Neurological Profile and Neurodevelopment of 88 Children Infected with HIV and 84 Seroreverter Children Followed from 1995 to 2002

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This study evaluated the degree of neurological compromise in HIV-infected children accompanied by the outpatient clinic of infectious diseases and pediatric neurology of the Clinical Hospital of the Federal University of Paraná (UFPR) starting in 1995. Long-term progressive prospective and cross sectional study of 88 children infected by HIV and 84 seroreverter children, using data from general neurological examinations, neuroimaging procedures (brain CT scan) and neurodevelopmental tests (CAT/CLAMS and DENVER I and II). Neurological and neurodevelopmental alterations were found in 82% of the HIV-infected patients and in 36% of the HIV-seroreverter group (P <0.01). In the CAT/CLAMS test, the development quotient (DQ) of the HIV-infected group was significantly lower than that of the HIV-seroreverter group. CAT/CLAMS scores lower than 70 (mental deficiency) were found in 31% of the HIV-infected patients during the first year of life and in only 1% of the patients of the HIV-seroreverter group, demonstrating the validity of this screening test for precocious detection of alterations in the neurodevelopment of infected patients. The same occurred with the Denver I and II tests, as the HIV-infected group failed more frequently than the HIV-seroreverter group. Nine HIV-infected children presented altered brain CT scans; calcification of basal ganglia was the main finding (five cases). Encephalopathy due to HIV causes early arrest of neurodevelopment, which can be detected with screening tests during the first year of life.

Key Words: HIV-infected children, HIV-seroverter children, CAT/CLAMS, DENVER I, DENVER II, neurodevelopment.

The human immunodeficiency virus (HIV) is a lymphotropic and neurotrophic retrovirus that belongs to the Lentiviridae subfamily, causing a slow and chronic infection [1], affecting several organs and systems. Among them, the central nervous system (CNS) is frequently affected, causing delays in neurodevelopment that can be one of the first symptoms of the disease [1-6]. Children with vertically-transmitted HIV can develop rapid or slow progressive psychoneuromotor development deceleration, which can begin as soon as six months of age. Other children may have static encephalopathy [1-6].

A great deal of research has been done on the involvement of the CNS in the course of AIDS [6,7]. Anatomo-pathological findings demonstrating cortical and subcortical atrophy, encephalitis, neuronal apoptosis, diffuse leuko-encephalopathy and calcification of the basal ganglia are evidence of the consequences of HIV infection in the CNS. Some of these findings can be seen in neuroimaging exams, such as computerized axial tomography of the brain (CT scan) or evidenced in specific screening tests and revealed in the accompaniment of neurodevelopment, demonstrating a compromise of the CNS.

Received on 17 May 2006; revised 22 September 2006.
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The Brazilian Journal of Infectious Diseases 2006;10(5):322-326.
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We evaluated the degree of neurological compromise in HIV-infected children accompanied by the Infectious Diseases service of the Clinical Hospital of UFPR, compared with an HIV-seroreverter group of newborns exposed to maternal HIV, using a sequence of clinical evaluations, with emphasis on the neurological pattern of development, appraised through neurodevelopmental tests and neuroimaging exams. The results of the neurodevelopmental tests were analyzed in several phases of HIV infection to determine aspects of neurodevelopment that could be related to the evolution of the disease, the use of medication and/or environmental factors.

Material and Methods

A long-term progressive prospective and cross sectional study was applied to two groups of patients accompanied at the Pediatric Infectology and Neurology outpatient clinics of the Clinical Hospital of UFPR.

- Group 1: children diagnosed with infection by HIV (HIV infected)
- Group 2: children negative for HIV (HIV seroreverters), who had been exposed to HIV (intra-uterus or peri-natal) in whom the infection was excluded through serological and/or virological tests.

The analysis of HIV-infected children consisted of periodic neurological evaluations started in March 1995 and finished in July 2002, to detect neurological alterations with the aim of making early interventions in patients with neuroAIDS. HIV seroreverters also had neurological and neurodevelopmental evaluations during the same period.

