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COMMUNICATIONS C15
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Malnutrition decreases the odds of attaining motor milestones in HIV exposed children: results from a paediatric DREAM cohort

La malnutrizione infantile ritarda lo sviluppo motorio nei bambini esposti a HIV: risultati dalla coorte pediatrica del programma DREAM

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Abstract

Objective. HIV and malnutrition are the two major causes of infant mortality in Sub-Saharan Africa. The study describes the impact of malnutrition on motor milestone development in HIV-exposed children.

Design. Randomized community intervention trial (SMAC, Safe Milk for African Children).

Setting and participants. Growth, motor development, and malnutrition were assessed in a sample of 76 HIV-exposed children, aged 0-24 months, at the Blantyre Dream Centre in Malawi.

Main outcome measures. We assessed growth and selected motor milestone achievement in agreement with WHO/UNICEF criteria. Odds ratios and 95% confidence intervals were calculated according to motor milestones and malnutrition indices. Multivariable logistic regression was performed with 18 months data.

Results. High rates of malnutrition were observed. Underweight increased by 6.7/9.2 and 3.2/5.5 the odds of not standing alone and not walking alone at 15 and 18 months. Stunting increased by 9.7 the odds of not standing alone at 11 months and by 6.1 the odds of not walking alone at 18 months. Wasting increased by 5.5/10.3 the odds for not walking with assistance at 12 and 18 months. Low weight for age was associated with delay in walking at 18 months (HR=2.9).

Conclusion. Malnutrition in HIV-exposed children decreases the likelihood of adequate development.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 108-112)

Key words: malnutrition, motor milestones, HIV-exposed, DREAM program

Riassunto

Obiettivi. HIV e malnutrizione sono le principali cause di mortalità infantile nell'Africa sub-sahariana. Lo studio descrive l'impatto della malnutrizione sul raggiungimento delle *motor milestones* in bambini esposti a HIV.

Disegno. Trial clinico randomizzato (SMAC, Safe Milk for African Children).

Setting e partecipanti. Crescita, sviluppo motorio e malnutrizione sono stati valutati in un campione di 76 bambini HIV esposti (0-24 mesi), del Centro DREAM di Blantyre in Malawi.

Principali misure di outcome. La crescita e lo sviluppo motorio sono stati valutati in accordo con i criteri WHO/UNICEF. Sono state calcolate mensilmente le odds ratio (IC95%) per malnutrizione e "motor milestones". Una regressione logistica multivariata è stata realizzata a 18 mesi.

Risultati. Sono stati osservati alti tassi di malnutrizione. Il sottopeso aumenta il rischio di non stare in piedi da solo e di non camminare da solo a 15 (6.7/9.2) e a 18 mesi (3.2/5.5). Lo «stunting» aumenta il rischio di non stare in piedi da solo a 11 mesi (9.7) e di non camminare da solo a 18 mesi (6.1). Il «wasting» aumenta il rischio di non camminare con assistenza a 12 e 18 mesi (5.5/10.3). Il basso peso per età era associato al ritardo nel camminare da solo a 18 mesi (HR=2.9).

Conclusioni. La malnutrizione in bambini HIV-esposti diminuisce la probabilità di un adeguato sviluppo neuromotorio.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 108-112)

Parole chiave: malnutrizione, *motor milestones*, HIV-esposti, programma DREAM

INTRODUCTION

Childhood malnutrition is a critical issue in Africa and elsewhere.[1] Prior research studies have shown an association between malnutrition and delayed motor and cognitive development.[2,3] Early childhood malnutrition and HIV have been associated with delayed development. Limited data exist, however, about the timing of developmental delay early in life, particularly for HIV-exposed children.

