Journal of
AIDS & Clinical Research

Navaneethapandian et al., J AIDS Clin Res 2016, 7:9
DOI: 10.4172/2155-6113.1000604

Research Article Open Access

Growth of Infants Born to HIV-Infected Women in Madurai, South India

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Abstract

Objective: To compare the growth patterns of HIV-infected and HIV-exposed, uninfected infants.

Methods:

Design: Prospective cohort study.

***Setting*:** Clinic of National Institute for Research in Tuberculosis, Madurai located in the Governement Rajaji Hospital (GRH) campus.

Participants: Infants born to HIV-infected women in GRH, Madurai between January 2006 to October 2008. Infants were excluded if they were too ill, or had congenital abnormalities.

Intervention: Baseline socio-demographic details and feeding patterns were recorded. Clinical assessment, anthropometric measurement, complete blood count, CD4 and CD8 counts and DNA PCR testing were performed. Anthropometric assessments and immunology profile were repeated once in 3 months till 24 months of age.

Main outcome: Rate of change of weight and CD4% in HIV exposed and infected infants.

Results: Of 76 infants enrolled, 25 were found to be HIV-infected by DNA PCR and fourteen of them died (11 before their first birthday). Weight gain in HIV-infected infants was 0.144 kg ((95% CI: -0.237, -0.051), *P*=0.003) less per month compared to negative infants, after adjusting for age, gender and feeding practice. Similarly, when compared to HIV negative infants, the decline in CD4 percentage was 3.1% ((95% CI: -4.735, -1.461), *P*<0.001) more in HIV positive infants. Changes in height, CD4 count, head circumference and haemoglobin were not associated with HIV status.

Conclusion: Growth faltering occurs early in life in HIV-infected infants and its identification is important for developing appropriate treatment and nutritional management strategies. Mortality is high in the absence of early antiretroviral treatment.

Keywords: HIV; Infants; HIV-exposed; CD4%; Growth

Introduction

Growth failure is a well-recognized complication of HIV infection in children which can present as stunting, weight loss, failure to thrive and severe acute malnutrition. Poor growth has been reported in HIV-infected children and is associated with decreased survival [1-3]. Growth faltering in vertically HIV-infected children may be an early marker of infection or progression of disease [1,2]. Paediatric HIV infection is associated with growth retardation and is likely a significant contributor to infant malnutrition and morbidity [4]. HIV-infected infants with poor growth have as much as a fivefold increase in the risk of early death [5].

There is a significant effect of HIV status of the mother on the growth of the fetus, which means that even if the neonates have not been infected, their growth and nutrition in intrauterine period is significantly affected by the maternal HIV status [6]. As programmes to prevent mother-to-child HIV transmission, including short course antiretroviral drugs around delivery, become more widespread in the country, more and more infants of HIV-infected mothers will remain uninfected resulting in growing numbers of HIV exposed but uninfected (HEU) children in these settings.

The negative effects of HIV infection on postnatal growth have been consistently observed and well documented in studies performed in both industrialized and developing countries. Disturbances in growth are detectable well before the onset of opportunistic infections or other manifestations. Height and weight impairment increases with age. Moye et al. [7] observed that HIV-infected children were 0.7 kg lighter and 2.2 cm shorter than children 18 months of age exposed to but not infected with HIV. European cohorts have described normal growth in HIV-exposed children compared with children born to HIV-uninfected mothers [3,8] However, small studies from Durban, South Africa [2] and Zambia [9] have suggested lower weights in HIV-uninfected infants born to HIV-infected mothers compared with population standards or infants of HIV-uninfected mothers.

In the U.S. and Europe, the effects of HIV on pediatric growth, morbidity, and mortality have been studied extensively among both HIV infected and exposed uninfected children through prospective perinatal cohort studies. However, in resource-limited settings, with the largest pediatric HIV burden, there is a paucity of literature addressing the growth and survival of infants born to HIV infected women. To date, there have

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Received June 28, 2016; **Accepted** July 18, 2016; **Published** July 26, 2016

Citation: Navaneethapandian PGD, Rajendran M, Ramesh K, Elangovan T, Subramanyan S, et al. (2016) Growth of Infants Born to HIV-Infected Women in Madurai, South India. J AIDS Clin Res 7: 604. doi:10.4172/2155-6113.1000604

been very few studies in India comparing growth patterns of HIV-infected infants with those of HIV-exposed but uninfected infants [10].

Owing to the close association of growth with immune function and clinical progression, an understanding of growth patterns may be an important tool to ensure the provision of appropriate care to HIV-infected and exposed children. Hence, we compared the growth patterns of HIV-infected and HIV-exposed but uninfected infants born to HIV-infected mothers in Madurai, from birth to 24 months of age. We also assessed the role of various factors, including the type of infant feeding, on growth.