Patients were included in the study if they underwent at least one neurological evaluation. The exclusion criteria were neurological complications, such as neonatal meningitis, congenital toxoplasmosis or cytomegalovirus, hypoxic isquemic encephalopathy, and so on.

The neurological data came from general neurological exams, neuroimaging (brain CT) and neurodevelopmental tests. The children were subdivided by age: 1-12 months, 12-24 months, 24-36 months, 36-72 months and >72 months of age. The neurological exam consisted of a comprehensive evaluation of the cognitive and mental functions, cranial nerves, motor function –(tonus, trophism, strength, deep and superficial tendon reflexes and walk), motor coordination, sensory, and head circumferences according to the NELLHAUS graph [8].

Computerized tomography (CT) of the brain was only performed on HIV-infected children. For the neuro-developmental tests, CAT/CLAMS tests [9] and the Denver I (DDST) and II Tests were applied. The CAT/CLAMS test (Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale) consists of a scale of 100 items applied in a standardized way, according to the age of the patient; it basically evaluates neuropsychomotor development between 0 and 36 months. The test is divided into two parts: CAT (CLINICAL ADAPTIVE TEST) and CLAMS (CLINICAL LINGUISTIC AND AUDITORY MILESTONE SCALE) [9-14]. The data obtained from CAT was derived from the examiner's direct evaluation, while the data obtained from CLAMS consisted of the caregivers' information on language acquisition. Each item that the child accomplished resulted in a score, also known as a development quotient (DQ), in which normal DQ is considered to be above 85, borderline DQ from 70-85, and mental deficiency with scores below 70 [9-14].

The so-called Denver I test [15] was initially known as the DDST (Denver Developmental Screen Test), and a more complete version, Denver II test [16,17], was derived from it. It consists of an evaluation of various areas of neurodevelopment, language, personal-social, adaptive and fine and gross motor, varying the aptitude requirements in accordance with age; it can be applied from 0 to 6 years of age.Children can pass or fail the Denver test. A child is considered to have failed when he or she is unable accomplish tasks that more than 90% of the children are capable of doing.

The Denver II test increases coverage of language, allowing for greater fidelity/credibility in this area [16,17]. This test began being applied in the outpatient clinic of the neuropediatric unit of HC-UFPR at the end of 1999.

Analysis of variance (ANOVA) and the Student's t test were used to examine differences between means. Fisher's exact test and the chi-square test were used to find significant associations among variables. Pearson's coefficient of correlation was applied to look for correlations among variables. The statistical analysis was made using the program, "Statistica version 5.0". In all analyses, a level of significance of 5% was established ($P < 0.05$).

This study was approved by the Committee of Ethics in Research on human beings of the Clinics Hospital of UFPR, with caregiver or parental consent.

Results

Eighty-eight HIV-infected children were selected, who had received at least one neurological evaluation, and 84 seroreverter children were selected. All evaluations were made by the same neuropediatric team, together with the Pediatric Infectology physicians.

The neurological evaluations were undertaken according to the age of the children in both groups. The neurological parameters used in the evaluations were: CAT/CLAMS test and Denver I and II, complete neurological exam and CT scan; the latter one was not available for all children.

There was a significantly greater percentage of children with mental deficiency (CAT/CLAMS scores lower than 70) in the HIV-infected children (Chi-square test, Table 1). The neurological alterations were more frequent in HIV-infected children (Tables 2 and 3). The neurological exams of the seroreverter children revealed hyperactivity as the main alteration. There was no significant association of neurological alterations and head circumference. The head circumference in the two groups was within the normality curve range, although six HIV-infected children presented microcephaly.

Among the 88 HIV patients, CT scans were available for 48 children (55%). Among eight children which had a second CT scan, one showed calcification only in the second exam. The alterations found were basal ganglia calcification (five children), ventricle asymmetry and preeminence of the extra-axial space, cerebral atrophies, cerebral atrophies associated with subdural collection and retractile lesion of the left frontal region.

