



Growth and Neurodevelopmental Status in HIV Infected Children

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Abstract

Background: HIV infected children are at risk of growth and developmental disorders.

Objectives: We assessed growth and neurodevelopment outcomes in 0 - 5 years old HIV infected children.

Methods: A cohort study was carried out in a referral HIV clinic. Twenty eight HIV infected children and 47 healthy children aged 0 - 5 years were compared with regard to growth and neurodevelopmental status within two consecutive 6 months. During this period, some parent based interventions were achieved and antiretroviral treatment was optimized in case of necessity.

Results: Among the growth parameters measured, the only significant difference between case and control groups at the beginning of the study was the head circumference percentile ($P = 0.07$) and for the developmental variables, abnormality in speech and language ability were more common in case group than in control group ($P = 0.04$). The difference between controlled and uncontrolled HIV patients at enrollment was marginally significant in gross motor function ($P = 0.059$) and a significant difference was seen in social ability ($P = 0.01$). The score changes among parameters before and after intervention between case and control groups were significant in language ability ($P = 0.01$), fine motor ($P = 0.001$) and social ability ($P = 0.02$). The score changes among parameters before and after intervention were also significant in head circumference percentile ($P = 0.02$) between the two groups, and for weight percentile ($P = 0.04$) and length percentile ($P = 0.04$) between well and poorly HIV controlled patients.

Conclusions: The growth and developmental disorders could be preventable with antiretroviral treatment and some simple parent based interventions.

Keywords: HIV Infection, Child Development, Growth, Children

1. Background

HIV (human immunodeficiency virus) infected children are at risk of growth failure and developmental disorders (1). Many interventions were implemented to prevent transmission of HIV infection from mother to child; nevertheless the prevalence of pediatric HIV is still high (2). Based on the UNAIDS report, about 420,000 new HIV infections occurred in children below 15 years in 2007 (1) and in 2013 this statistics reached 240,000 (3). About 90% of these children live in the developing countries (4).

Growth failure is common in HIV-infected children; they are shorter and thinner than healthy counterparts (5). Severe neurodevelopmental, cognitive and motor dysfunctions have also been shown since the first reports of pediatric AIDS in the 1980s (1, 4, 6).

HIV associated neurologic disease was demonstrated in 30% - 60% of infected children and adolescents (7). Neu-

rological sequels and neurocognitive disorders in infected children are due to static or progressive encephalopathy that influences different domains such as speech and language, memory, learning, information processing and motor functioning. Time of infection, viral load, CD4 count, antiretroviral medication, co-morbid diseases and environmental conditions are effective factors (8-10).

The prevalence of delay in cognition, motor function, speech and language was reported in 8% - 60% of HIV-infected children by Van Rie (4). Ruel et al. also showed significant motor and cognitive disorders in 93 HIV-infected children with CD4 cell counts of 350 cells/ μ L and percentages of more than 15% (6). Boyede et al. also demonstrated that RPM cognitive scores (nonverbal test of general intelligence) were lower for HIV-positive compared with HIV-negative children (11). Baillieu et al. indicated significant delay in both cognitive and motor development in 40 HIV-

positive children aged from 18 to 30 months (12).

On the other hand, medical treatment including combination of antiretroviral therapy (ART) and supportive medications prolong survival and also promote growth and developmental status (10). Foster also showed among 62 HIV-1 infected children less than 3 years old, growth parameters were significantly improved with antiretroviral therapy (13).

In spite of high prevalence of HIV associated growth and neurodevelopmental disorders, less attention has been focused on these aspects especially in developing countries. To our knowledge, there have been no such studies in Iran. As identifying the long term developmental outcomes is crucial in order to design programs to relieve HIV related morbidities, we investigated the growth and neurodevelopmental status in HIV infected children in a referral HIV clinic in Tehran.

2. Methods

2.1. Study Design

To achieve the main objectives of the current research, we carried out a cohort study in 6 months.

2.2. Study Participants and Setting

We recruited 28 infants infected with HIV as the case and 47 healthy children as the control group from January 2014 to June 2015. Patients had been diagnosed and registered at a referral HIV clinic located in an academic hospital in the capital city of Tehran. Eligible participants had to be less than 5 years old with no history of neural or psychomotor anomalies and have their parents' consent to participate in the study.