Methodology

Population and study design

This was a prospective study conducted at National Institute for Research in Tuberculosis (NIRT) clinic in Madurai in South India from January 2006 to October 2008. Infants born to HIV-infected women in Government Rajaji Hospital Madurai were referred to NIRT for HIV testing and enrolment in the cohort. Infants were excluded if they were too ill, required ventilation or had congenital abnormalities. The study was approved by Institutional Ethics Committee and written informed consent was obtained from the parent or guardian after pre-test counseling by trained counselors.

Baseline socio-demographic details, birth history, feeding patterns were recorded. Mothers were counselled on infant feeding practices. Women who decided to breastfeed were encouraged to breastfeed exclusively for 6 months. Clinical assessment and anthropometric measurement was done. Anthropometric measurements were performed by an experienced study nurse trained in standard anthropometric techniques. Weight was measured to the nearest 100 g using a standard weighing scale, and length was measured to the nearest 0.1 cm in a recumbent position using an infantometer.

Sample collection and laboratory analysis

Complete blood count was measured using COULTER® Ac•T™ 5diff Hematology Analyzer *(Beckman CoulterInc, Miami, USA)*. CD4 and CD8 counts were determined by flow cytometry (Epics Altra flow cytometer, Beckman Coulter, USA) using a standard 4-colour staining protocol (CD45/14/4/8). DNA PCR testing was performed using Roche Amplicor HIV-1 DNA v1.5 kit, following manufacturer's instructions. Anthropometric assessments and immunology profile were repeated once in 3 months till 24 months of age. Children who tested positive were referred to government antiretroviral treatment (ART) centers for further assessment and initiation of treatment.

Statistical analysis

Analysis was performed using SPSS (version 16) software. Data were expressed as percentages, mean values (with standard deviations), or median values (with Inter Quartile Ranges). Differences between groups were analyzed with the Mann Whitney U test for medians, Independent sample t-test for means and Chi-square test and Fisher's exact test for proportions. Multiple regression models with growth parameters as the dependent variable were used for multivariate adjustment of predictor variables. Results were defined as statistically significant when the *P* value (2-sided) was less than 0.05.

Results

Of 76 cases followed up, 25 infants tested DNA PCR positive (HIV-infected). Table 1 shows the demographic details of the 76 infants. The median age at registration was 3.5 months (1.5-7.6 months) in DNA PCR positive infants and 1.9 months (0.9- 3.0 months) in DNA PCR negative (HIV exposed but uninfected) infants. The median birth weight was similar in both the groups. Most of them were delivered vaginally and were full term. Of 25 DNA PCR positive infants fourteen of them died (11 before their first birthday). The effect of prophylactic antiretrovirals given to both mother and infants was statistically significant in preventing mortality.

	PCR Positive	PCR Negative	p-value
Age (in months)			
N	25	51	0.019‡
Median, IQR	3.5 (1.5, 7.6)	1.9 (0.9, 3.0)	
Gender			
N	25	51	
Male	13 (52.0)	32 (62.7)	0.370*
Female	12 (48.0)	19 (37.3)	
Birth Weight (in kg)			
N	20	50	0.432‡
Median, IQR	2.6 (2.1, 2.9)	2.7 (2.4, 3.0)	
Type of Delivery			
N	23	49	
Vaginal	22 (95.7)	42 (85.7)	0.385*
Elective Caesarian	1 (4.3)	4 (8.2)	
Non Elective Caesarian	-	3 (6.1)	
Neonatal Status			
N	23	49	
Full Term	21 (91.3)	48 (98.0)	0.238**
Premature	2 (8.7)	1 (2.0)	
Type of Feeding			
N	25	50	
Breast Feed	12 (48.0)	16 (32.0)	0.087*
Bottle Feed	3 (12.0)	18 (36.0)	
Mixed Feed	10 (40.0)	16 (32.0)	
Duration of Breast Feed (in months)			
N	20	28	0.125‡
Median, IQR	4.0 (3.0, 6.0)	6.0 (5.0, 6.0)	
ARV to Mother			
N	23	48	
Yes	11 (47.8)	38 (79.2)	0.008*
No	12 (52.2)	10 (20.8)	
ARV to Newborn			
N	23	48	
Yes	12 (52.2)	39 (81.3)	0.011*
No	11 (47.8)	9 (18.8)	
Death			
Yes	14 (56.0)	2 (3.9)	
No	11 (44.0)	49 (96.1)	<0.001*

*- Pearson Chi-Square Test; ** - Fisher's Exact Test; ‡ - Mann Whitney U Test
IQR: Interquartile Range; ARV: Antiretrovirals
P<0.05 is considered to be statistically significant.

Table 1: Demographic details (For 76 Cases) at baseline.

