Growth and Development Status in the First Two Years of Uninfected Children Born From HIV Positive Mothers

Hosein Dalili[1], Yasamin Mohamadzadeh[1], Farnoush Davoudi[2], Zahra Farahani[3], Mehrnaz Rassolinejad[4], Mamak Shariat[3], Amirali Ghahramani[5]

[1] *Department of Neonatology, Breast Feeding Research Center, Family Health Institute, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Department of Community Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*

[3] *Department of Neonatology Maternal, Fetal and Neonatal Research Center, Family Health Institute, Tehran University of Medical Sciences, Tehran, Iran*

[4] *Department of Infectious Diseases, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[5] *Department of Neurology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

Received: 06 Jul. 2017; Accepted: 18 Dec. 2017

Abstract- Recently prevention of HIV transmission from mother to child by antiretroviral regimens has resulted in growing the numbers of HIV exposed but uninfected children (HIV-EU). The aim of present study was evaluation of growth and neurodevelopment status among less than 2-year-old HIV exposed uninfected children. A cohort study was carried out at Vali-e-Asr Hospital (Tehran-Iran). Thirty-nine HIV-EU neonates were recruited (2014 to 2016). Neonates and infants with concern to growth and neurodevelopment status were evaluated at 6, 12, 18, and 24 months by an expert physician. Neurodevelopment assessment was based on WHO Milestones Chart and Age and Stage Questionnaire. Of all children, 22 were male, and 17 were female. Regarding growth indices, although mean birth weight in half of the neonates was lower than normal population; no postnatal descending trend was observed in their growth chart. No significant differences were found between two groups' height and head circumference. Among the neurodevelopmental parameters measured, in 6th months of life, 2 cases had abnormality in the gross motor while at 12 months, 6 cases had delay in language, social problem, and motor disorders. At 18 and 24 months, 7 infants showed developmental problems of which 71.4% of their mothers were younger than others (age<25 years, P=0.009). Prevalence of neurodevelopmental disorders including delay in language, motor, and social domains was common among HIV-EU children. As several environmental factors may involve the etiology of neurodevelopmental disorders, nearly-full postnatal control and prevention seem necessary.

Acta Med Iran 2018;56(3):176-180.

Keywords: HIV seronegativity; Infant; Growth; Development

Introduction

About 70% decreasing trend has been reported globally in the incidence of new pediatric HIV infections from 2000 to 2015. Some factors like the implementation of antenatal screening policies, antiretroviral (ARV) drug and prevention activities against mother to child transmission are involved in such a remarkable achievement (1). The progress in mother-to-child preventive strategies results in growing numbers of HIV exposed but uninfected (HIV-EU) children in these settings (2).

Although the efficacy of implementation of these strategies is well documented, several studies have indicated some adverse outcomes among HIV-exposed uninfected children including lower birth weight, higher infectious morbidity, and mortality during the first two years of life compared to HIV-unexposed children. Other potential contributing factors like deprivation of breastfeeding, early maternal death, abnormalities in the immune system and adverse effects of antiretroviral medications may also be involved (3,4,5,6). Some reports also reported higher risk of neurodevelopmental delay, declines in cognitive and motor functioning

Corresponding Author: M. Shariat
Department of Neonatology Maternal, Fetal and Neonatal Research Center, Family Health Institute, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 66591316, Fax: +98 21 66591315, E-mail address: mshariat@tums.ac.ir

among HIV-exposed uninfected Infants. On the other hand, other studies have demonstrated the safety or mild childhood risks related perinatal ARV regimens, evidence of increased risk for congenital malformations, early childhood cancers or growth abnormalities (7-10).

Although HIV prevalence was higher among women in reproductive age particularly in antenatal period than among non-pregnant women, to our knowledge few studies are available related to early growth and neurodevelopmental patterns of HIV uninfected neonates (11-13). This study aimed to determine growth and neurodevelopmental status of HIV-EU infants during first two years of life to collect some evidence for health problems among HIV-EU children.

