Neurodevelopmental Testing of Children Born to Human Immunodeficiency Virus Type 1 Seropositive and Seronegative Mothers: A Prospective Cohort Study in Kigali, Rwanda

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ABSTRACT. *Objective.* The results of developmental testing of 218 children born to human immunodeficiency virus (HIV)-seropositive mothers and infected or uninfected themselves were compared with those of 218 children born to HIV-seronegative mothers in an ongoing cohort study in Kigali, Rwanda.

Methods. When the children were 6, 12, 18, and 24 months of age, a specific neurodevelopmental examination was performed blindly by study physicians assessing gross motor development, fine motor development, language acquisition, and social contacts.

Results. Only one acute severe HIV-related encephalopathy was identified among the 50 infected children. The proportion of abnormal neurologic examinations in HIV-infected children varied from 15% to 40% according to age and was always higher than in HIV-uninfected children born to HIV-seropositive and seronegative mothers (≤5% or less of abnormal examinations at each time period). After excluding those children with clinical acquired immunodeficiency syndrome (AIDS) from the analysis, the proportion of abnormal examinations in infected children was 12.5% at 6 months, 16% at 12 months, 20% at 18 months, and 9% at 24 months of age and was still more frequent than in HIV-uninfected children. The developmental delay was principally due to significantly lower gross motor scores.

Conclusions. HIV-1-infected children are more frequently developmentally delayed than uninfected children during the first 2 years of life in this African population. This developmental delay is related to the AIDS stage of pediatric HIV infection. *Pediatrics* 1993; 92:843–848; *human immunodeficiency virus type 1, neurodevelopment, Africa.*

ABBREVIATIONS. HIV-1, human immunodeficiency virus type 1; AIDS, acquired immunodeficiency syndrome; IVDU, intravenous drug use; WHO, World Health Organization.

Severe neurologic manifestations have been well described in children infected with human immunodeficiency virus type 1 (HIV-1) in industrialized countries. For example, 60% to 90% of the children with acquired immunodeficiency syndrome (AIDS) in the United States have severe neurologic impairment such as loss of developmental milestones, pyramidal signs, ataxia, hypertonia, and seizures.[1–3] In European prospective cohorts which consisted almost exclusively of children born to women who had acquired HIV-1 infection by intravenous drug use (IVDU),[4–6] the frequency of neurologic impairment in HIV-infected children is in the range of 20% to 30%. Few studies in the United States or Europe have focused on the comparison of infected and uninfected children born to HIV-seropositive women and have included, as a reference group, children born to HIV-seronegative women of the same socioeconomic status.[7,8] In these latter series, infected infants performed more poorly than uninfected children born to HIV-seropositive mothers (seroreverters) and than children born to HIV-seronegative mothers.[7,8]

Very limited data are currently available on the neurologic manifestations of HIV-infected children in African countries where the prevalence of HIV infection is very high.[9,10] Indeed, it is difficult to explore the neurologic impairment in children from developing countries, because of limited access to sophisticated diagnostic technology. On the other hand, the perinatal cohort studies carried out in Africa present two advantages in the neurodevelopmental assessment of HIV-infected children. First, the vast majority of these children are born to women infected through heterosexual contacts.[11] Therefore, the impact of HIV infection on the neurologic assessment is not confounded by IVDU. Second, most of these prospective studies[12–14] have included a control group of children born to HIV-seronegative mothers of the same socioeconomic status for the calculations of excess mortality attributable to HIV infection.[15] Thus, these studies should theoretically be able to evaluate the contribution of HIV infection in child neurologic impairment.

We report here the results of a prospective cohort study, comparing the results of developmental testing of children born to HIV-seropositive mothers, infected or uninfected themselves, with those of children born to HIV-seronegative mothers in Kigali, Rwanda, Central Africa.

SUBJECTS AND METHODS

Subject Selection

A prospective cohort study on mother-to-infant transmission of HIV-1 and on the natural history of HIV-1 infection in children

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during the first 2 years of life was launched in Kigali, the capital city of Rwanda, in November 1988. Details about enrollment and follow-up procedures are described elsewhere.[14] Briefly, after the mothers gave their verbal consent for participation to the study, 218 infants born to 215 HIV-seropositive mothers were enrolled at birth between November 1988 and June 1989 at the maternity ward of the Centre Hospitalier de Kigali. These children were matched with 218 children born to HIV-seronegative mothers of the same age and parity.

