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Evaluation of motor and cognitive development among infants exposed to HIV☆

Kaitiana Martins da Silva [a,1], Cristina dos Santos Cardoso de Sá [b,*], Raquel Carvalho [b]

[a] Federal University of São Paulo, Brazil
[b] Movement Science Department, Federal University of São, Brazil

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ABSTRACT

This study of a prospective and cross-sectional nature compared the motor and cognitive development of HIV-exposed and unexposed infants in their first 18 months of age. 40 infants exposed to HIV and antiretroviral therapy (Experimental Group - EG) and 40 unexposed infants (Control Group - CG) participated in the study. They were divided into four age groups of 4, 8, 12 and 18 months old, with 10 infants from EG and 10 from CG in each group. The infants were evaluated once on motor and cognitive development by the Bayley Scale of Infant and Toddler Development. Performance category grading and comparisons among scaled score, composite score and percentile rank were held. There was significant group effect for scores in motor and cognitive domains showing lower scores for EG regardless of age. In comparison to the CG, the EG presented lower scores for cognitive domain at 8 and 18 months. In the performance categories, all infants were classified at or above the average for motor and cognitive development, except of one EG-18 month old infant classified as borderline for motor development. Infants exposed to HIV and antiretroviral therapy own adequate cognitive and motor development in the first 18 months. However, the lower scores found, particularly on the 8th and 18th month for cognitive development, may indicate future problems, highlighting the need for systematic follow-up of this population.

1. Introduction

The Human Immunodeficiency Virus (HIV) infects about 35.3 million people worldwide, including 3.3 million children. In 2013, 260,000 new cases were discovered of children with the HIV virus in the global context [1].

Vertical transmission is the main form of HIV transmission from mother to children and it can occur during pregnancy by hematogenous dissemination, at the time of birth due to infant's contact with the mother's blood and secretions, or after delivery through invasive procedures such as airway and stomach suction. Breastfeeding also represents an important risk factor of vertical transmission and it is associated with the disease stage of mother [2]. HIV has a greater affinity for the immune system and the nervous system cells [3]. When the infection and/or exposure to the virus occurs while the central nervous system (CNS) is immature, the infant may acquire a variety of neurological sequelae, such as neuropsychomotor developmental delay and encephalopathies [4,5,6,7].

Several studies have investigated the development of HIV-infected and HIV-exposed children and found lower levels of development compared to typical children. HIV-positive children showed global developmental problems [8,9,10], and motor development was the most severely affected [9]. Comparisons between HIV-infected and HIV-exposed infants indicated that neurological and neurodevelopmental alterations were found in 82% of HIV-infected infants and in 36% of HIV-exposed infants indicating that both groups can be affected [11]. Additionally, both infected and exposed infants demonstrated developmental delay compared to unexposed infants [12].

HIV infection by vertical transmission has reduced since the 1990s with the use of antiretroviral drugs, the C-section, the replacement of breast milk, among other factors [13,14]. However, intrauterine exposure to HIV, even without infection of the fetus, can cause immunological changes due to extended and direct contact with the virus and viral proteins, which become evident by the presence of anti-HIV memory cells in these infants [6]. Furthermore, the exposure to antiretroviral therapy increases the risk of mitochondrial dysfunction, especially the exposure to nucleotide inhibitors of reverse transcriptase, which could induce CNS changes and consequently neuropsychomotor development [10,15,16]. Yet, there is no consensus in literature on the real effects of using high amounts of antiretrovirals, related to virus exposure on the

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* Corresponding author.
E-mail addresses: kaitianafisio@hotmail.com (K.M. da Silva), Cristina.sa@uol.com.br (C.S.C. de Sá), raquelpcarvalho@gmail.com (R. Carvalho).
[1] Mailing address: Rua MB, Quadra M Lote 10, Condomínio Costa do Sol, Bertioga-SP, Brasil.

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neurological development of infants [17,18,19,20]. CNS infection by HIV can occur earlier in infected infants through vertical transmission. A variety of CNS abnormalities are associated with HIV infection, including cortical atrophy, calcification of the basal nuclei and frontal white matter, ventricular dilatation and low attenuation of white substance [21].

The Brazilian Ministry of Health recommends that CD4 T lymphocyte cell count and plasma HIV RNA (viral load) should be measured at the 2nd, 4th and between 16th and 18th months of age. However, Yoshimoto et al. [22] stated that, on average, seroreversion in Brazil is confirmed only at 16 months, therefore delaying any treatment. Thus, the investigation of motor and cognitive development of infants exposed to HIV and antiretroviral therapy is essential, since inspections will allow the infant to be guided to early-intervention programs, aiming to minimize further sequelae.

Thereby, the aim of this study was to compare the motor and cognitive development of infants exposed and unexposed to HIV in the first 18 months. Taking into consideration the possible effects of exposure to HIV and the administration of antiretroviral drugs in infants born to HIV-positive mothers, the hypothesis raised for this study was that infants aged 4, 8, 12 and 18 months exposed to HIV and antiretroviral therapy would present delayed motor and cognitive development compared to their unexposed peers.

2. Methods

This cross-sectional, prospective and descriptive study included a non-probabilistic convenience sample of 40 infants born to HIV-positive mothers (seropositive) (experimental group-EG) and 40 infants with no history of exposure to HIV (control group-CG), from both genders and aged 4, 8, 12 and 18 months. HIV-positive mothers attended the care program for pregnant women in the referral center of AIDS in the city of Santos/São Paulo -Brazil. All EG's mothers followed the Guidelines for HIV-infected mothers; antiretroviral therapy since the 14th week of pregnancy and during delivery, as well as, their infants for the first six weeks after birth. Additionally, C-section and breastfeeding interruption were also implemented. The sample size calculation estimated 13 infants in each age group and power of 0.8. However, we achieved only 10 infants in each age group and assumed a power of 0.7.