Fifty eight cases were included for analysis as they had data at 3 time points. Table 2 shows the demographic details of the 58 cases. Table 3 shows the rate of change in growth parameters (per month) in HIV positive and HIV negative infants. The rate of change was significantly different between the two groups with reference to both weight and CD4 percentage and also marginally with the head circumference.

	PCR Positive	PCR Negative	p-value
Age (in months)			
N	12	46	0.125‡
Median, IQR	2.9 (1.6, 7.8)	2.0 (0.9, 3.5)	
Gender			
N	12	46	
Male	6 (50.0)	29 (63.0)	0.513**
Female	6 (50.0)	17 (37.0)	
Birth Weight (in kg)			
N	11	45	
Median, IQR	2.5 (2.0, 2.9)	2.7 (2.4, 3.0)	0.318‡
Type of Delivery			
N	11	44	
Vaginal	11 (100.0)	37 (84.1)	0.367*
Elective Caesarian	-	4 (9.1)	
Non Elective Caesarian	-	3 (6.8)	
Neonatal Status			
N	11	44	
Full Term	9 (81.8)	43 (97.7)	0.099**
Premature	2 (18.2)	1 (2.3)	
Type of Feeding			
N	12	45	
Breast Feed	6 (50.0)	15 (33.3)	0.450*
Bottle Feed	2 (16.7)	15 (33.3)	
Mixed Feed	4 (33.3)	15 (33.3)	
CD4 Percentage			
N	12	46	
Median, IQR	42.0 (23.0, 55.2)	44.0 (39.0, 53.2)	0.558‡
CD4 Count			
N	12	46	
Median, IQR	3452.5 (1624.7, 4125.5)	3826.0 (2591.5, 5145.0)	0.155‡

*- Pearson Chi-Square Test; ** - Fisher's Exact Test; ‡ - Mann Whitney U Test
IQR: Interquartile Range; ARV: Antiretrovirals
P<0.05 is considered to be statistically significant.

Table 2: Baseline demographic details (For 58 cases).

	PCR Positive		PCR Negative		p-value
	N	Mean (SD)	N	Mean (SD)	
Weight (in Kg)	12	0.23 (0.18)	46	0.43 (0.16)	<0.001
Height (in cm)	12	1.18 (0.84)	46	1.81 (1.32)	0.126
CD4 Percentage	9	-3.05 (3.27)	42	-0.20 (1.68)	<0.001
CD4 Count	9	-202.81 (347.07)	41	-63.70 (294.62)	0.220
Head Circumference	10	0.46 (0.49)	46	0.86 (0.58)	0.049
Haemoglobin	9	-0.12 (0.31)	42	-0.01 (0.24)	0.260

Independent sample t-test
P<0.05 is considered to be statistically significant

Table 3: Rate of change in various parameters (per month) in PCR positive and PCR negative babies.

It was found that the weight gain in PCR positive infants was 0.144 kg (95% CI: -0.237, -0.051, *P*=0.003) less per month than the corresponding PCR negative infants after adjusting for age, gender and feeding practice. Similarly, when compared to PCR negative infants, the decrease in CD4 percentage was 3.1% (95% CI 4.735, 1.461, *P*<0.001) faster in PCR positive infants. The rate of change of other parameters like height, CD4 count, head circumference and hemoglobin were not associated with HIV Status. The Kaplan-Meier survival curve shows the significant difference in survival between the two groups (Figure 1).

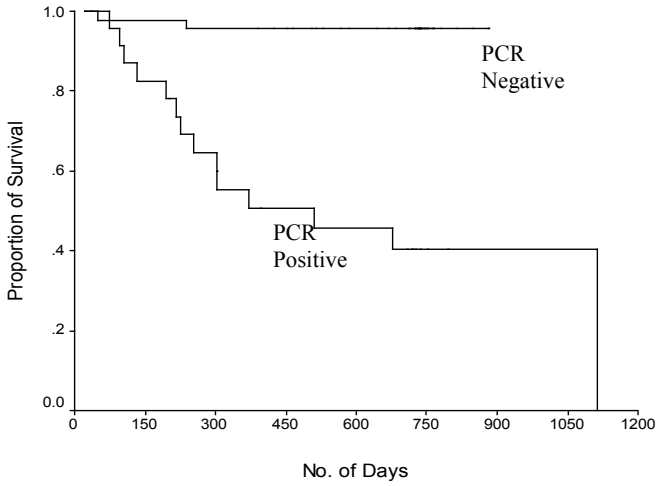

Figure 1: Kaplan-Meier survival curve showing cumulative mortality for HIV-infected and HIV negative babies.

Discussion

The major finding from our study is that growth of HIV-infected babies is affected right from the beginning, with lower monthly weight gain compared to HIV exposed but uninfected infants. This is similar to findings from other studies [11-15]. We also found an effect of HIV infection on head circumference, suggesting that brain growth could also be affected early in life. However, birth weight was not significantly different between the two groups and while increase in length was lower in HIV-infected infants, it was not statistically significantly different.