Clinical Follow-up

A physician systematically examined the children every 3 months until 24 months of age, looking in particular for signs and symptoms of the World Health Organization (WHO) clinical case definition of AIDS in children.[16] One modification was made to this definition: if present, severe and/or recurrent pulmonary infection was considered as a major sign in the place of chronic cough as a minor sign.[17] When necessary, children were seen in the outpatient department or hospitalized in the department of Pediatrics and treated free of charge. None of the children enrolled in this study received antiretroviral therapy during the study period.

Definition of Pediatric HIV-1 Infection and Classification of Children

Criteria used to classify children born to seropositive mothers as infected with HIV-1, uninfected, or with an indeterminate status were drawn from a working group consensus on mother-to-child transmission of HIV.[18] The use of this classification was restricted to children who had reached or could have reached the cutoff age of 15 months at the time of analysis. It took into account the HIV-1 antibody serostatus at 15 months of age and, when the child died before 15 months of age, the presence or absence of signs and symptoms possibly related to HIV infection. Death was defined as HIV related either (1) in a child with AIDS or (2) in a child with at least one HIV-related sign/symptom when last seen and dying from severe infection or persistent diarrhea (≥14 days) beyond the first 4 weeks of life. The following signs and symptoms were regarded as HIV related: persistent diarrhea, failure to thrive (<80% of weight for age), persistent generalized lymphadenopathy, oral candidiasis (beyond the neonatal period), severe or recurrent pneumonia, chronic parotitis, and herpes zoster infection. Children with at least two major and two minor signs of the modified WHO clinical case definition of pediatric AIDS[16,17] were considered to have AIDS.

The children born to HIV-seropositive mothers were considered HIV infected (group 1) (1) if they had clinical AIDS at any moment of the follow-up; or (2) if they were positive for HIV antibody at 15 months of age; or (3) if they died before 15 months of age, when their death was considered HIV related. They were considered HIV uninfected or seroreverters (group 2) (1) if they were negative for HIV antibody at 15 months or (2) if they died before that age, when their death was probably not of HIV-related cause and when they were HIV seronegative. Children born to HIV-seropositive mothers who were lost to follow-up before 15 months of age were considered uninfected when HIV negative at 9 months of age or beyond. In all the other circumstances, the HIV infection status of children born to HIV-seropositive women was considered indeterminate (group 4). One child born to an HIV-seropositive mother transiently seroreverted before becoming persistently seropositive[19] and was excluded from the analysis.

The 218 children born to HIV-seronegative mothers (group 3) were retested for HIV antibody every 3 months. Nine of them who became HIV-1 seropositive before the age of 24 months[20] were considered uninfected until the clinical examination preceding seroconversion. They have been excluded from the analysis since the time of seroconversion.

Neurodevelopmental Follow-up

Simple, rapid (consisting of about 15 items), and reproducible psychomotor assessments were elaborated for children aged 6, 12, 18, and 24 months (the tests given at 12 and 24 months are shown in Tables 1 and 2). The items used were selected from validated developmental screening tests such as the abbreviated and revised Denver score[21] and Illingworth's *The Development of the Infant and Young Child*.[22] The selected items covered the following aspects: gross motor development, fine motor development, language acquisition, and social contacts. These psychomotor assessments were pretested for feasibility and appropriateness before being adopted in this study. After completing the neurodevelopmental questionnaire, the physician was also asked to give a global evaluation of the neurodevelopmental assessment of the child ("normal" vs "abnormal"). The physicians were blinded to the HIV infection status of the children until the children were 18 months of age. Finally, physicians actively looked for signs of encephalopathy at each examination.

TABLE 1. Neurodevelopmental Test for 12-Month-Old Children of Human Immunodeficiency Virus (HIV)-Seropositive and HIV-Seronegative Women in Kigali, Rwanda, 1989–1990

Gross motor
1. Does the child walk, one hand held?
2. Does the child hold in standing position without help?
3. Does the child walk without help?
Fine motor
4. Does the child do pincer movement of forefinger and thumb?
5. Does the child drink alone?
Social contact
6. Does the child show what he wants?
7. Does the child look for hidden objects?
8. Does the child do "bravo" + "bye-bye" + "peak-a-boo"?
Language
9. Does the child know 2 or 3 words with meaning?
10. Does the child know the meaning of more than 3 words?
11. Is the child jargoning?

