Impact of the HIV/AIDS Epidemic on the Neurodevelopment of Preschool-Aged Children in Kinshasa, Democratic Republic of the Congo

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Abstract

OBJECTIVES—Pediatric HIV infection is a growing problem in most regions of the world. Data on the effects of HIV on the neurodevelopment of children in resource-poor settings are scarce but necessary to guide interventions. The purpose of this study was to compare the neurodevelopment of preschool-aged HIV-infected, HIV-affected (HIV-uninfected AIDS orphans and HIV-uninfected children whose mother had symptomatic AIDS), and healthy control children in Kinshasa, Democratic Republic of Congo.

METHODS—Thirty-five HIV-infected, 35 HIV-affected, and 90 control children aged 18 to 72 months were assessed by using the Bayley Scales of Infant Development II, Peabody Developmental Motor Scales, Snijders-Oomen Nonverbal Intelligence Test, and Rossetti Infant-Toddler Language Scale, as appropriate for age.

RESULTS—Overall, 60% of HIV-infected children had severe delay in cognitive function, 29% had severe delay in motor skills, 85% had delays in language expression, and 77% had delays in language comprehension, all significantly higher rates as compared with control children. Young HIV-infected children (aged 18–29 months) performed worse, with 91% and 82% demonstrating severe mental and motor delay, respectively, compared with 46% and 4% in older HIV-infected children (aged 30–72 months). HIV-affected children had significantly more motor and language expression delay than control children.

CONCLUSIONS—The impact of the HIV pandemic on children's neurodevelopment extends beyond the direct effect of the HIV virus on the central nervous system. AIDS orphans and HIV-negative children whose mothers had AIDS demonstrated significant delays in their neurodevelopment, although to a lesser degree and in fewer developmental domains than HIV-infected children. Young HIV-infected children were the most severely afflicted group, indicating the need for early interventions. Older children performed better as a result of a "survival effect," with only those children with less aggressive disease surviving.

Keywords

HIV; AIDS; neurodevelopment; child; Africa

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THE HIV/AIDS EPIDEMIC continues to affect millions of children in developing countries, because access to prevention of mother-to-child transmission interventions and highly active antiretroviral treatment (HAART) have not yet reached wide coverage in many high HIV prevalence countries. At the end of 2006, an estimated 2.3 million children were living with HIV/AIDS and 530 000 were newly infected with HIV in 2006. The Democratic Republic of Congo (DRC) is home to an estimated 120 000 children living with HIV and 680 000 AIDS orphans.[1]

Since the first reports of pediatric AIDS in the 1980s, delayed neurodevelopment has been a well-recognized complication of HIV disease.[2,3] Experiences from the United States and Europe indicate that HIV central nervous system (CNS) involvement can occur before there is significant immunosuppression and may be the first AIDS-defining illness in as many as 18% of pediatric patients.[4,5] HIV-related encephalopathy can present as static or progressive HIV encephalopathy, with microcephaly, delay or loss of developmental milestones (motor, mental and language), and pyramidal tract symptoms.[6] Before HAART was introduced, encephalopathy was reported in 35% to 50% of children with a diagnosis of AIDS in the United States.[5,7–10] HAART can prevent and reverse encephalopathy present at the time of HAART initiation.[11,12] Consequently, the introduction of HAART in the United States has reduced the incidence of encephalopathy to <2%.[11]

Results from studies in the United States and Europe may not be generalizable to the population in Africa and other resource-poor settings, where there is also a high prevalence of malnutrition, malaria, tuberculosis and other opportunistic infections, and substantially different child-rearing environments. Despite that sub-Saharan Africa is home to 80% of HIV-infected children, there is a paucity of data on neurodevelopment from this region. Results of the few studies demonstrated HIV-related CNS involvement at similar or higher prevalence rates compared with the United States. A study of Rwandan children 6 months to 2 years of age observed that 40% of HIV-infected children had an abnormal neurodevelopmental examination at 18 months compared with only 5% of HIV-exposed uninfected children, and gross motor scores were significantly lower at all studied time points in HIV-infected children.[13] A study in the DRC documented developmental impairment in both asymptomatic HIV-infected children and HIV-exposed, uninfected children compared with control children, supporting the idea that there may be an environmental component compounding the delay as a result of the presence of HIV in the CNS.[14] A study of Ugandan children from birth to 2 years found that HIV-infected infants not only scored lower in mental and motor development but also demonstrated greater deceleration in their rate of motor development compared with HIV-exposed, uninfected infants and a control group.[15] At school age (6–12 years), these HIV-infected children experienced poorer growth and more acute illness but were not significantly different in their neurologic, motor, and psychometric development compared with control children, suggesting that children with more aggressive encephalopathy may not survive to school age in the absence of HAART.[16] A study of children in Tanzania found that the developmental scores decreased with increasing age, suggesting a cumulative risk for poor neurodevelopment caused by HIV, poverty, and the stress placed on families who care for HIV-infected individuals.[17] This study aimed to examine the effects of the HIV epidemic on the cognitive, motor, and language development of preschool-aged children in Kinshasa, capital of the DRC.

