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Major Article

Influence of exposure and vertical transmission of HIV-1 on the neuropsychomotor development in children

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Abstract

Introduction: Exposure to human immunodeficiency virus (HIV)-1 during pregnancy is a major risk factor for neurodevelopmental delay and deleterious effects in children. However, limited information about these conditions exists in poor geographical areas in Brazil. Prevention of vertical transmission of HIV-1 is dealt differently in different regions of the country and in poorer areas it is more difficult to evaluate the impact of the prevention methods. The outcomes of the exposure to HIV-1 and the impact of vertical HIV-1 transmission on neuropsychomotor development was evaluated for the first time in children born to HIV-infected mothers in the North region of Brazil, where the majority of the population has poor access to health services. **Methods:** Sixty children born to HIV-1-infected mothers (case group) and 58 born to non-infected mothers (control group) were followed for the first 12 months of life in a prospective case-control study. Neuropsychomotor development was assessed using the Denver II test. **Results:** Suspected neuropsychomotor developmental delays were more frequent in the case group (33.3%), namely in language (38.9%) and gross motor skills (27.8%). These delays were reversed in most children after 12 months of life due to therapeutic intervention. The delays were not reversed in three children, all of whom belonged to the case group. Only one of these was infected with HIV-1, and this child had the poorest neuropsychomotor outcomes. **Conclusions:** Maternal HIV-1 infection negatively affected the neuropsychomotor development in children, although other factors may have played a role.

Keywords: HIV-1. Vertical transmission. Neurological damage.

INTRODUCTION

The spread of the human immunodeficiency virus (HIV)-1 in Brazil has been marked by different epidemiological settings. In the first half of the 1980s decade, HIV-1 was reported to affect homosexual men, with sexual contact being the main route of transmission, in addition to blood transfusions and needle sharing (among intravenous drug users). However, between the late 1980s and early 1990s decades, HIV-1 was also found to be transmitted via heterosexual sex, which became the main route of transmission[1]. This led to a significantly higher prevalence of HIV infection in women of childbearing age and to a subsequent increase in the number of children exposed to HIV-1[2].

The incidence of HIV-1 infection in Brazilian pregnant women has increased from 2.1 cases/1,000 live births in 2006 to 2.7 cases/1,000 live births in 2015. More pronounced increases were found in the North and Northeast regions, where the incidence rose from 1.2 cases/1,000 live births to 2.9 cases/1,000 live births (in the North region) and 2.0 cases/1,000 live births (in the Northeast region) in the same period[3].

Neurological symptoms are more frequent in children than in adults with acquired immunodeficiency syndrome (AIDS), as their central nervous systems are immature and more susceptible to injury[4]. Encephalopathy is an indirect consequence of

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infection and is characterized by neurodevelopmental delay. The most common neurological findings include hyporeflexia, delayed neuropsychomotor development, language delay, mental retardation, pyramidal syndrome, and cerebral palsy. Vertical HIV-1 transmission leads to impaired development in 6-60% of infants, which includes cognitive impairment and motor or language delays, resulting in severe deleterious effects later in life, when compared to children who are not infected with or exposed to the virus[5].

Few studies in Brazil have assessed the neuropsychomotor outcomes in children who were exposed to HIV-1 during pregnancy, irrespective of vertical transmission. The scenario of the country's North region is of particular concern, due to the high level of illiteracy and the poor access to health care for a significant part of the population in this region. As a large, universal and free healthcare service is offered to the general Brazilian population, the main objectives of the present study were to evaluate how the Brazilian healthcare service contributes to avoid that children be affected by the current HIV-1 epidemic and the clinical outcomes of affected children.

METHODS

Ethical aspects

This study was approved by the Nursing Program Research Ethics Committee, State University of Pará (UEPA) under the technical opinion number 0053.0.321.000/10 and were in accordance with the ethical standards of the responsible committee on human experimentation (institutional, regional, or national) and in keeping with the Helsinki Declaration of 1964, as revised in 1975, 1983, 1989, 1996, and 2000. All mothers were informed about the project, and those who agreed to participate provided written informed consent.