In Malawi, HIV and malnutrition are the two major causes of infant morbidity and mortality.[4,5] Children born to HIV-positive women are particularly susceptible to malnutrition. Following review of recent HIV perinatal guidelines, the World Health Organization proposed the administration of antiretroviral therapy to mothers during the lactation period. Malnutrition nevertheless remains a challenge to the health of HIV-exposed children.[6,7] There is very limited data on motor milestone achievement in these children. The DREAM Program (Drug Resource Enhancement Against AIDS and Malnutrition), sponsored by the Community of Sant'Egidio, an Italian faith-based non-governmental organization, has been a pioneer in the prevention of mother-to-child transmission of HIV/AIDS in Sub-Saharan Africa.[8,9] The present study describes the assessment of growth and four motor milestones (standing with assistance, walking with assistance, standing alone, walking alone) in a sample of 76 HIV-exposed children originally randomized to an interventional study at the Blantyre DREAM Centre in Malawi.

MATERIALS AND METHODS

The study was approved by the National Health Sciences Research Committee of Malawi (approval number 486), with a separate informed consent signed by the mothers/guardians of participants.

Study population included HIV-exposed children born to pregnant women attending the DREAM program antenatal clinic in Blantyre. DREAM is a public health program aimed at the prevention and treatment of HIV/AIDS with multiple centres in 10 African countries. The DREAM program's approach to the diagnosis, treatment, and prevention of HIV/AIDS in Africa has been described in prior studies.[8-10]

Subjects in this analysis were a subpopulation of 76 children followed in the interventional SMAC study (Safe Milk for African Children)[11] from April 2008 to August 2009. The current analysis encompasses 35 males (46.1%) and 41 females (53.9%), all HIV-exposed, followed from the time they were born up to 24 months of age. Motor milestone assessment was initiated prospectively at 9 months of age. Infants were exposed to ARTs in utero and were given prophylactic AZT after birth. Their primary exposure was ART prophylaxis. HIV-exposed children were breastfed up to 6 months of age (the recommended duration of breastfeeding at the time of the study). All women received antiretroviral therapy and monthly nutritional supplementation as part of program guidelines. All mothers came from low socioeconomic households. At baseline all children were HIV-uninfected based on viral load testing.

Anthropometric and clinical exams of HIV-exposed children were performed monthly and measures were registered through a software package obtained in collaboration with the Department of Nutrition of the World Health Organization. Motor development assessed in terms of age of achievement of motor milestones was included as part of the DREAM software.[12-14]

Following WHO criteria, malnutrition indices were defined as stunting (length for age <-2 SD), wasting (weight for length <-2 SD), and underweight (weight for age <-2 SD).

Malnutrition was assessed and managed in accordance with the Malawian guidelines for the management of malnutrition.[15]

The assessment of motor behaviour, which is an essential aspect of child development, includes six specific milestones: sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone, and walking alone. Evaluation of motor milestone performance consists in observing whether a child can perform a milestone independently or after being placed into position. In this study, all milestones were assessed by a dietician using standardized testing procedures of the WHO Multicentre Growth Reference Study Group.[14] Details on our nutritional rehabilitation program have been previously described.[16,17]

Only HIV-exposed children 9-24 months were included (N=76). WHO Anthro Software (Version 3.2.2, January 2011) was used to compute children's weight-for-age (WAZ), weight-for-length (WLZ), and length-for-age (LAZ) z-scores per WHO standards. Further analysis of the data was completed using SPSS software system 20.0 (IBM Somers, NY, USA).

Median age of the highest observed milestone was calculated (age of MM achievement) and compared with the WHO reported median for the following selected motor milestones: standing with assistance, walking with assistance, standing alone, walking alone.

From 9 to 24 months the odds ratios (95%CI) between malnutrition indices (underweight, wasting, stunting) and motor milestone achievements were estimated. At 18 months, the odds ratio (95%CI) was calculated through a multivariate logistic regression analysis in order to assess the associations between growth parameters and walking alone.