METHODS

Study Participants

A total of 160 children aged 18 to 72 months were enrolled in the study between November 2004 and September 2005: 35 HIV-infected children; 35 uninfected, affected children; and 90 uninfected healthy control children. HIV-infected children (group 1) were identified through

a pediatric HIV care and treatment program. Children were enrolled in the study at the time they presented to the HIV care and treatment program. Consequently, children were ART-naive or had received <1 week of HAART before neurodevelopmental assessment. HIV-affected children (group 2), defined as HIV-uninfected maternal AIDS orphans or HIV-uninfected children living with a mother with symptomatic AIDS, were recruited through a nongovernmental organization for social support to HIV-infected women in Kinshasa. Control children (group 3) were of HIV-uninfected healthy mothers and healthy fathers, with healthy defined as the absence of an illness that interferes with daily activities. Control children were identified at a maternity clinic with prevention of mother-to-child transmission of HIV activities. The control group was composed of 5 boys and 5 girls for every 6-month age class between 18 and 72 months. Children were excluded from the study when they presented with an acute infectious disease at the time of planned neurodevelopmental assessment. The study was approved by the institutional review boards of the Schools of Public Health of the University of North Carolina at Chapel Hill and the University of Kinshasa.

Data Collection

Clinical and anthropometric data, socioeconomic status, and health status of the parents were collected at enrollment. Socioeconomic status was assessed by inquiring about access to running water, number of bedrooms, income, type of toilet, adequacy of income, and food.

For younger children (aged 18–29 months), the Bayley Scales of Infant Development, 2nd Edition, was used to assess mental (Mental Development Index) and motor development (Psychomotor Development Index), and the Rossetti Infant-Toddler Language scale (1990 version) was used to evaluate language development. Older children (aged 30–72 months were assessed using the Peabody Developmental Motor Scales (2nd edition), the Snijders-Oomen Nonverbal (SON) Intelligence test 2½–7 (abridged 2004 version including situations, mosaics, categories, and patterns), and the Rossetti Infant-Toddler Language scale for children up to 36 months of age. Language development was not assessed for children who were older than 36 months. Assessment tools were translated into Lingala, the local language.

Neurodevelopmental assessment was performed by 1 pediatrician and 2 physiotherapists, who had received an 8-week neurodevelopmental assessment training (Bayley, Rossetti) in Cape Town, South Africa. In addition, the pediatrician (Dr Mupuala) had received training that consisted of 108 hours in neurodevelopmental testing procedures (Bayley, Peabody, and SON), 140 hours of neuropediatric consultations, and 72 hours of consultations at care institutions for children with neurodevelopmental disorders in Leuven, Belgium.

Data Analyses

Group means were calculated for the norm-referenced Bayley Scales of Infant Development-II, Peabody, and SON. The neurodevelopment of children was classified as "no delay" when their score fell within 1 SD of the mean standardized score, (100) "moderate delay" when they scored between 1 and 2 SDs from the mean (ie, 70–84), or "severe delay" when they score <2 SDs (≤69). For the Rossetti test, we computed a global baseline and ceiling age level (ie, the oldest 3-month age level at which the child mastered all items in language expression and language comprehension). Children were considered to have "no delay" when their score fell within their 3-month age category or when they scored in the 3-month age category below their age. They were considered "delayed" in their language development when they scored ≥2 3-month categories below their age.

Group means were compared by using *t* tests or the nonparametric Wilcoxon ranked-sum tests. The χ^2 test for contingency tables and Fisher's exact tests compared categorical and event frequency data. Analysis was conducted by using SAS 8.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Demographic, Socioeconomic, and Clinical Characteristics

The mean age of participants was 43.7 months and did not differ significantly a groupings (Table 1). Approximately 50% of children were male. None of the control children were orphans (by inclusion criteria). Among HIV-infected children, 28.6% were maternal and 40% were paternal orphans. Among affected children, 35.5% were paternal and 8.6% were maternal orphans. Malnutrition and stunting, defined as z scores >2 SDs below the mean weight for age and height for age, was significantly more prevalent among HIV-infected and HIV-affected children, but even 16.7% of control children were malnourished, reflecting the high level of poverty in the DRC. HIV-affected children and HIV-infected chil-dren had a significantly poorer socioeconomic living standard compared with control children. The proportion of children aged <60 months with microcephaly, defined as head circumference less than the third percentile, was the highest among HIV-infected children (11.1%), compared with 6.7% among HIV-affected children and 1.4% among control children (Table 1).