With the sample size of 75, the study had a power of 80%. The level of significance was considered $P < 0.05$. Forty seven healthy infants who attended a health clinic in Tehran for regular health check-up were taken as the control group. Regarding inclusion and exclusion criteria and after individual age matching, the ratio of control to case group was sequentially selected as 2.5:1. Members of both groups matched for age, sex and social status. Children with congenital or chromosomal anomalies, metabolic or any underlying diseases such as AIDS defining illnesses and history of opportunistic infection were excluded from the study.

2.3. Measurements

1. Anthropometric data: weight, length, head circumference and growth percentiles were determined based on standardized protocol (14) and recorded in check lists.

2. Response to antiretroviral therapy: viral load and CD4 in first visit and after 6 months were measured in HIV infected children who received antiretroviral therapy.

3. Neurodevelopment assessment: cognition status, fine and gross motor function, speech and language ability, problem solving and social development based on WHO milestones chart and age and stage questionnaire (ASQ) were evaluated by an expert specialist in two visits with a 6 month interval. According to our experience, this interval not only was enough for presentation of abnormalities, precluded also loss of participants. 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, and the scores were used to calculate the variable changes.

2.4. Intervention

Case group parents were trained for simple instructions like performing gentle skin massage, hydrotherapy (water game), and use of mental targeted games during 6 months investigator-led study. A study nurse called the parents and invited them to attend the HIV clinic for reevaluation after 6 months with regard to growth and neurodevelopmental status.

Healthy children were also evaluated clinically and examined for physical and psychomotor development both at the time of enrollment and 6 months later.

Poorly controlled HIV infected patients with viral load more than 1000 copies/mL were evaluated for HIV drug compliance and resistance. The treatment changed in case of necessity.

2.5. Primary/Secondary Outcomes

Our primary objective was to assess the growth and neurodevelopment in HIV infected infants in comparison with control group, and also the difference between well and poorly controlled HIV patients at enrollment.

The secondary objective was to evaluate changes of the mentioned parameters before and after intervention.

2.6. Ethical Considerations

The study protocol was approved by the Ethics Board of the Tehran University of Medical Sciences (registration number: 92-01-91-22083). Written consent forms that were developed according to the Helsinki declaration consent were received from children's parents prior to enrollment. They were assured about confidentiality of the personal information, and their right to discontinue the study course whenever they wished.

2.7. Data Analysis

We used the Shapiro-Wilk test to see whether data were normally distributed. Descriptive baseline characteristic comparisons were tabulated as median (inter-quartile range) or as percentages. Comparisons between the two groups for categorical data were statistically analyzed using Kruskal-Wallis test, and for continuous data, the Mann-Whitney U test was applied. Acquired data were entered and analyzed using statistical package for social sciences (SPSS version 16.0). A P value of less than 0.05 was considered significant and P values between 0.05 and 0.1 were considered as marginally significant.

3. Results

Of 76 subjects, one case was excluded because of autism. Total number of participants was 75, of which 43 (57%) were male and 32 (43%) female. All of the patients but three were taking antiretroviral (ARV) drugs at the time of testing and five patients did not follow the study. Mean age of children was 32.8 (standard deviation = 16.2) months.

The infants with undetectable viral load or those who did not need to take ARV (48%) were considered as good HIV controlled patients.

Among the growth parameters measured, the only significant difference at the beginning of the study was the head circumference percentile with median of 50 (25 - 50) in case group and median of 75 (25 - 90) cm in control group ($P = 0.007$); and for the developmental variables, abnormality in speech and language ability were more common in case group than control ($P = 0.04$) (Tables 1 and 2).

At enrollment, 43.8% of poorly controlled patients and 9.1% of well controlled patients had social disabilities ($P = 0.01$) and 31.3% of poorly controlled patients and 9.1% of well controlled patients had gross motor dysfunction ($P = 0.059$) (Table 3).

