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Neurocognitive function in HIV-positive children in a developing country☆

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SUMMARY

Objectives—We aimed to characterize neurological outcomes and determine the prevalence of HIV encephalopathy in a cohort of HIV-infected children in Jamaica.

Methods—Data for 287 HIV-infected children presenting between 2002 and 2008 were reviewed and neurological outcomes characterized. A nested case–control study was conducted between July and September 2009 used 15 randomly selected encephalopathic HIV-infected children aged 7–10 years and 15 matched controls (non-encephalopathic HIV-infected). Their neurocognitive functions were evaluated using clinical assessment and standardized tests for intelligence, short term memory (visuo-spatial and auditory), selective attention, and fine motor and coordination functions. Outcomes were compared using Fisher's exact test and the Mann–Whitney *U*-test.

Results—Sixty-seven (23.3%) children were encephalopathic. The median age at diagnosis of HIV encephalopathy was 1.6 years (interquartile range (IQR) 1.1–3.4 years). Predominant abnormalities were delayed milestones (59, 88.1%), hyperreflexia (59, 86.5%), spasticity (50, 74.6%), microcephaly (42, 61.7%), and quadriparesis (21, 31.3%). The median age of tested children was 8.7 years (IQR 7.6–10.8 years) in the encephalopathic group and 9 years (IQR 7.4–10.7 years) in the non-encephalopathic group. Encephalopathic children performed worse in all domains of neurocognitive function ($p < 0.05$).

Conclusions—A high prevalence of HIV encephalopathy was noted, and significant neurocognitive dysfunction identified in encephalopathic children. Optimized management through the early identification of neurological impairment and implementation of appropriate interventions is recommended to improve quality of life.

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Keywords

Encephalopathy; HIV; HAART; Neurocognitive; Pediatric; Jamaica

1. Introduction

Jamaica, a middle-income developing country in the Caribbean with a gross national income per capita of US $5020, has an HIV seroprevalence of 1.7%.[1,2] In 2002, the Kingston Paediatric and Perinatal HIV/AIDS Program (KPAIDS) was established as a multidisciplinary collaboration between the Elizabeth Glaser Pediatric AIDS and Pfizer Foundations, the University of the West Indies, Mona, and the Jamaica Ministry of Health.[3,4] The primary focus of the program has been the prevention of mother-to-child transmission (MTCT), while improving the quality of life of infected children and adolescents.[3,4] Since its inception, great progress has been made in the characterization and management of infected children, including clinicopathologic findings, outcomes of antiretroviral therapy (ART), and adherence.[3,4]

One of the most deleterious complications of pediatric HIV disease is HIV-associated neurological disease. Since the beginning of the pandemic, with continuing advances in the development and increased use of ART, there has been a noticeable reduction in the prevalence of HIV-associated neurological disease in developed countries, from 50–60% to 13–23%.[5–7] In the developing world, there is still a relatively high prevalence of neurological disease associated with pediatric HIV disease. Neurological disease is three times more common in children than adults, and is often the initial presentation of HIV disease, with 75% of cases occurring within the first 2 years of life.[8–15]

The majority of children with HIV-associated neurological disease are infected by maternal–fetal transmission. Through this route, there is an increased risk of irreversible brain damage, including cerebral atrophy, intracerebral calcifications, and microcephaly, as well as various degrees of developmental delay and cognitive impairment.[16,17] The most common and the most well described form of HIV-associated neurological disease in children is HIV encephalopathy. Clinical features include loss or failure to achieve appropriate developmental milestones, impaired brain growth, and global or selective impairments in cognitive, language, motor, attention, behavior, and social skills that may affect day-today functioning. With latency to HIV encephalopathy ranging from 2 months to 5 years, some of these children may rapidly progress to death, while others may experience intermittent periods of stability interspersed with periods of deterioration.

HIV is neurotropic. Early in the course of HIV infection, a rapid rate of productive central nervous system (CNS) viral replication occurs, which leads to early manifestations of neurologic disease. These neurologic manifestations can occur before immune suppression by the virus,[10] and are sometimes used as clinical indicators of HIV infection. Highly active antiretroviral therapy (HAART) has been shown to suppress viral replication, improve immune function, and decrease the likelihood of AIDS-related death. It has also been shown to improve neurological functioning in children affected by HIV encephalopathy.[18,19]

With a dearth of existing data for developing countries in general, and for the Caribbean in particular, we aimed to describe the neurological outcomes of HIV-infected children in Jamaica and determine their neurocognitive function.