Neurodevelopment of Control Children: Comparison With Normative Reference Population

Mean standardized test scores of 70 healthy control children 18 to 29 months of age were 85.3 (SD: 18.0) for the Bayley Mental Development Index and 94.1 (SD: 13.1) for the Bayley Psychomotor Development Index. The mean standardized test scores for the 20 healthy control children 30 to 72 months of age were 84.6 (SD: 22.4) for the SON and 99.2 (SD: 7.9) for the Peabody. Compared with the normative reference population (1700 children from the United States for the Bayley, 2003 children from the Unites States for Peabody, and 1124 children from the Netherlands for SON), these mean scores were significantly lower for mental development (P < .0001 for Bayley Mental Development Index and SON) but similar for motor development (P = .08 for Bayley Psychomotor Development Index and 0.7 for Peabody).

Both moderate (26.7%) and severe (24.4%) delay in mental development was observed, and mental delay was more frequent in older children. In contrast, severe motor delay was not observed among control children, and moderate motor delay was present in 7.8% and was more frequent among young children (aged 18–29 months) than older children (30–72 months), with 25% and 2.9% moderate motor delay, respectively (Table 2). Among the children tested for language development (aged 18–36 months), delay in language comprehension and language expression was found in 12.9% (Table 3).

Mental Development in HIV-Infected and HIV-Affected Children

Performance on the assessment of mental development was significantly poorer among HIV-infected children compared with control children (Table 2). Severe delay was present in 60% of HIV-infected and 40% of HIV-affected children. Severe mental delay was again more frequently observed among younger HIV-infected children, with 90.9% of HIV-infected children aged 18 to 29 months presenting with severe delay compared with 46% among HIV-infected children aged 30 to 72 months.

Motor Developmental in HIV-Infected and HIV-Affected Children

Severe delay in motor development was observed in 28.6% of HIV-infected and 14.3% of HIV-affected children, and moderate delay was present in 40% of HIVinfected and 14.3% of HIV-affected children (Table 2). Motor delay was more prevalent among younger children (aged 18–29 months), with 81.8% of HIV-infected and 38.5% of HIV-affected young children presenting with severe delay, compared with only 4% of older HIV-infected and 0% of HIV-affected children.

Language

HIV-infected children 18 to 36 months of age demonstrated significantly higher rates of delay in language expression (84.6%) and language comprehension (76.7%) compared with control children ($P < .0001$). Language expression but not language comprehension was delayed in the HIV-affected children compared with the control children ($P < .02$; Table 3).

DISCUSSION

Moderate to severe delay in mental, motor, and language development was observed in the majority of HIV-infected children and in a substantial proportion of HIV-affected children. Young HIV-infected children demonstrated more frequent and more severe delay in mental and motor development compared with older HIV-infected children.

The frequent delay in neurodevelopment among HIV-infected children was also observed in the previous studies of African HIV-infected children.[13–15,18] Comparison of results between studies is difficult because of differences in age groups studied and the diversity of neuroassessment tools used. Two studies that also used the Bayley scales (versions I and II) observed that, by 18 months of age, severe motor delay was observed among 27% to 30% and severe mental delay in 26% to 27% of HIV-infected children.[15,18]

In contrast to previous studies,[15,19–21] we observed that mental and not motor delay was most severely affected by HIV infection. The high prevalence of delay in cognitive development may in part be attributable to differences in child-rearing practices and lack of exposure to educational toys and multimedia by African children. This is supported by the high frequency (24.4%) of severe delay in mental development among the healthy control children, which is much higher than a 2.2% rate that one would expect if the distribution were similar to that in the reference population.