TABLE 2. Neurodevelopmental Test for 24-Month-Old Children of Human Immunodeficiency Virus (HIV)-Seropositive and HIV-Seronegative Women in Kigali, Rwanda, 1989–1990

Gross motor
1. Does the child run?
2. Does the child go up and down stairs alone?
3. Does the child jump?
4. Does the child kick a ball?
5. Does the child put on pants?
Fine motor
6. Does the child make a tower of six cubes?
7. Does the child succeed in getting a pill out of a little bottle?
8. Does the child imitate vertical stroke on paper?
Social contact
9. Does the child copy mother in cleaning?
10. Does the child obey 3 simple orders?
Language
11. Does the child know at least 10 words?
12. Does the child join 2 or 3 words in sentences?
13. Does the child name pictures of common objects?

Statistical Methods

Each item was scored 0 if the child was unable to do it, and 1 if he/she succeeded. For each component of the developmental assessment, a score was elaborated as the sum of all the items and the mean score was computed with its standard deviation for the following three groups: infected children (group 1), seroreverters (group 2), and children born to HIV-seronegative mothers (group 3). We also compared the frequency of abnormal development according to the physician's global assessment during each examination. The analysis was stratified on birth weight (<2500 g and ≥2500 g) and on gestational age defined according to the Finnström's score[23] (<38 weeks and ≥38 weeks). Two-sided χ^2 test, Fisher's Exact Test, Student's t test, and analysis of variance were used for comparisons when appropriate.

RESULTS

Follow-up and Number of Neurologic Examinations Performed

Among the 218 children born to HIV-seropositive mothers, after 24 months of follow-up, 50 could be

classified as HIV infected (group 1), 136 as uninfected (group 3), and 32 as indeterminate for HIV infection (group 4). Table 3 summarizes the number of children alive at each time of clinical examination and the number of children with a neurologic test performed. The children examined represent 94% and 83% of the children alive at 6 months and 24 months, respectively. Group 1 represented over time 11% to 7% of the children examined; group 2, 27% to 39% of the total; and group 3, 50% to 54%. In 90% of cases, the neurologic assessment was performed within 2 weeks of the scheduled date of examination.

The number of group 1 children fulfilling the WHO clinical definition of pediatric AIDS and examined for neurologic development was 3 of 43 at 6 months of age, 8 of 36 at 12 months, 10 of 25 at 18 months, and 9 of 20 at 24 months.

Global Neurodevelopment

One acute encephalitis occurred in a HIV-infected child, 2 weeks before his death at 16 months of age. No abnormal or pathologic reflexes were observed. No chronic progressive HIV-related encephalopathy was identified among the HIV-infected children during the follow-up period. On the other hand, 27% (3/11) of the HIV-infected children with abnormal examinations surviving at 12 months had stable encephalopathy and remained on a plateau during the second year of life.

Table 4 describes the evolution of the global neurodevelopmental assessment from 6 to 24 months of age among the three groups of children with a confirmed status for HIV infection. The proportion of abnormal neurodevelopmental examinations was significantly higher in group 1 children than in children from groups 2 and 3, who had a comparable evolution with 5% or less of abnormal examinations at each time period. We therefore compared the proportion of abnormal examinations among children from group 1 with that of groups 2 and 3 combined. The difference was highly significant at all ages ($P < .0001$ for all the comparisons). When stratifying on gestational age or on birth weight, the proportion of abnormal examinations remained significantly higher in group 1 than in the two other groups.

Among the children with clinical AIDS, the global neurodevelopmental examination was considered abnormal in 2 (66%) of 3, 7 (87.5%) of 8, 7 (70%) of 10, and 2 (22%) of 9 at 6, 12, 18, and 24 months of age, respectively. After excluding those children from the analysis, the proportion of abnormal examinations in group 1 was 12.5% at 6 months, 16% at 12 months, 20% at 18 months, and 9% at 24 months of age. Abnormal examination was still more frequent in infected children than in uninfected children, but the difference only reached statistical significance in 6-month-old children ($P = .0003$, Fisher's Exact Test).