2. Methods

2.1. Setting and participants

The medical records of infected children and adolescents (aged 0–18 years) enrolled in four KPAIDS clinics in the Greater Kingston Metropolitan area between September 2002 and August 2008 were reviewed. Three hundred thirty-six children were enrolled during the study period. Their serostatus was confirmed by HIV DNA PCR (Roche) and/or HIV ELISA (EIA/Rapid Determine) with confirmatory Western blot at the point of enrolment during the period of study. Follow-up care was facilitated by healthcare personnel trained in pediatric ambulatory management and using unified management protocols, facilitated access to care, and implementation of monitoring and evaluation mechanism[4].

2.2. Measurements

2.2.1. Neurological characterization: medical database review—Demographic data, clinical neurological characteristics, immunologic and virologic indices at diagnosis of HIV infection, and HIV encephalopathy were retrospectively collated from a secure client management database[4,5] and validated through a review of the medical records. Clinical findings congruent with the US Centers for Disease Control and Prevention (CDC) criteria for HIV encephalopathy were also identified.[20]

CDC criteria for HIV encephalopathy require at least one of the following to have been present for the past 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings: (1) loss of previously acquired skills, (2) significant drop in cognitive test scores, generally to the borderline/delayed range, with functional deficits (deficits in day-to-day functioning), (3) cognitive test scores in the borderline/delayed range, with functional deficits (and no history of significant drop or previous testing available), (4) significantly abnormal neurologic exam with functional deficits (i.e., significant tone, reflex, cerebellar, gait, or movement abnormalities), (5) significant improvement in cognitive test scores over approximately a 6-month period associated with a new treatment when baseline scores are in the borderline to delayed range (no history of previous testing), with or without significant brain imaging or neurologic abnormalities.

Record reviews of all 287 infected children were used to determine the prevalence of neurological characteristics for the entire cohort. The initial time of HIV diagnosis, start of HAART, and the end of the study time period were used as the time points of review for the entire cohort. Additionally, two other time points were used for determining the prevalence of neurological deficits in encephalopathic children (at initiation of HAART and 12 months post-start of HAART). HAART was defined as an antiretroviral drug treatment plan in which two nucleoside reverse transcriptase inhibitors were administered in conjunction with a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor.[20]

2.2.2. Neurocognitive evaluation—Using a nested case–control cohort design, we randomly selected a group of 15 encephalopathic children, aged 7–10 years, from our cohort. They were matched by age, sex, education, type of caregiver (family or government institution), and ART use with infected, non-encephalopathic controls ($n = 15$) with CDC category N, A, or B disease[21] from our cohort. The median duration of HAART use in the encephalopathic group was 5.5 years (interquartile range (IQR) 4.8–7.5 years), as compared to 2.3 years (IQR 0–5.3 years) for the non-encephalopathic group.

2.3. Questionnaire and clinical examination

Validated questionnaires were used to determine demographic, socioeconomic, and educational backgrounds of the children and their caregivers.[22] Clinical neurological examinations were performed by pediatricians. The primary investigators were blinded to the results of the examinations.

2.4. Neurocognitive testing

Several tests were used to assess the children's cognitive and motor functions. These tests were chosen by a child development specialist as they had previously been used in several studies in Jamaica and had shown differences between nutritionally deprived and well nourished children from similar backgrounds.[23,24] The tests were administered using Standard English (UK), the native language of Jamaica.

The tests administered assessed: (1) Intelligence: general intelligence was measured with Raven's Coloured Progressive Matrices. Participants were asked to find the missing pattern from a series of options, with each successive set of items becoming more challenging. With increasing levels of difficulty, the analytical skills of the child were assessed.[25,26] Full intelligence quotients (IQ) were not determined. (2) Memory: visuo-spatial memory was assessed with the Corsi Block test (Milner and Corsi, 1972). In this test, children were asked to reproduce various sequences that blocks were pointed at.[27] Auditory memory was measured with Digit Span Forward from the Wechsler Intelligence Scale for Children fourth edition (WISC-IV). In this test, participants were asked to repeat various sequences of random numbers read aloud to them.[28,29] (3) Attention: Map Mission Search, a subtest from the Test of Everyday Attention for Children, TEACh[30,31] was used to measure selective attention. In this test, children were asked to find as many pictures of an object shown to them on a map. The total number of pictures found within a minute was recorded. (4) Fine motor and coordination:[32–36] (a) posting coins (subtest of the Movement Assessment Battery for Children, 1992) required the children to place a selected number of coins in an enclosed box as quickly as they could. The average time taken to complete the task twice was recorded; (b) the grooved pegboard test (Matthews and Klove, 1964) required the children to place grooved pegs into slots on a metal board. The average time taken to complete the task was recorded; (c) the hand pronation–supination test (Physical and Neurological Assessment of Subtle Signs; Denckla, 1985) required that children rapidly rotate their forearms. The average time taken to complete two sets of 20 rotations was recorded.