In this study, the impact of HIV infection on both mental and motor development was most pronounced among the younger children. Although we cannot exclude the effect of using different assessment tools in the 2 age groups, we believe that the observed increased prevalence of delay in the younger HIV-infected group can most likely be attributed to the absence of access to HAART before the start of this study. In the absence of HAART, children with fast progression and more aggressive disease are likely to die before reaching the age of 2.[22,23] The older children included in the study may thus represent a group of children with milder disease. A similar "survival effect" was reported from Uganda, where HIV-infected children aged 6 to 12 years were no longer different in their neurodevelopment compared with control children.[16]

Three other studies also assessed the development of HIV-exposed, uninfected children in sub-Saharan Africa.[13–15] Two studies did not observe significant differences between HIV-exposed, uninfected children and control children. In contrast to our study, these children were younger (<2 years of age), and the socioeconomic status and quality of the home environment of HIV-exposed children was not different from that of control children, indicating that the living conditions of these children was not substantially affected by HIV. In the remaining study, HIV-exposed, uninfected children who were aged ≥2 years had a significantly poorer performance on global cognitive measures but comparable motor performance.[14] No data were presented on the living conditions of these children. In our study, in which children affected by AIDS in the family were selected, we observed higher frequencies of poor motor, mental, and language expression development among HIV-affected, seronegative children. The data suggest that AIDS in the family may lead to poverty, poor health, poor living conditions, and fewer positive parent– child interactions that are conducive to a child's neurodevelopment.

Several limitations to the study should be noted. The sample size was too small to model the impact of covariates and comorbidities using logistic regression. The cross-sectional nature of this study did not allow exclusion of factors that may have had an impact on the child's neurodevelopment before study assessment. Neurologic imaging and standardized classification of neurologic examination were not available. Assessment of the language development was not available for the older children, because we were unable to adapt an existing tool for use in Lingala. Using the classification as normal, moderate, and severe neurodevelopmental delay based on US or European norms may have led to misclassification of children and biased the results to a higher prevalence of mental delay. We chose not to modify the Bayley assessment tools to make the assessment culturally appropriate because we were interested in comparisons between groups and preferred to facilitate comparability between past and future studies in other settings.

CONCLUSIONS

HIV-infected children who presented for care in Kinshasa performed poorly compared with HIV-affected and control children on assessments of motor, mental, and language development. HIV orphans and children who were living with parents who had AIDS were also at increased risk for developmental delay. Compared with control children, they achieved lower scores for motor development and tended to have slower scores for cognitive development. Our results suggest that HIV affects the neurodevelopment of children through both a direct pathway (ie, the presence of HIV in the CNS) and its effect on the child's living conditions. The high rate of developmental delay in HIV-infected and HIV-affected children as compared with control children underscores the need for screening for and prevention of neurodevelopmental delay at an early age and calls for access to early interventions and nutritional and care programs for these vulnerable children.[24–27]

What's Known on This Subject

In the United States, HIV encephalopathy occurred in 35% to 50% of children with AIDS before HAART. Results are not generalizable to Africa. Only 6 studies have assessed the effect of HIV on neurodevelopment in Africa, 5 of infants and 1 of school-aged children.

What This Study Adds

We demonstrate that young HIV-infected children are the most severely affected group, indicating the need for early intervention. Our study is the first to demonstrate that AIDS orphans and children who live with parents with AIDS also experience delayed neurodevelopment.

Abbreviations

HAART   highly active antiretroviral treatment

DRC	Democratic Republic of Congo
CNS	central nervous system
SON	Snijders-Oomen Nonverbal

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TABLE 1

Demographic, Anthropometric, and Socioeconomic Characteristics According to HIV Infection and Exposure Status

Indicator	HIV-Infected Group 1, n (%)	HIV-Affected Group 2, n (%)	Control Group 3, n (%)	p^a		
				Group 1 vs 3	Group 1 vs 2	Group 2 vs 3
Total No. of children	35	35	90			
Age, median, mo	45.7	33.4	45.6	.9000	.6800	.2200
Male gender	15 (42.9)	20 (57.1)	45 (50.0)	.4700	.2300	.4700
Orphan						
Maternal	10 (28.6)	3 (8.6)	0 (0.0)	–	.0300	–
Paternal	14 (40)	13 (34.3)	0 (0.0)	–	.8800	–
Both	3 (8.6)	0 (0.0)	0 (0.0)	–	.2400	–
WAZ less than −2 SD	20 (57.1)	14 (40.0)	15 (16.7)	<.0001	.1500	.0050
HAZ less than −2 SD	19 (54.3)	14 (40.0)	6 (6.7)	<.0001	.2300	<.0001
BMI, mean	14.9	15.2	15.5	.0900	.5200	.3900
Microcephaly^b	3 (11.1)	2 (6.7)	1 (1.4)	.0600	.6600	.2100
Poor access to water	11 (31.4)	11 (31.4)	12 (13.3)	.0200	>.99	.0200
No flushing toilet	13 (37.1)	20 (57.1)	16 (17.8)	.0200	.0900	<.0001
≤1 bedroom	12 (34.3)	23 (65.7)	32 (35.6)	.8900	.00900	.0020
Inadequate income^c	20 (57.1)	28 (80.0)	19 (21.1)	<.0001	.0400	<.0001
Inadequate food^d	4 (11.4)	21 (60.0)	7 (7.8)	.4900	<.0001	<.0001

WAZ indicates weight-for-age z score; HAZ, height-for-age z score.