When all the alterations in the neurological evaluations were taken together, 82% of the HIV-infected children (n = 72) presented alterations, significantly more than the 36% (n = 30) found in the seroreverters (Fisher test, $P<0.0001$). Frequent alterations in all or any combination of the tests used (CAT/CLAMS, Denver I and II tests, neurological exams, brain CT scans) were seen in the group-1 children. The age group 24 to 36 months was chosen to compare these results in the Denver I and II and CAT/CLAMS tests (Table 4).

Discussion

The neurological evaluation was an attempt at early detection of neurodevelopmental alterations, because even at the end of 1999, reversion of HIV infection in exposed newborns was based on serological negativation of anti-HIV, which generally occurs after 18 months of age. Up to 1999, diagnosis of non-symptomatic infection in newborns exposed

Table 1. CAT/CLAMS scores of HIV infected and serereverter children

Age (Months)	Score HIV infected			Score seroreverter			P**
	<70	70-85	>85	<70	70-85	>85	
1-12	5/16	7/16	4/16	1/84	23/84	60/84	0.00000
	*31	*44	*25	*1	*27	*72	
12.1-24	12/23	6/23	5/23	4/71	22/71	45/71	0.000000
	*52	*26	*22	*6	*31	*63	
24.1-36	11/30	11/30	8/30	3/46	21/46	22/46	0.00341
	*37	*37	*26	*6	*46	*48	

CAT/CLAMS scores: <70: Mental deficit: 70-85; Borderline: >85; Normal: DQ. *percent (%). **P<0.05.

Table 2. Distribution of cognitive abnormalities in HIV-positive children

Cognitive abnormalities	1-12*	12.1-24*	24.1-36*	36.1-72*	>72*
Language	1	1	1	1	0
Mental Retardation	2	2	3	9	8
Hyperactivity	0	3	3	4	5
Apathy	0	2	3	4	0
Total / number	3/16	8/23	10/30	18/44	13/28

* Age in months. Observation: The cognitive abnormalities were analyzed in groups, so a single child could have more than one abnormality in different age periods.

Table 3. Distribution of motor abnormalities in HIV-positive children

Motor abnormalities	1-12*	12.1-24*	24.1-36*	36.1-72*	>72*
Hypotonia	3	7	3	3	1
Hypertonia	4	0	0	0	0
Hemiplegia	1	3	0	3	3
Spastic Diplegia **	0	1	3	3	2
TOTAL / number	8/16	11/23	6/30	9/44	6/28

* Age in months. Observation: The motor abnormalities were analyzed in groups, so a single child could have more than one abnormality in different age periods.

Table 4. Comparison between the HIV and seroreverter children at 24.1 - 36 months of age, using global neurological evaluation

Factor	HIV	Seroreverter	P
N	30	46	
CAT	72.1+/-10.4	80.17+/-8.8	0.005
CLAMS	75.7+/-20.8	87.06+/-13.4	0.0005
CAT/CLAMS	73.89+/-14.4	83.41+/-8.8	0.0006
Denver I	13 failed (43%)	7 failed (16%)	0.0086
	17 passed	39 passed	
Denver II	6 failed (77%)	5 failed (30%)	0.0134
	4 passed	12 passed	

to HIV was only possible after 18-24 months of age, through the persistence of positive serology, as there was no available viral load exam for the early detection of AIDS. These children were maintained under periodical clinical observation until it was possible to diagnose HIV infection *versus* seroreversion. Despite the fact that this was a long-term project, a comparative study could only be made with a cross-section sample, because the HIV-infected children were diagnosed, in most cases, after two years of age, when a comparison could be made between the infected and seroreverter patients. We opted for the CAT/CLAMS test evaluation because it is an objective procedure for screening the alterations in neuropsychomotor development (NPMD) in children at risk [11]. More recently, it was found that the CAT/CLAMS test is

easy to apply and has both sensibility and specificity for subjects under three years of age [19].

The Denver I test, or DDST, can be used to screen for qualitative alterations in neurodevelopment of at-risk children and has the advantage that it can be applied by general pediatricians [15,18]. Because of the reduced sensibility of the Denver I test for language development, a more complete test was developed, Denver II [16]. The Denver II test has improved sensibility for the detection of deficits in the area of language (>85%) [17]. We started our study in 1995, using the Denver I test, and from 1999 on we also began to use Denver II.