When we considered the 19 HIV-infected children who had an abnormal global neurodevelopmental examination at least at one of the follow-up visits, the cumulative mortality was 58% in this group after 24 months of follow-up. Among these 11 children who died, 10 were at the AIDS stage at the time of death.

We analyzed the mortality of the children born to HIV-seropositive mothers according to their neurodevelopmental assessment during the first 2 years of follow-up. Children with at least one abnormal examination more frequently died (11/28) than children with no abnormal examination (13/144) ($P < .0001$). Among group 1 children, this relation between developmental abnormality and mortality was not statistically significant (11 deaths among 18 children with abnormal examination vs 11/22 children with no abnormal examination; $P = .30$).

Components of the Developmental Assessment

The gross motor score (Table 5) was repeatedly lower in group 1 children than in those from groups 2 and 3 ($P < .0002$ at all ages, analysis of variance).

For fine motor development (Table 6), the mean score in group 1 was constantly lower than in groups 2 and 3 during the follow-up period but this difference was only statistically significant at 6 and 12 months of age.

For language acquisition (Table 7), children from group 1 always performed more poorly than the others but the mean score was only statistically different at 24 months of age.

For social contacts (Table 8), children from group 1 performed significantly more poorly at 6 and at 24

TABLE 3. Summary of the First 2 Years of Follow-up and of Neurodevelopmental Examinations Performed in the Cohort of Children Born to Human Immunodeficiency Virus (HIV)-Positive and HIV-Negative Mothers in Kigali, Rwanda, 1989–1991*

Group	6 mo	12 mo	18 mo	24 mo
HIV-infected children (group 1)	43/45 (96)	36/37 (97)	25/28 (89)	20/25 (80)
Uninfected children born to seropositive mothers (group 2)	133/136 (98)	133/134 (99)	123/133 (92)	113/124 (91)
Uninfected children born to seronegative mothers (group 3)	193/202 (96)	180/197 (91)	167/192 (87)	156/186 (84)
Indeterminate HIV status (group 4)	15/17 (88)	0/7	0/7	0/7
Excluded from analysis†	10	9	9	8
Total	384/410 (94)	349/384 (91)	315/369 (85)	289/350 (83)

* See "Subjects and Methods" section for group definitions. Values represent examined/alive (percent).
† See "Subjects and Methods" section for exclusion criteria.

TABLE 4. Proportion of Abnormal Neurodevelopmental Examinations in Children Aged 6 to 24 Months According to Their Human Immunodeficiency Virus (HIV) Infection Status, Kigali, Rwanda, 1989–1991*

	6 mo	12 mo	18 mo	24 mo
HIV-infected children†	16 (7/43)	31 (11/36)	40 (10/25)	15 (3/20)
Uninfected children both to seropositive mothers†	1.5 (2/133)	5 (7/133)	5 (6/123)	0 (0/113)
Uninfected children born to seronegative mothers†	1.5 (3/193)	5 (9/180)	5 (9/167)	3 (5/156)
Total	3.3 (12/369)	7.7 (27/349)	7.9 (25/315)	2.8 (8/289)
P value‡	.0001	.0001	.0001	.006

* Values represent percent with abnormal results according to the physician's assessment.
† See definitions in "Subjects and Methods" section.
‡ When comparing group 1 to groups 2 and 3 combined, by Fisher's Exact Test.

TABLE 5. Gross Motor Mean Score* in Children Aged 6 to 24 Months According to Their Human Immunodeficiency Virus (HIV) Infection Status, Kigali, Rwanda, 1989–1991

	6 mo	12 mo	18 mo	24 mo
HIV-infected children†	3.00 [1.28] (n = 40)	1.03 [0.91] (n = 36)	1.80 [1.26] (n = 25)	3.25 [1.41] (n = 20)
Uninfected children born to seropositive mothers†	3.62 [0.63] (n = 128)	1.83 [0.87] (n = 133)	2.65 [0.72] (n = 120)	4.36 [0.83] (n = 109)
Uninfected children born to seronegative mothers†	3.54 [0.74] (n = 186)	1.84 [0.92] (n = 179)	2.71 [0.67] (n = 167)	4.20 [1.17] (n = 151)
Maximum possible value of the score	4	3	3	5
P value‡	.0001	.0001	.0001	.0002

* Mean number of positive responses in each group. Standard deviations are in brackets.
† See definitions in "Subjects and Methods" section.
‡ Analysis of variance.