[a] Based on χ^2, Fisher's exact, Kolmogorov-Smirnov, or ANOVA results on nonmissing data.

[b] Defined as a head circumference below the third percentile for the child's age and assessed for children age≤60 months.

[c] Participants stated that they never had enough money to meet their needs in the past month.

[d] Participants stated that they were hungry most of the time in the past month.

TABLE 2

Mental and Motor Development According to HIV Infection and Exposure Status Among Children Aged 18 to 72 Months

Parameter	Group 1, HIV-Infected, n (%)	Group 2, HIV-Affected, n (%)	Group 3, Control, n (%)	p^a		
				Group 1 vs 3	Group 1 vs 2	Group 2 vs 3
All children (18–72 mo)						
Total No. of children	35	35	90			
Mental development delay				<.0001	.2200	.0900
No	5 (14.3)	10 (28.6)	44 (48.9)			
Moderate	9 (25.7)	11 (31.4)	24 (26.7)			
Severe	21 (60.0)	14 (40.0)	22 (24.4)			
Motor development delay				<.0001	.0030	.0005
No	11 (31.4)	25 (71.4)	83 (92.2)			
Mild	14 (40.0)	5 (14.3)	7 (7.8)			
Severe	10 (28.6)	5 (14.3)	0 (0.0)			
Children 18–29 mo[b]						
Total No. of children	11	13	20			
Mental development delay				<.0001	.0090	.2200
No	0 (0.0)	3 (23.1)	11 (55.0)			
Moderate	1 (9.0)	6 (45.2)	6 (30.0)			
Severe	10 (90.9)	4 (30.8)	3 (15.0)			
Motor development delay				<.0001	.0380	.0060
No	1 (9.0)	7 (53.9)	15 (75.0)			
Moderate	1 (9.0)	1 (7.7)	5 (25.0)			
Severe	9 (81.8)	5 (38.5)	0 (0.0)			
Children 30–72 mo[c]						
Total No. of children	24	22	70			
Mental development delay				.0600	.6500	.2400
No	5 (20.8)	7 (31.8)	33 (47.1)			
Moderate	8 (33.3)	5 (22.7)	18 (25.7)			
Severe	11 (45.8)	10 (45.5)	19 (27.1)			
Motor development delay				<.0001	.0090	.0300

Parameter	Group 1, HIV-Infected, *n* (%)	Group 2, HIV-Affected, *n* (%)	Group 3, Control, *n* (%)	p[a]		
				Group 1 vs 3	Group 1 vs 2	Group 2 vs 3
No	10 (41.7)	18 (81.8)	68 (97.1)			
Moderate	13 (54.2)	4 (18.2)	2 (2.9)			
Severely delayed	1 (4.2)	0 (0.0)	0 (0.0)			

Neurodevelopment was classified as "no delay" when the score fell within 1 SD of the mean standardized score (100), "moderate delay" when the scored fell between 1 and 2 SDs from the mean (ie, 70 to 84), or "severe delay" when score fell below 2 SDs ($\geq$69).

[a]Based on χ^2 or Fisher's exact on nonmissing data.

[b]Motor development was assessed by using the Bayley Scales of Infant Development II.

[c]Mental and motor development were assessed by using the abbreviated SON and Peabody Developmental Motor Scales, respectively.

TABLE 3

Language Development According to HIV Infection and Exposure Status Among Children Aged 18 to 36 Months

Parameter	Group 1, HIV-Infected, n (%)	Group 2, HIV-Affected, n (%)	Group 3, Control, n (%)	p^a		
				Group 1 vs 3	Group 1 vs 2	Group 2 vs 3
Total No. of children	13	19	31			
Language comprehension delay				<.0001	.0002	>.99
No	3 (23.1)	17 (89.50)	27 (87.1)			
Yes	10 (76.9)	2 (10.5)	4 (12.9)			
Language expression delay				<.0001	.0620	.0180
No	2 (15.4)	10 (52.6)	27 (87.1)			
Yes	11 (84.6)	9 (47.4)	4 (12.9)			

According to the Rossetti Infant-Toddler Language Scale manual, children were considered to have "no delay" if their score fell within their 3-month age category or if they scored in the 3-month age category below their age; and considered "delayed" in their language development if they scored two or more 3-month categories below their age.

a Based on Fisher's exact test on nonmissing data.