RESULTS

A total of 76 HIV-exposed children (53.9% females) born between April 2008 and August 2009 were enrolled. The characteristics of the children at birth and at 18 months of age and maternal data are reported in table 1. The mean weight for age z-score at birth was –0.8 SD with 20.8% of the sample having a low birth weight (< 2.5 kg). Mean duration of breastfeeding was 24.7 weeks. At baseline, mothers had a mean CD4 cell count of 390/mm^3. At 18 months, all children were tested for HIV for the last time before being discharged from the DREAM prevention mother-to-child transmission program. Final HIV status was available for all children. Among them one acquired HIV infection. No deaths occurred during the 24-month study period.

At 18 months, mean WAZ score was -1.5, mean LAZ score was -2.4 and mean WLZ was -0.5. Eight children (10.5%) were

Characteristics	Value
mothers*	
age in years, mean (SD)	28 ± 4.8
HIV WHO stage, N (%)	
I	55 (72.4%)
II	16 (21%)
III	4 (5.3%)
IV	1 (1.3%)
CD4+cell count/mm^3, mean (SD)	390 ± 238
BMI in kg/m^2, mean (SD)	23.4 ± 2.9
duration of breastfeeding (weeks), mean (SD)	24.7 ± 4.5
children**	
girls: n (%)	41 (53.9%)
birth weight (kg), mean (SD)	2.9 ± 0.6
birth weight, weight for age z score, mean (SD)	-0.8 ± 1.1
low birth weight (<2.5 kg): N (%)	16 (20.8%)
HIV positive at 18 months: N (%)	1 (0.1%)
weight at 18 months (kg), (SD)	9 ± 1.3
WAZ at 18 months, mean (SD)	-1.5 ± 1.2
length at 18 months (cm), mean (SD)	75.2 ± 3.5
LAZ at 18 months mean (SD)	-2.4 ± 1.3
WLZ at 18 months mean, (SD)	-0.5 ± 1.1
WAZ <-2 at 18 months: N (%)	28 (36.8%)
LAZ <-2 at 18 months: N (%)	46 (60.5%)
WLZ <-2 at 18 months: N (%)	8 (10.5%)
walking alone at 18 months: N (%)	60 (78.9%)

*at first visit during pregnancy, **at birth and at 18 months

Table 1. Characteristics of HIV-exposed children and their mothers.
Tabella 1. Caratteristiche dei bambini HIV-esposti e delle loro madri.

wasted and 16 (21%) were not able to walk alone. The t-test did not show any statistically significant associations between maternal characteristics (age, CD4 count, BMI, duration of breastfeeding) and the ability of a child to walk alone at 18 months.

The median ages (in months) at achievement of the four specific motor milestones are illustrated in table 2 and compared with results from other studies. In the present study, for the four milestones, the median age was 10 months for standing alone, 12 months for walking with assistance, 15 months for standing alone, and 15 months for walking alone.

Among the sample, 34 children were delayed in achieving motor milestones when evaluated based on the WHO window of achievement assessment: 2 children in standing with assistance (2.6 %), 6 in walking with assistance (7.8%), 10 in standing alone (13.1%), and 16 in walking alone (21%). Among them, 24 children (70.5 %) were underweight. This data confirms the role of malnutrition in the retardation of achievement of motor milestones.

Table 3 reports the odds ratios and 95%CI by month between malnutrition indices and motor milestone achievement. The risk of not being able to walk with assistance at 12 months increased 5.5 times (95%CI 1.3-23.6) in wasted children. A high risk for not standing alone at 18 months was also seen in wasted children (OR 10.3; 95%CI 2.0-52.1). Similar risks of not standing alone were seen in children who were stunted at 11 months (OR 9.7; 95%CI 1.1-83), underweight at 18 months (OR 9.2; 95%CI 1.7-47.2), and also underweight at 15 months (OR 6.6; 95%CI 2.2-19.3). At 18 months the risk of not walking alone increased 8.6 times (95%CI 1.8-41.5) in wasted children, 6.1 times in stunted children (95%CI 1.3-29.3) and 5.5 times in underweight children (95%CI 1.6-18.4).