TABLE 6. Fine Motor Mean Score* in Children Aged 6 to 24 Months According to Their Human Immunodeficiency Virus (HIV) Infection Status, Kigali, Rwanda, 1989–1991

	6 mo	12 mo	18 mo	24 mo
HIV-infected children†	3.21 [1.29] (n = 33)	1.48 [0.76] (n = 33)	1.14 [0.91] (n = 21)	1.88 [1.17] (n = 17)
Uninfected children born to seropositive mothers†	3.78 [1.10] (n = 116)	1.77 [0.44] (n = 126)	1.40 [0.66] (n = 107)	2.16 [0.77] (n = 108)
Uninfected children born to seronegative mothers†	3.83 [1.00] (n = 169)	1.69 [0.51] (n = 168)	1.38 [0.67] (n = 140)	2.04 [0.77] (n = 134)
Maximum possible value of the score	5	2	2	3
P value‡	.02	.02	.28	.30

* Mean number of positive responses in each group. Standard deviations are in brackets.
† See definitions in "Subjects and Methods" section.
‡ Analysis of variance.

months of age than children from the two other groups. At 12 and 18 months of age the difference did not reach statistical significance.

There were no statistically significant differences between groups 2 and 3 for gross motor, fine motor, language acquisition, and social contact scores during the study period.

DISCUSSION

The neurodevelopmental assessments we performed in this study were not based on the classic tests recommended in the literature.[21,22] The time that would have been required to examine each child according to these guidelines and the absence of validity studies in the African context lead us to propose a simplified version of these tests. However, as these batteries of tests were used for the purpose of comparison between HIV-infected and uninfected children, we do not believe that these simplifications have affected the validity of our results. Moreover, the fact that two physicians (P.M. and P.L.) performed more than 80% of the total number of examinations strengthens the reliability of the study. The knowledge by the physicians of the HIV infection status of children aged beyond 18 months of age might have introduced a bias. However, the proportion of HIV-infected children with an abnormal score was constantly and substantially higher at all ages, so that chance is unlikely to explain this finding. The proportion of HIV-infected children with an abnormal neurodevelopmental examination was lower at 24 than at 12 or 18 months of age. This is most likely the reflection of a neurodevelopmental improvement over time in some of these children together with the death of the most severely affected children during the second year of life. This study confirms that these

TABLE 7. Language Mean Score* in Children Aged 6 to 24 Months According to Their Human Immunodeficiency Virus (HIV) Infection Status, Kigali, Rwanda, 1989–1991

	6 mo	12 mo	18 mo	24 mo
HIV-infected children†	0.79 [0.41] (n = 43)	1.83 [0.94] (n = 36)	1.08 [0.86] (n = 25)	1.42 [1.07] (n = 19)
Uninfected children born to seropositive mothers†	0.89 [0.32] (n = 133)	2.01 [0.88] (n = 132)	1.23 [0.81] (n = 99)	2.03 [0.86] (n = 106)
Uninfected children born to seronegative mothers†	0.89 [0.31] (n = 191)	1.94 [0.84] (n = 179)	1.23 [0.75] (n = 167)	2.16 [0.78] (n = 138)
Maximum value of the score	1	3	2	3
P value‡	.18	.54	.66	.002

* Mean number of positive responses in each group. Standard deviations are in brackets.
† See definitions in "Subjects and Methods" section.
‡ Analysis of variance.

TABLE 8. Social Contact Mean Score* in Children Aged 6 to 24 Months According to Their Human Immunodeficiency Virus (HIV) Infection Status, Kigali, Rwanda, 1989–1991

	6 mo	12 mo	18 mo	24 mo
HIV-infected children†	2.31 [0.75] (n = 42)	2.47 [0.84] (n = 32)	2.05 [1.05] (n = 20)	1.35 [0.49] (n = 20)
Uninfected children born to seropositive mothers†	2.64 [0.59] (n = 128)	2.47 [0.69] (n = 118)	2.41 [0.81] (n = 106)	1.99 [0.09] (n = 112)
Uninfected children born to seronegative mothers†	2.63 [0.55] (n = 185)	2.39 [0.76] (n = 158)	2.47 [0.90] (n = 139)	2.00 [0.0] (n = 154)
Maximum value of the score	3	3	4	2
P value‡	.004	.63	.13	.0001

* Mean number of positive responses in each group. Standard deviations are in brackets.
† See definitions in "Subjects and Methods" section.
‡ Analysis of variance.