Study design, location, and period

This was a prospective, case-control study involving two groups of pregnant women and their newborn children. One group was composed of children born to HIV-1-infected mothers (case group), and the other group was composed of children born to non-infected mothers (control group). The case group included mothers and children seen in two reference centers in the city of Belém, state of Pará (URE-DIPE Section in the Specialized Mother, Infant and Adolescent Reference Center, [UREMIA] and the city of Belém's Casa Dia), and the control group included women and children attending the Comprehensive Children's Health Care Program (PAISC) in a municipal health unit in the city of Ananindeua, state of Pará, from 2010 to 2012.

Study groups

Neuropsychomotor development was assessed in 60 children who were exposed to HIV-1 (case group) and 58 children who were not exposed to HIV-1 (control group), who were matched for age and sex. Children whose parents or guardians did not agree to participate in the study were excluded.

Study protocol

The neuropsychomotor development was assessed two, four, six, nine, and 12 months after birth. Information on social, demographic, economic, prenatal, natal, and postnatal variables was provided by the mothers through a questionnaire. The neuropsychomotor development was evaluated by the Denver II Test[6], which is a standardized instrument used to screen children at risk of neurodevelopmental delay and includes four sections: personal-social, fine motor adaptive, language, and gross motor skills. Each score was graded as "caution," when the child failed or refused a test item that is expected to be passed by 75 to 90% of younger children, or "delayed," when the child failed or refused an item that is expected to be passed by more than 90% of younger children. The final result was considered to be normal, when the child scored no more than one "caution" and no "delayed"; suspected, when the child scored one "delayed" and/or two or more "cautions"; and abnormal, when the child scored two or more "delays"[7].

Statistical analysis

The chi-square test, G test, T test, and Fisher's exact test were used to compare demographic, social, and economic characteristics and to evaluate differences in the performance in the Denver II test between the two groups during the first year of life. A significance level of 5% was used for all tests. The statistical analyses were performed using the BioEstat program, version 5.3[8].

RESULTS

A predominance of female children was observed in both groups (**Table 1**). The most frequent maternal age range was 17-22 years old in the control group (57%) and 23-28 years old in the case group (39.7%), which was statistically different ($p = 0.0005$). Almost half of the mothers were in a stable relationship (49.2%), and both case and control groups had a predominance of mothers who did not complete 9 school years (58.7% in the case group and 52.4% in the control group). The monthly family income was reported to be lower than the minimum wage by 58.7% of women in the case group, while 33.3% of women in the control group reported a monthly family income of 1-2 minimum wages, which was significantly different ($p=0.0003$).

Most women in the case and control groups started having prenatal care appointments during the first 4 months of pregnancy (96.8% and 100% in the case and control group, respectively), had no complications during pregnancy (52.4% and 76.2%, in the case and control group, respectively), and were tested for HIV-1 infection (54.0% and 85.0% in the case and control group, respectively). The case group had a predominance of women with 1-6 prenatal care appointments, while the control group had a predominance of women with six or more appointments, with a statistically significant difference between the two groups ($p = 0.0001$). Most HIV-1-infected women (92.1%) underwent cesarean sections, while normal labors were more common among women in the control group (55.6%). The birthweight was between 2.5 and 3.0 kg in 42.9% of children born to HIV-1-infected mothers, and between 3.0 and 3.5 kg in 42.9% of children of the control group, with a statistically significant difference between the two groups ($p=0.0071$). None of the HIV-1-infected women breastfed their children, whereas 92.1% of women in the control group did it (**Table 2**).

TABLE 1: Demographic, social, and economic characteristics of mothers with and without HIV-1 infection and their children. Pará State, Brazil, 2010-2012 (n = 126).

Characteristics	Children of mothers with HIV-1		Children of mothers without HIV-1		*p*
	n	%	n	%	
Child's gender					
Female	36	57.1	36	57.1	-
Male	27	42.9	27	42.9	
Mother's age (years)					0.0005[3]
17 – 22	22	34.9	36	57.1	
23 – 28	25	39.7	13	20.6	
29 – 34	12	19.1	9	14.3	
35 – 40	2	3.2	1	1.6	
Over 40	2	3.2	4	6.4	
Mother's marital status					0.0322[1]
Married	6	9.5	15	23.8	
Stable relationship	31	49.2	33	52.4	
Single	26	41.3	15	23.8	
Mother's education level					0.0844[2]
Incomplete elementary school	29	46	17	27	
Compete elementary school	8	12.7	16	25.4	
Incomplete high school	12	19.1	12	19.1	
Complete high school	13	20.6	15	23.8	
Incomplete higher education	0	0	2	3.2	
Complete higher education	1	1.6	1	1.6	
Family income (in relation to the minimum wage)					0.0003[2]
< 1	37	58.7	21	33.3	
1 —| 2	17	27	36	57.1	
2 —| 3	5	7.9	0	0	
> 3	4	6.4	6	9.5	

[1] Pearson's chi-square test; [2]G test; [3]T test.