For all of these timed tests, lower scores indicated faster times taken to complete the test.

Inter-observer reliabilities (r) were established for all tests before the study began using HIV-negative children ($n = 7$), and all were greater than 0.97. These reliabilities were obtained by comparisons of examiner scores for all tests, where observers watched each other during testing of each HIV-negative child.

Between July and September 2009, the children were each tested during a single session at their respective clinics. Test administration required 2 h to complete. Each test was individually scored, with the results compiled and tabulated.

2.5. Statistical analysis

Demographic data were summarized and compared with those of controls using Fisher's exact test and the Mann–Whitney U-test. The change in prevalence of neurological characteristics at 12 months post-HAART was compared with baseline findings using a paired t-test. Clinical findings from the nested case–control study were compared with the Mann–Whitney U-test. The raw scores of the neurocognitive testing were also compared using the Mann–Whitney U-test. The cognitive scores and time taken to complete fine motor tasks were compared using the Mann–Whitney U-test. Data were analyzed with the Statistical Program for Social Sciences version 12.0 (SPSS Inc., Chicago, IL, USA).

2.6. Ethics statement

Ethical approval was received from the University Hospital of the West Indies/University of the West Indies Faculty of Medical Sciences Ethics Committee. Informed consent was obtained from primary caregivers, and assent from infected children who were aware of their HIV status (>8 years of age).

3. Results

3.1. Demographics

Three hundred thirty-six children were enrolled in the KPAIDS program between September 2002 and August 2008. Twenty-six medical records were missing, and 23 children were lost to follow-up less than 1 year after enrolment. The medical records of 287 children were subsequently reviewed. The record review reporting points for encephalopathic children were at initial diagnosis of HIV, diagnosis of HIV encephalopathy, initiation of HAART, and 12 months post-start of HAART. For non-encephalopathic children the reporting points were at initial diagnosis of HIV, initiation of HAART, and at the end of the study period.

Just over half (53.3%; 153/287) of the cohort was female. MTCT was the most common mode of infection in our cohort, accounting for 89.9% (258/287) of cases.

3.2. Neurological characteristics

Sixty-seven (23.3%) children were diagnosed with HIV encephalopathy, with 88.1% (57/67) being diagnosed at less than 5 years of age. The median age at diagnosis was 1.6 years (IQR 1.1–3.4 years). The common neurological deficits identified on diagnosis of HIV encephalopathy (Table 1) were delayed milestones (59, 88.1%), hyperreflexia (58, 86.5%), spasticity (50, 74.6%), microcephaly (42, 61.7%), and quadriparesis (21, 31.3%).

Of non-encephalopathic children, 15.5% (34/220) had other neurological deficits, including learning deficits (reading and basic arithmetic), delayed milestones, isolated hyperreflexia, isolated microcephaly, and progressive multifocal leukoencephalopathy. These clinical findings were not congruent wit CDC criteria for HIV encephalopathy, as they were either isolated clinical findings or had been present for less than 2 months.

Sixty-four (95.5%) were started on HAART. The majority of these children (60/64) started HAART after they were diagnosed with HIV encephalopathy, with the median time to start HAART of 22 days (IQR 0–92 days). There was a small reduction in the prevalence of neurological deficits at 12 months post-HAART (Table 2), although not statistically significant ($p > 0.05$).

3.3. Neurocognitive evaluation

The median age of tested children was 8.7 years (IQR 7.6–10.8 years) in the encephalopathic group and 9 years (IQR 7.4–10.7 years) in the non-encephalopathic group. The encephalopathic group achieved lower test scores than their non-encephalopathic peers in the Raven's Progressive Coloured Matrices. Additionally, they achieved lower test scores in the Corsi Block, Digit Span, and Map Search tests. They also took longer times to complete the motor tests – the grooved pegboard, posting coins, and the hand pronation–supination tests (Table 3). Two encephalopathic children were unable to complete the grooved pegboard test due to significant motor impairment; they were severely spastic.