Materials and Methods

A cohort study was carried out at a referral academic center; Vali-e-Asr Hospital affiliated with Tehran University of Medical Sciences (Tehran-Iran). Thirty-nine HIV exposed uninfected neonates born from HIV positive mothers were recruited from January 2014 to January 2016. All subjects had been visited and diagnosed by an expert specialist. Except 6 cases, other neonates received 6 weeks' antiretroviral prophylaxis. Inclusion criteria were HIV positive mother, children with at least 2 negative PCR virology tests and gestational age $\geq$36 weeks. All parents' participants gave written consent and accepted in time of attending for receiving routine neonates' visits. Preterm neonates, children with congenital, metabolic disorders or chromosomal anomalies (based on the results of screening test) and any underlying diseases such as AIDS-defining illnesses were excluded from the study. Moreover, lack of data or parents' unwillingness for participation in the study was considered as exclusion criteria. Anthropometric data like neonates' weight, length, head circumference, the z scores of weight for age, length for age, and weight for length were determined at birth, 6, 12, 18 and 24 months by standard anthropometric techniques and equipment based on standardized protocol. Neurodevelopment assessment such as cognition status, fine and gross motor function, speech and language ability, problem-solving and social development based on World Health Organization (WHO) Milestones Chart and Age and Stage Questionnaire (ASQ) were also evaluated by an expert specialist during first 2 years of children's life. ASQ questionnaire has been translated into Persian and validated for Iranian children by Child Bureau of Iran Health Ministry. Conclusions were stated as normal or abnormal according to cut off point for each domain and age. All collected data were recorded in some checklists. Our primary outcome was assessment of the growth and neurodevelopmental trend among 2-year-old HIV exposed but uninfected children.

Data analysis

The software package SPSS version 19 was used to perform the statistical analysis. Data are presented as mean$\pm$standard deviation for continuous variables and frequency/percentage for categorical variables. The t-test and *Chi*-square analysis were applied to analyze the correlations and relationships between variables. The study had a power of 80% and $P<0.05$ was used as statistical significance.

Ethical considerations

Participants were assured about the confidentiality of the personal information. No extra cost was imposed on subjects, and they also had their right to discontinue the study course whenever they wished. Ethics approval for the study was obtained from the institutional review board of Tehran University of Medical Sciences according to Helsinki declaration.

Results

Thirty-nine uninfected newborns born to HIV seropositive mothers (mean age 28±5.2 years old) entered the study and were assessed with regard to growth and neurodevelopmental outcomes. Of all mothers, one of them had smoking, and 82% had no history of any underlying diseases; however, anemia was reported in 2 cases (5.12%). Of all neonates, 22 cases were male, and 17 cases were female (Table 1). No neonates suffered from chromosomal anomalies and metabolic disorders. Type of delivery in all subjects was cesarean section except one case. Two cases (5.1%) had gestational age between 36 and 37 weeks and 10 cases (26%) were low birth weight (<2500 gr).

Regarding growth indices, although mean birth weight in half of the neonates was lower than normal population; no postnatal descending trend was observed in their growth chart. Newborns' length and head circumference were normal at birth and afterward. No significant decrements were observed in these 2 parameters, and neonates did not need any interventions. Anthropometrics measurements are shown in table 2.

In evaluating the neurodevelopmental status of infants in 6th months of life, 2 cases showed abnormality in gross movement. By 12 months after birth, 1 case had

social problem, 2 had abnormal language, 2 cases showed combined abnormality in gross movement and language and a child showed both social problem and abnormality in language. At age 18 and 24 months, 7 subjects (17%) had abnormal neurodevelopmental status in social and language development. A significant inverse correlation was observed between frequency of neurodevelopment abnormality and mother's age. This risk was notable among children whose mothers were younger (age<25 years) (*P*=0.009). Seventy-five percent of mothers who received antiviral medication during post-partum period had children with abnormal developmental status (*P*=0.11). Of 6 neonates without antiviral prophylaxis, 4 cases (66.7%) showed abnormality in neurodevelopmental outcomes (*P*=0.11). Abnormal neurodevelopmental status was observed in 75% of neonates whose mothers did not receive postpartum antiviral medication (*P*=0.11).

Table 1. Demographic data related neonates and their mothers

Variables		N (%)
Gender	**Male**	22 (56.5)
	Female	17 (43.5)
Education	**Lower diploma**	16 (42)
	Diploma and higher	23 (58)
Occupation	**Employed**	2 (5)
	Housekeeper	37 (95)

Table 2. Indices of growth among neonates with different ages

Indices of growth variables	At birth	6 months	12 months	18 months	24 months
Weight (Kg)	2.8816±.42	5.3500±3.75	7.5916±4.67	8.4818±5.53	9.8951±2.36
Head circumference (Cm)	34.50±1.84	33.50±18.78	34.16±30.1	36.80±20.62	38.45±20.1
Length (Cm)	49.37±2.76	65.25±3.71	74.07±3.61	80.50±3.56	87.42±3.42

Discussion

Nowadays growing numbers of HIV exposed but uninfected (HEU) children show efficient strategies against HIV transmission from mother to child. On the other hand, recent studies have shown the high mortality, risk of poor growth, under-nutrition, neurocognitive dysfunction among HEU children that may be related to low birth weight, malnutrition, and micronutrient deficiencies or recurrent infections. Environmental and behavioral factors like exposures to antiviral medication, maternal illness or death resulting lack of infant care and reduced breastfeeding maybe also involved (2,12,14).