Out of 63 HIV-1-infected women, 54 (85.7%) underwent antiretroviral therapy (ART) during pregnancy and nine (16.7%) underwent ART before pregnancy. A total of 15 (27.8%) women started ART during the first trimester, 22 (40.7%) during the second trimester, and eight (14.8%) during the last trimester of pregnancy. Most births (74.6%; 47/63) occurred between the 37th and 40th weeks of gestation. All children born to HIV-1-infected mothers were treated with azidothymidine (AZT) in an attempt to prevent vertical HIV-1 transmission.

Table 3 summarizes the results of the Denver II test. Although there were variations in frequency, there was no significant difference until the first year of life between children born to infected and non-infected mothers in the domain of the Denver II test associated with the potential neurodevelopmental delay.

Children in whom neurodevelopmental delay was suspected were mostly motor, personal-social and language skills (**Table 4**). Although there was a higher rate of impairment in these skills among children who were born to HIV-1-infected mothers, no statistically significant difference was observed between the two groups.

Vertical HIV-1 transmission was investigated in 24 (38%) children who were exposed to the virus during pregnancy. The remaining children were over 18 months old at the end of the study but were no longer seen due to changes in the parental consent after birth, absence in routine laboratory tests, lack of material, technical resources, excessively delay in scheduling the examination and receiving their results in the reference centers. Among the 24 children that could be assessed, 23 (95.8%) were not infected by the virus. Out of 20 children

TABLE 2: Prenatal, natal, and postnatal characteristics of mothers with and without HIV-1 infection and their children. Pará State, Brazil, 2010-2012 (n = 126).

Characteristics	Children of mothers with HIV-1		Children of mothers without HIV-1		*p*
	n	%	n	%	
Received prenatal care					
Yes	61	96.8	63	100	0.4960[3]
No	2	3.2	0	0	
Start of prenatal care					
Up to the 4th month	43	70.5	55	87.4	0.0168[2]
5th to 6th months	15	24.6	8	12.6	
7th month or later	3	4.9	0	0	
Number of prenatal consultations					0.0001[1]
1-6	33	54.1	12	19.0	
6 or more	28	45.9	51	81.0	
Complications during pregnancy					0.0038[1]
Yes	30	47.6	15	23.8	
No	33	52.4	48	76.2	
Performed HIV-1 test					0.0001[1]
No	29	46.0	9	14.5	
Yes	34	54.0	53	85.5	
Type of birth*					0.0001[1]
Cesarean	58	92.1	28	44.4	
Normal	5	7.9	35	55.6	
Birthweight (kg)					0.0071[2]
2.0-2.5	9	14.3	4	6.3	
2.5-3.0	27	42.9	14	22.2	
3.0-3.5	20	31.7	27	42.9	
3.5-4.0	7	11.1	16	25.4	
≥4.0	0	0	2	3.2	
Postnatal Breastfeeding					
No	63	100	5	7.9	0.000[3]
Yes	0	0	58	92.1	

[1]Pearson's chi-square test; [2]G test; [3]Fisher's exact test.

*Children born to HIV-1-infected mothers were subdivided into those born by Cesarean delivery with elective Cesarean section (n = 41) and Cesarean section after membrane rupture (n = 17).

with neurodevelopmental delay, this status was reversed in 17 (85%) at the end of the first-year evaluation. Three children were unable to overcome the neurodevelopmental delays, one of whom was infected with HIV-1. This child presented the poorest performances in the Denver II test, especially in language and motor skills.