4. Discussion

This is the first comprehensive characterization of neurocognitive function among HIV-infected children in the Caribbean. Our prevalence of 23.3% of HIV encephalopathy concurs with international data from developed countries,[8–10] with prevalence data of 16–35%. The median age at diagnosis of encephalopathy was 1.6 years (IQR 1.1–3.4 years). This age is congruent with the period when deficits in major developmental milestones such as walking, talking, and basic communication skills become more noticeable. Schanbhag et al. noted a similar age in a North American cohort (1.75 years, range 0.33–9.33 years).[37] MTCT was the main mode of transmission in encephalopathic children (95.5%; compared to 88.2% in non-encephalopathic children). This is similar to the results of international studies that have shown MTCT to be the main mode of transmission in encephalopathic children.[8,12,14,15] MTCT is an important factor in the development of pediatric CNS disease. In the presence of elevated HIV viral load, the young developing brain will suffer significant insults both ante- and post-partum leading to the varied manifestations that have been shown to occur in HIV encephalopathy.

Despite the widespread use of HAART (95.5%), there was only a small reduction in the prevalence of neurological deficits at 1 year post-HAART in our cohort. Smith et al.[38] also showed that the prevalence and severity of neurological deficits did not significantly improve at 6 months post-HAART in a South African cohort. Postulated reasons include host factors (e.g., age <15 years, polymorphisms of receptors leading to increased chemokine release) and viral factors (e.g., emergence of resistant genotypes in the CNS).[39,40] Variable ART penetration and early viral sequestration in the developing brain may also impact on the

efficacy of treatment of pediatric CNS disease.[41,42] HAART primarily works to prevent further HIV replication and reduce the progression of HIV-induced cellular damage. By delaying the use of HAART, profound irreversible inflammatory changes will occur. So, although there may be a virological and immunological response to the use of HAART, severe irreversible neurocognitive deficits may be present. This possibly explains the unfavorable neurological outcome despite a median time of 22 days to the start HAART after diagnosis of HIV encephalopathy. Additionally, routine pediatric HIV care and prevention strategies in Jamaica were not introduced until 2002, and universal access to HAART occurred in 2005. With a lag in prevention of vertical transmission strategies compounded by inadequate access to HAART, the rate of deterioration of our encephalopathic children would have surpassed that of children in the developed world. Thus, late initiation of HAART in our children would not have been able to address the deleterious effects of advanced neurological inflammation and damage that occurs as a result of pediatric HIV disease.

Our data show an abnormal neurocognitive profile for the encephalopathic group. Despite similar socioeconomic and educational backgrounds, their performance in all of the cognitive and motor tests was significantly below that of their non-encephalopathic peers. The encephalopathic group achieved significantly lower scores for tests of general intelligence, memory, and selective attention. They were slower in all tests of motor function and coordination. These differences may not only be explained by motor impairments, but also by deficits in visuo-spatial memory and processing speed in encephalopathic children. Our results mirror the experience of others in the developed world,[42,43] who have reported significant impairment in visuo-spatial function and attention in HIV-infected children when compared to non-infected peers. With the absence of normal, non-infected children in our study, there is the possibility that infected non-encephalopathic children may already have various unrecognized neurocognitive deficits.

There was the possibility of inter-observer bias associated with the assessment and documentation of neurological findings with longitudinal follow-up of the cohort. However, the use of unified management protocols and supervision by senior pediatricians served to decrease this limitation. The use of trained investigators and pediatricians to conduct neurocognitive testing and neurological examinations strengthened the validity of the findings. Some statistically insignificant findings in our case–control study may have been due to low statistical power ($n = 30$).

Although we used few tests of development on a relatively small sample, we were able to show significant effects of HIV encephalopathy in this cohort. Longitudinal data regarding cognitive performance of the cohort are needed, but due to limitations in financial resources and time, we were unable to conduct formal cognitive evaluations. Formal IQ data (relating to scholastic achievement) and behaviors are also important areas of development that were not explored in this study, and would be very useful in providing a better perspective on the overall function of these children.