We found that mean birth weights in the half of neonates were lower than the normal population, however; no postnatal descending trend was observed in their growth chart. Moreover, newborns' length and head circumference were normal at birth and afterward. These findings were confirmed by other studies; Powis *et al*., showed a significant correlation between in utero exposure to antiretroviral therapy and low birth weight in HIV-uninfected infants born ≥37 weeks (*P*<.001), however during first 6 months of life this complication was rapidly corrected (15). Agostoni *et al*., also demonstrated that among HIV exposed uninfected infants a rapid weight gain was observed immediately after birth and despite negative z scores of mean weight for age and length for age at first months, these scores changed to positive ranges from the 4th and 9th month, respectively (16). As Morden *et al*., have indicated it is supposed that birth weight and feeding modality were influential and crucial determining factors for growth indices during first 6 months (17).

Although it has been indicated that all mean scores related to cognitive and intellectual function among HEU children are higher than same variables in HIV infected counterparts (18), results of the present study have revealed that HEU children may also be prone to some poor neurodevelopmental outcomes. The frequency of these disorders were more notable with increasing age of children; of all subjects at 6 months of age, 2 cases showed abnormality in gross movement while at 12 months; 6 cases and at 18 to 24 months, 7 cases had abnormal developmental status in different domains including social problem, language, and gross movement. It is supposed that some unfavorable social conditions during first two years of life like mother's health status, single parenthood, lower family income, feeding artificial formulas and infections may be

involved in progressive adverse outcomes (16,19). In accordance to our results, Kartik *et al*., demonstrated that differences in developmental indices among both HIV infected and HIV exposed but uninfected children were observed after birth and increased with children's age (20). Kerr *et al*., showed that poor neurodevelopmental outcomes were more frequent in the group of HIV EU children in comparison with HIV-unexposed uninfected children; of 166 HEU children aged 1-12 years, 81% and 3.3% had abnormality in language (P=0.002) and social problem (P=0.002), respectively. Moreover, 93% of them needed more care by parents (P=0.01) (21). Chase *et al*., indicated an age-dependent drop in both mental and psychomotor developmental indices in39.5% and 36.8% of 481 HEU children aged less than 30 months (9).Williams *et al*., also revealed that of 2680 HIV-uninfected children with mean age 2.4 years and positive history antenatal ARV exposure, abnormality in Language (13.2%) and metabolic disorders (11.4%) were the most common adverse outcomes (22). lower scores of 2 neurologic examinations with 6 weeks interval were also observed in 14% and 28% of 25 seroreverted children aged 3-30 months by Knight *et al.,* (23). Van Rie also showed that motor delay was significantly more frequent in 35 HIV uninfected aged 18 to 72 months in comparison with their healthy counterparts, however, delay in language and mental disorder was not notable (24).

We found that frequency of poor neurodevelopmental outcomes was significantly higher among children with younger mothers (age<25 years) (P=0.009). Consistent with our results, Agostoni *et al*., showed more growth and neurodevelopmental abnormalities in HEU infants with younger mothers in compared to subjects in the reference group (27 vs. 32.5-year-old, P<0.001) (16). Malee *et al*., also demonstrated that some maternal characteristics might associate with the prevalence of HIV and neonates adverse outcomes; mothers with several disorders and persistent complications were younger compared to those with no disorders (19).

A limitation of our study was few numbers of the cases and a long time required for data collection. Multi-centered data collection in more than one hospital or retrograde method (historical cohort study) would be beneficial. Moreover, we did not consider some social and postnatal factors like the route of feeding, infants' metabolic or infectious diseases, low family income, maternal comorbid disorders, anxiety and depression, psychiatric disorders and medication and/or therapy that may adversely affect on the care of children and contribute to the persistence of disorders.

Results of the present study showed that neurodevelopmental disorders in different domains during the first two years of life were common among HIV-EU children. Early-full postnatal control and prevention seem necessary.

Acknowledgments

This study was supported by Tehran University of medical sciences (TUMS). We acknowledge the parents for their participation in this study