DISCUSSION

The predominant age range of HIV-1-infected mothers was similar to that found in other areas of Brazil[2], and it was not different from the group most involved in the present HIV-1 epidemic. Most infected mothers were in a stable relationship, which corroborates a previous report[8] and indicates that HIV-1 infection can occur even during stable heterosexual relationships[9]. Although no difference was observed between the groups in terms of education, most infected women presented low educational level, which is a key determinant of higher susceptibility to infection, along with low monthly family income and low access to information about routes of transmission and infection[1,10]. Maternal education is an important health indicator variable for both newborns and children and is a good predictor of neonatal mortality[2].

The prenatal history of children at risk of vertical HIV-1 infection was characterized by absence of complications during pregnancy, according to maternal reports. Prenatal care started as late as the fourth month, and more than half of mothers did not complete six prenatal visits, reflecting the poor quality of maternal care. Uninfected mothers were more consistently treated, considering the minimum standards required by the Brazilian Ministry of Health's Program for Humanization of the Prenatal and Birth Periods (PHPN)[11].

Early initiation of prenatal care is fundamental for essential interventions during the early stage of pregnancy, including prevention of vertical syphilis and HIV-1 transmission, diagnosis of tubal pregnancy, anemia control, and management of hypertension and diabetes[12]. The first component of the

TABLE 3: Evaluation of the performance of children born to mothers with and without HIV-1 infection in the first year of life, according to the Denver II test, Pará State, Brazil, 2010-2012 (n = 118).

Denver II Test Result [1]	Children of mothers with HIV-1		Children of mothers without HIV-1		*p*
	n	%	n	%	
At 2 months of age					
Normal	56	93.3	56	96.6	0.6796[2]
Suspected delay	4	6.7	2	3.4	
Total	60	100	58	100	
At 4 months of age					
Normal	47	83.9	45	93.8	0.1370[2]
Suspected delay	9	16.1	3	6.2	
Not applied	4	-	10	-	
Total	60	100	58	100	
At 6 months of age					
Normal	50	92.6	40	83.3	0.5061[2]
Suspected delay	4	7.4	6	13	
Not applied	6	-	12	-	
Total	60	100	58	100	
At 9 months of age					
Normal	46	82.1	35	83.3	0.9080[3]
Suspected delay	10	17.8	7	16.7	
Not applied	4	-	16	-	
Total	60	100	58	100	
At 12 months of age					
Normal	57	95	55	94.8	1.0000[2]
Suspected delay	3	5	3	5.2	
Total	60	100	58	100	

[1]The number of children with suspected delays during the first year in a given month or across several months was 20/60 (33.3%) in the case group and 12/58 (20.6%) in the control group; [2]Fisher's exact test.

TABLE 4: Performance in the domains of the Denver II test of children born to mothers with and without HIV infection in whom developmental delay was suspected in the first year of life. Pará State, Brazil, 2010-2012 (n = 32).

Evaluated skills	Children of mothers with HIV-1		Children of mothers without HIV-1	
	*n	%	*n	%
Gross motor skills	10	27.8	7	24.1
Fine motor skills	6	16.7	10	34.5
Personal-social skills	6	16.7	4	13.8
Language skills	14	38.9	8	27.6
Total	36	100.0	29	100.0

*Neurodevelopmental delay was suspected in 20 children born to mothers infected with HIV-1 (suspected delay in 1 or more months) and 12 children born to mothers without HIV-1 (suspected delay in 1 or more months).

PHPN ("Incentives for Prenatal Care") recommends a minimum of eight quality criteria, including safeguarding the pregnant woman, conducting the first prenatal consultation before the fourth month of pregnancy and having at least six prenatal appointments[11]. Infected pregnant women need special prenatal care and should be monitored throughout the prenatal period with a minimum number of consultations, which provide them with extra care and advice, to ensure an effective ART to reduce the possibility of vertical transmission[9].

The absence of the HIV-1 test during the prenatal period is possibly due to the mother's knowledge of her infection status. However, it is the duty of the health professional to request a rapid HIV-1 test in the first prenatal consultation, and the test must be repeated during the third trimester of pregnancy[13]. The non-detection of HIV-1 infection due to the absence of the HIV-1 test during the prenatal care is considered a failure in prevention and early treatment, which can impair the efforts to control the vertical HIV-1 transmission[14].

