that the HIV infected group had significantly lower score than HIV-affected group (mean score of 83.8 versus 87.6).¹¹ The recently reported data among 58 Thai HIV-infected children with median age of 7 years and median CD4 percentage of 20 showed a median (IQR) of IQ of 72 (65–84).¹³

The poor neurocognitive function in school-aged HIV-infected children might be explained by many reasons. First, HIV infection may have a direct effect on neurodevelopment during the first few years of life, which is the time of rapid brain development, or it may have an indirect effect through recurrent infections or opportunistic, leading to poorer general health. A study among HIV-infected infants from Tanzania showed that infants with in utero infection had higher risk of delayed mental functioning compared to infants who were diagnosed at a later stage of life.³ Another study among HIV-infected children from the United States showed that higher plasma viral load greater than 50,000 copies per milliliter was correlated with poorer cognitive outcome.⁸

TABLE 3. PREDICTORS OF POOR COGNITIVE FUNCTION IN SCHOOL-AGED HIV-INFECTED CHILDREN

Characteristics	Univariate		Multivariate	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
HIV infected (vs. not infected)	6.06 (2.47–14.82)	<0.01	6.20 (1.92–20.09)	<0.01
Male gender (vs. female)	1.36 (0.67–2.79)	0.40	NA	
Age (per 1 year increment)	0.99 (0.78–1.26)	0.93	NA	
Live with caregiver other than biological parents	2.60 (1.17–5.74)	0.02	1.01 (0.35–2.96)	0.98
Caregiver education lower than primary school	0.34 (0.16–0.74)	<0.01	0.60 (0.23–1.55)	0.29
Family incomes per month (per 1000 baht increment)	0.92 (0.87–0.97)	<0.01	0.95 (0.89–1.01)	0.10

Note: Poor cognitive function defined as full-scale intelligence score. (FSIQ) <90.

NA, not applicable; CI, confidence interval.

A second factor that might contribute to poor neurocognitive outcome is low socioeconomic status, which could lead to a variety of obstacles hindering effective child rearing, such as inadequate food, lack of time for cognitively stimulating activities, and poor parent-child relationships as a result of stress¹⁴. In our study, HIV-infected children lived in families with lower socioeconomic status than the control group. Third, family structure also plays an important role in child development. In our study, 75% of HIV-infected children were raised by their grandparents and other relatives, which is consistent with other studies (26%–56%),^{15–17} while 73% of HIV-affected and almost all normal controls lived with their parents. A study in non-HIV-infected Thai children showed that children reared by grandparents were at higher risk of having developmental delay than those reared by their parents.¹⁸ A U.S. study (PACTG 338) also reported that children living with their biological parents were less likely to manifest conduct or learning problems when compared to those living with others.¹⁹ Nevertheless, in the multivariate logistic analysis which adjusted for the socioeconomic status and family structure, the HIV-infected children still had higher odds of having poor cognitive function compared to controls.

Several studies have shown that neurocognitive function does not improve after receiving antiretroviral therapy.^{6,8} In our study, the cognitive function among HIV-infected children was not improved after received NNRTI-based ART for 3 years, despite majority of children had undetectable viral load and normal CD4 cell. This is similar to previous reports by Jeremy et al.⁸ that showed only minor improvement in neuropsychological functioning after 48 weeks on protease inhibitor-based ART. A study among South African children who had a median age of 5 years, also reported no improvement in neurocognitive function after 6 months of ART. This might be explained by the timing of neurodamage which is likely to occur very early in life and is not easily corrected. This leads to a possible research question of whether starting ART earlier during infancy period will improve neurocognitive outcome in HIV-infected children.

The second cognitive assessment showed decline in verbal IQ but not performance IQ for all groups. The information and comprehension subtests were the two domains in which there were significantly lower scores in the second assessment across all groups of children. This may be explained by the lack of cultural sensitivity or language barrier of assessment tools on the verbal part. The limitation of the test was more prominent in the second assessment because children were getting older and were tested with more question items. The other possible explanation for the decline in verbal IQ in the second assessment are the interpersonal variability of the psychologists. However, since the result of performance IQ is consistent between first and second assessments, we therefore believe that it is not a case.

The strength of our study is that it is the first prospective long-term follow-up study of neurocognitive outcome in Asian HIV-infected children. The study design has included age-matched HIV-affected children and normal control groups. There are several limitations to this study. First of all, there was no baseline data for IQ scores prior to ART initiation, so we could not assess the effect of antiretroviral therapy, especially during the first 6 months of treatment. Second, we did not collect information on school performance and social

functioning from the subjects' schoolteachers because of the families' needs to maintain confidentiality about participating in the study. Third, the WISC-III instrument being translated into the Thai language may have been a cause of the lower cognitive score. However, given the results in the control group, we are confident that the poor cognitive function found in HIV-infected children is valid. Fourth, the HIV-infected children in this study were born when antiretroviral therapy was not widely available in Thailand. Therefore, they had advanced disease; more than half had experienced clinical category B and C symptoms and had very low nadir CD4 % prior to receive treatment. The findings might be bias toward severely poor cognitive function.

Currently, in medical practice we focus on clinical, immunologic, and virologic criteria to start ART and also to monitor the effectiveness of treatment in HIV-infected patients. However, for children who are infected with the HIV virus during the period of brain development, the neurocognitive aspect should be considered as a factor to consider for early initiation of ART, especially in infants and young children. The findings in this study indicate that school-aged children with HIV infection experience difficulties with their living and social functioning when compared with peers of the same age without a chronic illness. There is a need for future research to develop strategies to improve intellectual and school performance in this population.

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Author Disclosure Statement

No competing financial interests exist.

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