Inclusion criteria for EG consisted of infants whose mothers presented positive serologic diagnosis for HIV and who attended a monitoring program of children born to HIV-positive mothers. Pairing the EG infants in relation to age, gender and family's economic status were inclusion criteria for the control group. For both groups, infants had to be born at full-term (infants born after 37 weeks of gestational age), did not have malformations, genetic syndromes, congenital abnormalities, postural deformities, related diseases or other alterations that could jeopardize neuropsychomotor development or that, for further reasons, have not completed the evaluation protocol. For the EG, the non-compliance of the measures recommended by the Ministry of Health of Brazil was criteria for exclusion. The Research Ethics Committee of the Federal University of São Paulo has approved this study (No. 656061) and the guardians signed the Informed Consent authorizing the participation of their children in the study.

The infants were divided into age groups according to the ages of 4, 8, 12 and 18 months, with each group composed of 10 infants exposed and 10 infants not exposed to HIV. The choice of the ages above is justified due by the vesting period of the main motors mileposts: at 4 months the children reach the midline; at 8 months most children drags himself and/or crawls; at 12 months they reach posture maintenance without support and independent walking acquisition and at 18 months most are able to kick a ball forward in an independent manner.

The economic levels of infants' families were classified by the Brazilian Economic Classification Criteria that divides the economic class into five categories, with A as the highest and E as the lowest.

Motor and cognitive development was evaluated by the use of the Bayley Scale of Infant and Toddler Development (BSITD III). The Bayley Scale is a tool to identify, measure and evaluate children's development aged from 16 days to 42 months, consisting of different scales which examine five key-areas of development: motor (gross and fine), cognition, language (expressive and receptive communication), adaptive behavior and social-emotional [26]. In this study, only the motor and cognitive scales were applied. The evaluation took place only once, with 15 days tolerance before or after the monthly birthday date [23], performed by a single properly trained examiner for its application.

For this study, scaled score, composite score and percentile rank for the motor and cognitive areas of Bayley were calculated. The Scaled Score is a standardized score that compares the infant to their peers of the same age. Composite Score is a compound score and allows comparison between the subscales. The Percentile Rank defines the percentage of the infant's rank in relation to the normative group.

As of composite score, the infants have been classified according to performance categories upon: much higher (equal or higher than 130), upper (120 to 129), medium high (110 to 119), middle (90 to 109), low middle (80–89), borderline (70–79) and extremely low (equal or below 69).

Two statistical analyses were employed in order to verify differences between groups (CG and EG) and age (4, 8, 12 and 18 months old). The first statistical analysis was a 2×4 (group $\times$ age) MANOVA and the dependent variables were scaled score (fine and gross motor together), composite score and percentile rank for motor domain. The second statistical analysis was a 2×4 (group $\times$ age) MANOVA and the dependent variables were scaled score, composite score and percentile rank for cognitive domain. Appropriate follow-up ANOVA and the Tukey post-hoc tests were performed when applicable. The level of significance used was 0.05.

3. Results

The four age groups presented have similar gender and family economic status and minor age variations between the EG and the CG. The 4 months old group consisted of 1 female and 9 male infants, 3 belonging to economy class B, 5 to class C and 1 to class D, aged 128.4 ($\pm$8.4) days for the CG and 127, 3 ($\pm$7.8) days for the EG. The 8 months old group consisted of 6 female and 4 male infants, 1 belonging to class B and 9 to class C, aged 243 ($\pm$8.9) days for the CG and 248, 3 ($\pm$7) days for the EG. The 12 months old group consisted of 5 female and 5 male infants, 1 belonging to class A, 1 to class B and 8 to class C, aged 370 ($\pm$7.8) days for the CG and 370.1 ($\pm$7, 1) days for the EG. At last, the 18 months old group consisted of 6 female and 4 male infants, belonging all to economic class C, aged 551.1 ($\pm$7.3) days for the CG and 547.1 ($\pm$11) days for the EG. The birth weight and length for EG were 2900 g ($\pm$500) and 46.7 cm ($\pm$2.2). For CG, the birth weight and length were 3500 g ($\pm$200) and 49.7 cm ($\pm$1.7). For all infants in EG, virologic diagnostic tests performed at 16 months of age were negative for HIV.

For motor domain, there were significant group effects (Wilks' Lambda = 0.84, $F(3,70) = 4.57$, $p = 0.006$), and age effects (Wilks' Lambda = 0.62, $F(9170) = 4.2$, $p < 0.01$). There was no difference for group and age interaction. For cognitive domain, there were significant group effects (Wilks' Lambda = 0.76, $F(2,71) = 11.11$, $p < 0.01$), age effects (Wilks' Lambda = 5.15, $F(6,142) = 9.31$, $p < 0.01$) and group and age interaction (Wilks' Lambda = 0.81, $F(6142) = 2.59$, $p = 0.02$).

For motor domain, ANOVA showed significant group effects for scaled score ($F(1,72) = 8.25$, $p = 0.005$), composite score ($F(1,72) = 8.6$, $p = 0.004$) and percentile rank ($F(1,72) = 11.42$, $p = 0.001$) and revealed that CG was higher than EG for motor variables. There were significant age effects for scaled score ($F(3,72) = 8.6$, $p < 0.01$), composite score ($F(3,72) = 8.59$, $p < 0.01$) and percentile rank ($F(3,72) = 9.68$, $p < 0.01$). Post-hoc showed that scaled score and composite score at 8 and 12 months were higher than 4 months, and 8 months was higher than 18 months. For percentile rank, 8 and 12 months were higher than 4 months (Table 1).