The rate of cesarean sections was high, although there were few complications during the prenatal care. Most cesarean deliveries were elective, in order to ensure the minimum possible contact between the newborn and infected maternal fluids. It is worth mentioning that, in some cases, the number of cesarean interventions was low, compared to the 58% rate among pregnant women who underwent cesarean sections in Teresina, Piaui[9]. Most infected mothers underwent highly active antiretroviral therapy (HAART) during pregnancy, starting from the second trimester. HAART is recommended for all pregnant women, regardless of the presence of symptoms or low $CD4^+$ T lymphocyte count[15], and its administration has brought relevant benefits, preventing approximately 35% of cases of mother-to-child HIV-1 transmission, especially when the drug was used during the final weeks of pregnancy[16].

In this study, children born to infected mothers were not breastfed, which is in accordance with existing guidelines. In the case of HIV-1-infected mothers, breast milk is replaced with a specific formula for infants, which is provided for the first 6 months of life by the Brazilian Health System (SUS)[17]. Breastfeeding exclusion reduces the odds of mother-to-child HIV-1 transmission by 20%[18]. Similarly, it was also found that all children underwent treatment with AZT syrup 10 mg/mL, which was initiated before the second hour post-partum, and administered at a dose of 2 mg/kg every 6 hours, for 6 weeks[19]. Despite of the poor access to health services, most infected mothers received the necessary attention and followed the measures to reduce the possibility of vertical HIV-1 transmission, which led to the low rate of children with confirmed HIV-1 diagnosis at the end of the follow-up.

A higher rate of children with suspected neuropsychomotor developmental delay was observed in the case group. Most suspected delays occurred in the areas measured by the Denver II test associated with language and motor domains and in the personal-social and fine motor domains. At the age of 12 months old, most children did not have any neurodevelopmental impairment. The incidence of neurodevelopmental delay was greater than the 15.4% rate observed in 143 children enrolled in a program for prevention of vertical HIV-1 transmission in Thailand. In this program, motor skills accounted for most of suspected delays, which was similar to our findings, but different from the findings of other Brazilian study, conducted in the city of Diamantina (southeastern region of Brazil), in which language skills accounted for most of suspected delays.

Although no statistically significant differences were seen between the groups regarding variables of neuropsychomotor development, children at risk of vertical HIV-1 infection were exposed to factors that are associated with delayed neuropsychomotor development, including low maternal educational level, low monthly family income, no breastfeeding and low birthweight. Thus, the risk of delayed neuropsychomotor development exists even when the possibility of vertical HIV-1 transmission is ruled out[21]. Intrauterine exposure to antiretroviral agents is other possible cause of impaired neurodevelopment[22]. Although there is no consensus regarding this subject, it has been suggested that environmental factors play a key role in the risk of neurodevelopmental delay in children born to HIV-infected mothers[20,21], as well as maternal stress upon discovery of the HIV-1 infection, which leads to emotional symptoms during pregnancy, such as anxiety[23].

Maternal competence strongly contributes to the neuropsychomotor development. This consists of four components (support network, marital satisfaction, maternal health, and child characteristics) that interact in a complex manner to determine the child's development[24]. In HIV-1 infected mothers, these components are likely to be crucial for the risk of developmental delays, as most patients with HIV-1 infection confront a range of psychological challenges, such as fear of death, prejudice, neglect and guilt.

Although previous studies have indicated that both exposure to and infection with HIV-1 can affect a child's development, HIV-1 infection can impair the neuropsychomotor development in a more serious way. In this study, three children completed the first year of life without reversing the neurodevelopmental delays. Only one of them was infected with HIV-1 (after vertical transmission) and this child had the poorest neuropsychomotor performances in the Denver II test, particularly in language and motor skills.

Most HIV-1-infected children showed motor and cognitive delays, which are indicators of disease progression. These abnormalities did not appear to be associated with other risk factors, such as socioeconomic variables described in another setting[25].

In conclusion, the subjects of this study showed demographic and social characteristics similar to those of the general population affected by the HIV-1 epidemic in the northern region of Brazil. Low educational level and low income play a key role in maintaining the epidemic, as the affected populations remain unaware of prevention measures and do not have access to quality health care. The incidence of suspected delay in child development was higher among those exposed to vertical transmission from mothers infected with HIV-1. Therapeutic intervention during the first year of life helped reverse the damaging effects in most children at the end of

the follow-up. The only HIV-1-infected child had the poorest neuropsychomotor development during the first year of life, particularly in language and motor skills.

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