The score changes among parameters before and after intervention in terms of neurodevelopment between case and control group were significant in language ability ($P = 0.01$), fine motor ($P = 0.001$) and social ability ($P = 0.02$) and any significant difference was seen between well and poorly HIV controlled patients. The score changes among parameters before and after intervention in terms of growth parameters were significant in head circumference percentile ($P = 0.02$) between case and control group and were significant for weight percentile ($P = 0.04$) and length percentile ($P = 0.04$) between well and poorly controlled patients (Table 4).

4. Discussion

The number of HIV infected children has increased in the Asian countries including Iran (15). Despite several Iranian epidemiological, serological and pathophysiological studies (16, 17), few reports assessed HIV growth and neurocognitive outcomes in children. This study is a survey of 6 months of growth and neurodevelopmental progress in HIV infected children.

Based on the results, 17.9% - 35.7% of HIV infected children had neurodevelopmental delay in different domains and after 6 months of medical treatment and physician's consultation this rate declined to 13% - 17.45% in several domains. Our findings were the same as the other reports. In a systematic review, 80% of studies showed significant correlation between HIV infection and childhood speech, mental and psychomotor disorders (18). The prevalence of delay in cognition, motor function, speech and language was reported in 8% - 60% of HIV-infected children (4). Koekkoek et al. also found that HIV infected children compared to healthy subjects had lower scores in neuropsychological tests and their attention and memory were improved by the start of antiretroviral therapy and increased CD4T-cell count (19). Prato et al. demonstrated that earlier HIV treatment in first year of life had dramatic effects on preventing HIV encephalopathy (20).

We found a significant increase in the prevalence of speech and language abnormality in case group at the beginning of study, also the gross motor function and social ability were impaired in badly controlled HIV patients. These findings were confirmed by other studies; Van Rie et al. reported that the delay in motor development, especially gross motor skills were seen more frequently in HIV infected infants due to abnormal muscle tone, less muscle bulk or less muscle strength (4). In another study, they also indicated that the neurodevelopment delay in HIV infected children was significantly more common than in control group ($P < 0.05$); among 35 HIV infected children, 60% had cognitive disorder, 29% delayed psychomotor, 85% delayed speech and language, and 77% delayed comprehension (21). On the other hand Brahmbhatt et al. showed that the children infected by HIV had no significant language impairment compared with HIV-negative controls except for receptive language scores. Receptive language is dependent on working memory and it may be affected by maternal illness or lack of environment stimulus for language learning (22).

On the other hand, our results showed that after 6 months of effective antiretroviral therapy and parent based interventions in case group, language and social ability score changes were significant compared to control group. It means that these two parameters were improved

Table 1. Comparison of Growth Variables Between Groups

Variables	Groups	Median (IQR)		Case vs Control	P Value Well vs Poorly
Weight percentile	Case	Good control	50 (10 - 50)	0.15	0.83
		Bad control	37 (27 - 57)		
	Total	50 (25 - 50)			
	Control	50 (25 - 90)			
Length percentile	Case	Good control	50 (37 - 50)	0.18	0.43
		Bad control	50 (25 - 90)		
	Total	50 (25 - 75)			
	Control	75 (50 - 90)			
Head Circumference Percentile	Case	Good control	50 (25 - 50)	0.007	0.81
		Bad control	50 (25 - 50)		
	Total	50 (25 - 50)			
	Control	75 (25 - 90)			

Table 2. Comparison of Developmental Variables Between Case and Control Groups^a

Variables	Groups	Case	Control	P Value
Speech language	And	Normal	18 (64.3)	0.04
		Abnormal	10 (35.7)	
Gross function	Motor	Normal	22 (78.6)	0.62
		Abnormal	6 (21.4)	
Fine function	Motor	Normal	21 (75)	0.45
		Abnormal	5 (17.9)	
Problem solving		Normal	42 (89.4)	0.21
		Abnormal	6 (21.4)	
Social abilities		Normal	20 (71.4)	0.33
		Abnormal	8 (28.6)	

^aValues are expressed as No. (%).

after intervention. Laughton et al. showed that after initiation of ART treatment for HIV infected children, neurological scores improved and no statistically differences were observed in children with and without HIV (23). However Puthanakit et al. demonstrated that despite ART treatment, neurodevelopmental scores (intelligence quotient, memory, behavioral and psychomotor) did not enhance and were worse than HIV-uninfected children. They suggested that some factors like infant's age, time of initiation of ART treatment and CD4 levels may be effective factors (24).