In conclusion, this study highlights the importance of evaluating neurocognitive outcomes in HIV-infected children, particularly those with HIV encephalopathy. One cannot

underestimate the impact of strengthening MTCT prevention strategies and early infant diagnosis in reducing the frequency and severity of pediatric HIV infection. Additionally, initiation of HAART for all infants less than 12 months of age[18,44] is likely to mitigate the deleterious viral effects on the developing brain.[43] This has already been confirmed by the CHER study.[45] Violari et al. showed the benefits of early HAART administration in infected children in preventing rapid disease progression. Our study suggests the need for judicious and early administration of HAART for the prevention of severe neurological morbidity. Van Rie et al.[46] demonstrated the benefit of early HAART in neurodevelopmental outcomes for these children. In a 1-year period, the motor skills of infected children aged less than 3 years improved with the early administration of HAART and judicious management protocols.

In addition to early diagnosis, treatment, and timely follow-up, measures to increase access to standard neurocognitive tests (as cost-effective screening tools) will promote early identification of neurocognitive dysfunction and enable implementation of targeted interventions such as physical, occupational, and speech therapies. Collectively, these strategies will contribute towards improving the quality of life of these children, while enabling them to make purposeful contributions to society as they transition through adolescence to adulthood.

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Table 1

Neurological abnormalities (from database review) in encephalopathic (n = 67) and non-encephalopathic (n = 220) children

Clinical findings	Encephalopathic, n (%)	Non-encephalopathic, n (%)
Delayed milestones	59 (88.1)	10 (0.05)
Hyperreflexia	58 (86.5)	20 (0.1)
Spasticity	50 (74.6)	–
Microcephaly	42 (61.7)	5 (0.02)
Quadriparesis	21 (31.3)	–
Milestone regression	15 (22.4)	–
Poor learning	14 (20.9)	30 (0.14)
Ataxia	10 (14.9)	–
Diplegia	10 (14.9)	–
Hemiplegia	4	–
Poor behavior	4	–
Poor coordination	1	–

Table 2

Neurological abnormalities at initiation and 12 months after start of HAART in children with HIV encephalopathy ($n = 64$)

Clinical parameters	Initiation of HAART, *n* (%)	12 months post-HAART, *n* (%)[a]
Hyperreflexia	55 (86.0)	49 (76.6)
Delayed milestones	53 (82.9)	45 (70.4)
Spasticity	45 (70.3)	41 (64.1)
Microcephaly	37 (57.8)	37 (57.8)
Quadriparesis	16 (25.0)	13 (20.4)
Milestone regression	13 (20.3)	9 (14.1)
Poor learning	13 (20.3)	18 (28.1)
Ataxia	11 (17.2)	20 (31.3)
Diplegia	10 (15.6)	13 (20.4)
Hemiplegia	4 (6.3)	4 (6.3)
Poor behavior	3 (4.7)	3 (4.7)
Poor coordination	1 (1.6)	1 (1.6)

HAART, highly active antiretroviral therapy.

[a]By paired *t*-test, all $p > 0.05$.

Table 3

Median (range) cognitive and motor test scores for encephalopathic (n = 15) and non-encephalopathic (n = 15) children

Variables	Encephalopathic Median raw scores (range)	Non-encephalopathic Median raw scores (range)	p-Value[a]
Intelligence			
Raven's Matrices (score)	13 (5–19)	18 (9–30)	0.006
Memory			
Corsi Blocks (score)	5 (1–8)	8 (3–11)	0.001
Digit Span (score)	5 (1–9)	8 (3–12)	0.012
Attention			
Map Search (score)	15 (1–36)	23 (10–47)	0.024
Motor/coordination[b]			
Posting coins: dominant hand (s)	20.6 (14.9–40.8)	17.1 (12.2–24.4)	0.020
Posting coins: non-dominant (s)	25.5 (16.9–48.3)	19.2 (13.8–27.6)	0.024
Grooved pegboard: dominant (s)[c]	62.1 (40.8–300.0)	46.8 (33.0–113.0)	0.007
Grooved pegboard: non-dominant (s)[c]	82.0 (56.2–300.0)	60.8 (39.0–93.3)	0.004
Hand movement: dominant (s)	16.9 (12.5–31.8)	13.9 (10.2–28.7)	0.062
Hand movement: non-dominant (s)	19.3 (14.0–33.4)	15.3 (10.9–22.8)	0.006

[a] Mann–Whitney U-test.

[b] Lower test scores indicate faster times.

[c] n = 13, encephalopathic group.