References

1. Okoko N, Owuor KO, Kulzer JL , Owino GP, Ogolla IA, Wandera R, et al. Factors associated with mother to child transmission of HIV despite overall low transmission rates in HIV-exposed infants in rural Kenya. Int J STD AIDS 2017;28:1215-23.
2. Kuona P, Kandawasvika G, Gumbo F, Nathoo K, Pedersen B. Growth and Development of the HIV Exposed Uninfected Children below 5 Years in Developing Countries: Focus on Nutritional Challenges, Mortality and Neurocognitive Function. Food Nutr Sci 2014;5:2000-7.
3. Briand N, Mandelbrot L, Le Chenadec J, Tubiana R, Teglas JP, Faye A, et al. No relationship between in-utero exposure toHAART and intrauterine growth retardation. AIDS 2009;23:1235-43.
4. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature deliveryin diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS 2007;21:1019-26.
5. Ekouevi DK, Coffie PA, Becquet R, Tonwe-Gold B, Horo A, Thiebaut R, et al. Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Cote d'Ivoire. AIDS 2008;22:1815-20.
6. Kelly MS, Wirth KE, Steenhoff AP, Cunningham CK, Mills TA, Boiditswe SC, et al. Treatment Failures and Excess Mortality Among HIV-Exposed, Uninfected Children With Pneumonia. J Pediatric Infect Dis Soc 2015;4:117-26.
7. Thorne C, Newell ML. Safety of agents used to prevent mother-to-child transmission of HIV: is there any cause for concern? Drug Saf 2007;30:203-13.
8. European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. J Acquir Immune Defic Syndr 2003;32:380-7.

9. Chase C, Ware J, Hittelman J, Blasini I, Blasini I, Smith R, Llorente A, et al. Early cognitive and motor development among infants born to women infected with human immunodeficiency virus. Women and Infants Transmission Study Group. Pediatrics 2000;106:E25.
10. Williams PL, Marino M, Malee K, Brogly S, Hughes MD, Mofenson LM, et al. Neurodevelopment and In Utero Antiretroviral Exposure of HIV-Exposed Uninfected Infants. Pediatrics 2010;125:e250-60.
11. Christofides NJ, Jewkes RK, Dunkle KL, Nduna M, Jama N, Sterk C. Early adolescent pregnancy increases risk of incident HIV infection in the Eastern Cape, South Africa: a longitudinal study. J Int AIDS Soc 2014;17:18585.
12. Filteau S. The HIV-exposed, uninfected African child. Trop Med Int Health 2009;14:276-87.
13. Businge CB, Longo-Mbenza B. Mathews V. Risk factors for incident HIV infection among antenatal mothers in rural Eastern Cape, South Africa. Glob Health Action 2016;9:29060.
14. Sugandhi N, Rodrigues J, Kim M, Ahmed S, Amzel A, Tolle M, et al. HIV Exposed Infants: Rethinking care for a lifelong condition. AIDS 2013;27:S187-95.
15. Powis KM, Smeaton L, Ogwu A, Lockman S, Dryden-Peterson S, van Widenfelt E, et al. Effects of in utero antiretroviral exposure on longitudinal growth of HIV-exposed uninfected infants in Botswana. J Acquir Immune Defic Syndr 2011;56:131-8.
16. Agostoni C, Zuccotti G, Giovannini M, Decarlis S, Giannì ML, Piacentini E, et al. Growth in the first two years of uninfected children born to HIV-1 seropositive mothers. Arch Dis Child 1998;79:175-8.
17. Morden E, Technau K, Giddy G, Maxwell N, Keiser O, Davies M. Growth of HIV-Exposed Uninfected Infants in the First 6 Months of Life in South Africa: The IeDEA-SA Collaboration. PLoS One 2016;11:e0151762.
18. Puthanakit T, Ananworanich J, Vonthanak S, Kosalaraksa P, Hansudewechakul R, van der Lugt J, et al. Cognitive function and neurodevelopmental outcomes in HIV-infected childrenolder than 1 year of age randomized to early versus deferred anti-retroviral therapy: The PREDICTneurodevelopmental study. J Pediatric Infect Dis Soc 2013;32:501-8.
19. Malee KM, Mellins CA, Huo Y, Tassiopoulos K, Smith R, Sirois PA. Prevalence, incidence, and persistence of psychiatric and substance use disorders among mothers living with HIV. J Acquir Immune Defic Syndr 2014;65:526-34.
20. Kartik KV, Mark NL, Elizabeth WT, Guy DB, Harwell J. Growth of infants born to HIV-infected women in South Africaaccording to maternal and infant characteristic. Trop Med Int Health 2010;15:1364-74.
21. Kerr SJ, Puthanakita TK, Ung V, Aurpibule L, Vonthanakf S, Kosalaraksag P, Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV. AIDS Care 2014;26:1327-35.
22. Williams PL, Hazra R, Van Dyke RB, Yildirim C, Crain MJ, Seage GR 3rd, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. AIDS 2016;30:133-44.
23. Knight W, Mellins CA, Levenson RL Jr, Arpadi SM, Kairam R. Effects of Pediatric HIV Infection on Mental and Psychomotor Development. J Pediatr Psychol 2000;25:583-7.
24. Van Rie A, Mupuala A, Dow A. Impact of the HIV/AIDS epidemic on the neurodevelopment of preschool-aged children in Kinshasa, Democratic Republic of Congo. Pediatrics 2008;122:e123-8.