It is known that HIV exposure *in utero* without subsequent infection may also affect growth in infancy and early childhood [16]. However, because we did not have a control group of HIV unexposed children, we cannot determine whether growth in these exposed children was different from the normal, expected rate. Growth faltering in HIV-infected children could have come from recurrent infections; food insecurity in HIV affected households as well as barriers to accessing health care. Many studies have described a variety of disturbed growth patterns, with disturbances in both height and weight among HIV-infected children, often apparent as early as 3 months of age and increasing with time. Isanaka et al. showed that when compared to HIV exposed but uninfected children, HIV-infected children were lighter by 0.61 to 0.65 kg at 6 mo, 0.75 kg at 12 mo, 0.63 kg at 24 mo and 0.71 to 0.90 kg at 48 mo after birth [17]. In an adjusted regression analysis, maternal mid-upper arm circumference, maternal CD4 cell count, infant birth weight and maternal HIV status had the biggest impact on infant growth [18]. In our previous study although we found an overall beneficial effect of HAART on growth and immunologic parameters, a substantial proportion of HIV-infected children were undernourished even at the end of one year and stunting persisted [19]. The early change in growth patterns was found to be not affected by feeding patterns. However, the small numbers in the various groups could have masked the adverse effects of mixed feeding in the present study.

This study also showed that when compared to HIV negative infants, the monthly rate of decline in CD4 percentage was 3.1 ((95% CI: -4.735, -1.461), *P*<0.001) percent more in HIV-infected infants. In healthy infants, absolute lymphocyte counts and CD4 counts are high at birth and decline rapidly over the first few months. However, in HIV-infected infants, this fall is more rapid [20]. Among HIV-infected children, the CD4 T-cell depletion rate is predictive of mortality and

poor clinical outcome [21]. Even among HIV-uninfected children, CD4 T-cell counts are of relevance as low counts may increase the severity of common childhood infections [22]. Roland et al. showed that CD4 T-cell counts were significantly lower among HIV-infected children compared to HIV-uninfected children at all-time points ($p \leq 0.02$) of 25 DNA PCR positive infants fourteen of them died (11 before their first birthday). Two of the 5 HIV positive infants started on ART died due to late start of ART. The other infants did not receive ART as pediatric formulations were not available at that time in the government ART centre. There was a very high rate of mortality in HIV-infected infants, which indicates that a substantial proportion of HIV-1 positive children infected perinatally in India are rapid progressors and will die in infancy unless diagnosed and treated early [23]. There were also two deaths in the uninfected group, exact reasons for which are not known but could be related to the mother's ill health. The findings in the study shows that the prophylactic antiretrovirals given peripartum and to infants significantly reduces the mother to child HIV transmission. Antiretroviral drugs reduce viral replication and can reduce mother-to-child transmission of HIV either by lowering plasma viral load in pregnant women or through post-exposure prophylaxis in their newborns. Previous studies had shown that toddlers of mothers who received single dose nevirapine had significantly lower risk of HIV-1 infection and higher probability of HIV-1-free survival [24].

Important strengths of the study include its prospective nature and the longitudinal physical growth measurements obtained by trained staff using calibrated measuring equipment. While follow-up was generally high, 21% of children were lost to follow up. Limitations include the relatively small number of children with follow-up in each group, the lack of details on the mother's health and other potential causes of poor outcomes and the observational nature of the study, with its attendant biases. Further, lack of access to antiretroviral treatment in infancy had a major impact on outcomes – subsequently, with pediatric ART program expansion, the outcomes of HIV-infected infants have improved substantially.

In conclusion, prevention, early detection and treatment of growth faltering in HIV-exposed and infected children is critical in order to achieve good outcomes, both for physical and brain growth. Further, antiretroviral treatment given to antenatal women and babies is essential to prevent HIV infection and early initiation of antiretroviral treatment in infected babies is essential to prevent deaths. Given the important relationship between HIV, nutrition, growth and survival of children living with HIV, it is recommended that nutritional assessment and support should be an integral part of the care plan of an HIV-infected infant or child.

What is Already Known on this Topic

Growth failure is a well-recognized complication of HIV infection in children which can present as stunting, weight loss, failure to thrive and severe acute malnutrition.

What this Study Adds

The growth of HIV-infected babies is affected right from birth, with lower monthly weight gain compared to HIV exposed but uninfected infants.

Acknowledgement

The authors thank the staff of the Department of Clinical Research of the National Institute for Research in Tuberculosis for their cooperation and support. We are grateful to the staff of the Obstetrics and Gynecology and Pediatric departments and ART centre in Government Rajaji hospital, Madurai, who collaborated on this study and all the infants who participated and their parents.

Funding

Indian Council of Medical Research.

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