We made 141 neurological evaluations of the HIV patients and 228 of the seroreverters. Among the HIV patients, there was a greater concentration of evaluations of children aged two years or above. There were 16 children aged 1 to 12 months, eight of them were born at the Clinical Hospital and were confirmed to have HIV infection in a follow up as outpatients. All seroreverter children had been born at the Clinical Hospital and had initiated outpatient care within the first months of life. Therefore all these children underwent evaluation in the first age group (1 to 12 months); the number of evaluations decreased with increasing age, due to failure to return for re-evaluation. This low rate of return was mainly justified by social problems, although the Social Services of the outpatient clinic tried to call them back to reinitiate clinical accompaniment.

Unlike the study of Wachtel et al. [11], who accompanied the same group of children through a long-term study (all with the same number of evaluations); most HIV-infected children in our study participated in only one neurological evaluation, usually after 24 months of age, and 18 children of this group only performed the neurological exam after they were over six years old. All 84 seroreverters had an evaluation at from 1 to 12 months of age, and there was a greater homogeneity in the total number of neurological evaluations (two to four evaluations in the different age groups). In the comparative analysis of CAT/CLAMS scores, , we found lower scores with significant differences between CAT, CLAMS and CAT/CLAMS in the three different age groups of the HIV-infected group compared to the seroreverters. The median quotient of CAT/CLAMS in group 1 was 70-85 (a borderline score) in the three age groups. The median scores of CAT/CLAMS of the HIV-infected group published by Wachtel et al. were also borderline at 12 months of age [11].

CAT/CLAMS scores below 70 were found in 31% of the HIV-infected patients in the first year of life, but in only 1% of the patients of the seroreverters. These results demonstrate the validity of this screening test for precocious detection of alterations in infected patients. We found from 31 to 52% CAT/CLAMS scores lower than 70 during the first three years of life, which was higher than the frequencies found by Wachtel et al. [11] in their study of an American population (6.2 to 23.5%). A study made by Chang et al. [19], to validate the CAT/CLAMS test among the normal Chinese population, demonstrated that socioeconomic level and family structure do not influence precocious NPMD (prior to three years of age). They suggested that the delay in neuropsychomotor development is directly associated with infection by HIV.

We found a failure rate of Denver I of over 40% by the HIV patients and less than 30% of the seroreverters; most of these HIV-infected children also presented a low DQ in CAT/CLAMS. However, some patients who passed the Denver I test presented low scores in the CAT/CLAMS test.

The Denver II test, which began to be used in 1999, could not be compared with the CAT/CLAMS test because most of the children were older than three years. We detected alterations in the neurological exam in 50% to 60% of the HIV-infected patients, without any cases of opportunistic infections in the CNS. The frequency of neurological alterations in the HIV-infected group was significantly higher than that of the seroreverters in the 12-24 month and 36-72 month age groups, similar to the findings of Belman et al. [20], who also compared HIV-infected and seroreverter children. Angelini et al. [21] found 48% encephalopathy among 62 children infected by vertical transmission. Bossi et al. [22], in a neurological evaluation of 50 HIV+ children aged 6 months to 8.5 years during a period of 10 years, found neurological alterations in 17 patients (34%).

A CT brain scan was performed on 48 HIV-infected children; 18% of these scans were altered, with a high prevalence of calcifications of the basal ganglia (5/9), which was also found by Carli et al. [23], who reported frequent basal ganglia calcifications in 100 CTs of cases of untreated symptomatic AIDS.

In our study, among the 46 children with normal CTs, there were many with low CAT/CLAMS scores, which was also found by Price et al. [24], who found normal CTs in 6 out of 23 children who had a delay in NPMD. This corroborates the hypothesis that not all children with a proven delay in NPMD present altered CT scans.

The significantly increased frequency of neurological alterations and/or delay in NPMD found in the HIV-infected children, points to the importance of neurological screening as a means of precocious detection of HIV infection, allowing for clinical measures to be taken that would make a successful therapeutic response more likely and improve the quality of patient lives.

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