HIV-infected survivors have milder complications,[4,24,25] including reduced neurologic impairment, than those in whom HIV-related disease develops early.

HIV-1 is known to invade the central nervous system.[26–28] However, few neurologic studies deal with infected children prospectively followed up since birth. Studies from North America have shown very pessimistic results, with 60% to 90% of the children with symptomatic HIV-1 infection having severe neurologic impairment.[2,3] The results from the European Collaborative Study[6] and from our study in Kigali have less negative conclusions. In the European Collaborative Study, neurologic manifestations were present in 31% (5/16) of infected children in whom AIDS developed, in none (0/23) of those who had less severe signs, and in 1% (2/164) of uninfected subjects.[6] Among infected children in Kigali, 31% of those aged 12 months and 40% of those aged 18 months were considered neurodevelopmentally delayed (vs 5% among uninfected control subjects). These proportions among infected children with AIDS were 87% and 70% at the same ages, respectively. This shows that the proportion of paucisymptomatic HIV-infected children who have abnormal findings on neurodevelopmental examination is usually low.

As described by others,[7] the neurodevelopmental delay was principally due to gross motor retardation in our cohort. Other neurodevelopmental aspects studied such as language and social contacts were affected later in life and to a much lesser degree than gross motor function. Condini et al,[29] who compared HIV-infected and uninfected children in Italy, found similar results for language performances. For fine motor tests, the difference between infected and uninfected children did not reach the statistical significance after 12 months of age. This is possibly due to our small numbers of HIV-infected children surviving beyond 12 months of age.

Despite the active surveillance carried out by physicians and social workers of the project, only one encephalopathy has been diagnosed among HIV-infected children in this study. This encephalitis was acute and could possibly be related to viral infection other than HIV infection. Factors that might be incriminated in the difference in occurrence of encephalopathy between North American studies and this study include selection bias, the role of IVDU on the central nervous system of the fetus, the geographic variability in the neuropathogenicity of different HIV-1 strains, and the fact that infected African infants may die before severe neurologic manifestations develop.

The occurrence of at least one abnormal neurodevelopmental assessment during follow-up was a risk factor for subsequent mortality in children born to HIV-positive mothers. The reason why this association between neurodevelopmental impairment and mortality was not found in the subgroup of HIV-infected children is probably due to the very high mortality of these subjects, irrespectively of their psychomotor status.[30]

In this study, seroreverters and uninfected children born to HIV-seronegative mothers had strictly comparable results on neurologic developmental assessments. The same observation has been made in a recent study in the United States.[8] It should be emphasized that in our study, seropositive and sero-

negative mothers had comparable socioeconomic status and were infected through heterosexual contacts. Therefore, maternal IVDU could not confound the results of the neurologic examinations in our pediatric population. It has recently been shown that seroreverters born to IVDU mothers in New York City had a significant delay found in neuropsychologic assessment.[31] In contrast, in Rwanda, the role of the extended family is important. When the mother is unable to take care of her children properly because of HIV-related disease, this family network could play a positive role on the psychomotor development of uninfected children of seropositive mothers, who therefore perform as well as children in the general population.

In conclusion, HIV-1-infected children in Kigali, Rwanda, were more frequently developmentally delayed than children born to HIV-seronegative mothers and than seroreverters. Seroreverters had neurodevelopmental performances similar to those of children born to seronegative mothers. The neurodevelopmental delay of HIV-1-infected children was principally observed among those with severe HIV-related symptomatology and was mostly a consequence of gross motor retardation. For the infected children, this delay was either a reflection of the chronicity of HIV-1 disease or a direct expression of central nervous system involvement or both. Further follow-up is planned to describe the long-term neurodevelopmental prognosis of these HIV-infected children.

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