Moreover, we supposed that parents' engagement in the treatment process and supportive care had been

strongly beneficial. It seems infants' illness deprives them from social communications and some environmental stimulus exposures. Massage, mental training, exercise, water game may enhance psychomotor, communicative and social abilities. Other studies also confirmed the positive role of such programs. Oswalt and Biasini revealed that daily massage as a quick, easy, and inexpensive intervention influences HIV infected infants growth (25). Perez et al. also found a statistical relationship between a 15 minute daily massage therapy and improvement of hearing, speech and general quotient scores (Griffiths scales) in HIV-infected infants ($P < 0.05$) (26).

Our results showed that head circumference per-

Table 3. Comparison of Variables Between Good and Bad Controlled HIV Patients^a

Variables		Groups	Good Control	Bad Control	P Value
Speech	And	Normal	8 (72.7)	9 (56.3)	0.16
Language		Abnormal	3 (27.3)	7 (43.8)	
Gross function	Motor	Normal	10 (90.9)	11 (68.8)	0.059
		Abnormal	1 (9.1)	5 (31.3)	
Fine Function	Motor	Normal	10 (90.9)	10 (62.5)	0.79
		Abnormal	0	5 (31.3)	
		Average	1 (9.1)	1 (6.3)	
		Normal	10 (90.9)	9 (56.3)	0.12
Problem solving		Abnormal	0	6 (37.5)	
		Average	1 (9.1)	1 (6.3)	
Social abilities		Normal	10 (90.9)	9 (56.3)	0.01
		Abnormal	1 (9.1)	7 (43.8)	

^aValues are expresses as No. (%).**Table 4.** Developmental Variable Changes After-Before Intervention Between Groups

Variables	Groups		Median	P Value	
			(IQR)	Case vs. Control	Good vs. Bad
Speech and language	Case	Good control	2.5 (-3.7 - 26.2)	0.01	0.94
		Bad control	0 (0 - 10)		
	Total	0 (0 - 15)			
	Control	0 (0 - 0)			
Gross motor function	Case	Good control	0 (-3.7 - 0)	0.82	0.49
		Bad control	0 (-5 - 5)		
	Total	0 (-10 - 0)			
	Control	0 (0 - 0)			
Fine motor function	Case	Good control	0 (-8.7 - 0)	0.00	0.60
		Bad control	0 (-1 - 0)		
	Total	0 (-1 - 0)			
	Control	0 (0 - 0)			
Problem solving	Case	Good control	-5 (-1 - 10)	0.95	0.23
		Bad control	0 (0 - 15)		
	Total	0 (-1 - 10)			
	Control	0 (0 - 0)			
Social abilities	Case	Good control	5 (-7.5 - 18)	0.02	0.76
		Bad control	0 (0 - 5)		
	Total	0 (0 - 15)			
	Control	0 (0 - 0)			

centile in HIV infected children was significantly lower than in healthy children at enrolment. This difference may

be due to HIV related encephalopathy and atrophy in brain cortex, medulla, basal ganglia and white matter (4). Although after 6 months of treatment the difference changes occurred more in control group, Raskino et al. indicated a significant linear progression in head circumference measurements during the initial 24 weeks combination therapy in HIV infected children ($P = 0.001$) (27).

Also the significant changes after intervention were seen between well and poorly controlled HIV infants with amelioration of weight and length percentile in poorly controlled infants. It is supposed that life style may influence infants' growth more than HIV (28). Newell et al. showed that weight and height differences in case and control groups were remarkable after age 10; by the age 10, HIV infected children were 7 kg lighter and 7.5 cm shorter than uninfected children (29).

In summary the prevalence of HIV associated growth and neurodevelopmental disorders is high and less attention has been focused on them especially in developing countries. We investigated the growth and neurodevelopmental status in HIV infected children in a referral HIV clinic and identified the long term developmental outcomes that were crucial for designing programs to relieve HIV related morbidities.

4.1. Conclusions

Present results showed that some growth and developmental disorders in HIV infected children were more frequent than in uninfected children. These complications could be preventable with antiretroviral treatment and some simple parent based interventions. However, we believe that this topic deserves more investigation with larger sample size.

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