In order to confirm these results, a multivariable logistic regression was performed with 18 months of age data, with anthropometric parameters: WAZ, LAZ, WLZ, weight assessed at 18 months of age versus the motor milestone «walking alone». The model verified an association between low values for WAZ and not walking alone at 18 months, with a hazard risk of 2.9 and 95%CI of 1.6-5.4 with a p-value of <0.001 (WLZ 0.25 p=0.61; LAZ 0.45 p=0.5; weight 1.09 p=0.29).

Table 4 shows the evolution of growth parameters, nutritional indices, and developmental milestones between ages 9 and 24 months.

DISCUSSION

The present data supports the conclusion that HIV-exposed children in Sub-Saharan Africa are a very vulnerable population who experience high rates of malnutrition. Prior studies have described delays in the age of achievement of specific motor milestones in malnourished children (14, 18-22) but few have investigated the relationship between malnutrition and motor development among HIV-exposed children. Our study demonstrates that during the first year of life, HIV-exposed children experienced significant growth and neuromotor development delays. Interestingly except for one child who acquired HIV-infection during the observation period via breastfeeding, 75 of 76 children in this analysis were uninfected. The findings of delayed motor development are tied to the effects of acute and chronic malnutrition which plague paediatric HIV-exposed and unexposed populations in many Sub-Saha-

Motor milestone	WHO median (ref. 14)	Vietnam median (ref. 21)	Zanzibar median (ref. 22)	Present study median	Indonesia median (ref. 20)	Malawi geometric mean (ref. 18)	Italy median (ref. 19)
study type	**longitudinal**	**cross-sectional**	**cross-sectional**	**longitudinal**	**cross-sectional**	**randomized trial**	**longitudinal**
standing with assistance	7.4	9.9	10	10	8	not assessed	not assessed
walking with assistance	9	12.2	12	12	11	10.6	not assessed
standing alone	10.8	13.2	12	15	13	11.3	11.2-11.4
walking alone	12	15.7	15	15	14	13.8	12.7-12.9

Table 2. Comparison of median age in months at motor milestone achievement between different studies of non-HIV-exposed children and the present study.
Tabella 2. Confronto dell'età media di raggiungimento (in mesi) delle *motor milestones* di bambini "non HIV-esposti" in differenti studi e nel presente studio.

	Hands-and-knees crawling	Standing with assistance	Walking with assistance	Standing alone	Walking alone
underweight 11 months	1.5 (0.3-5.7)	4.6 (0.4-46.8)	0.9 (0.3-2.4)	5.8 (0.7-49.7)	1.1 (1-1.2)*
wasting 11 months	4.7 (0.6-32.9)	5.2 (0.4-61.6)	1.7 (1.4-2.2)*	1.1 (1-1.2)*	1.1 (1-1.1)*
stunting 11 months	0.8 (0.2-3.3)	2.8 (0.3-28.6)	1.5 (0.6-4)	9.7 (1.1-83.6)*	1.1 (1.0-1.3)*
wasting 12 months	5.5 (1.1-23.6)*	0.8 (0.6-1.1)	5.5 (1.3-23.7)*	3.1 (0.4-26.1)	1.3 (0.1-11.8)
underweight 15 months	2.5 (0.5-12)	0.9 (0.9-1)	3.8 (0.6-22.4)	6.7 (2.2-19.3)*	3.2 (1.2-8.3)*
wasting 15 months	1.1 (1-1.2)*	1 (0.9-1)	1 (1-1.1)*	5 (0.8-29.5)	2.5 (0.4-14.6)
stunting 15 months	1 (0.2-4.9)	0.9 (0.9-1)	1.6 (0.3-9.2)	3.2 (1.1-9.4)*	3.1 (1.2-8.3)*
underweight 18 months	1.1 (0.1-7.3)	0.9 (0.9-1)	3.6 (0.3-41.8)	9.2 (1.7-47.2)*	5.5 (1.6-18.4)*
wasting 18 months	1 (1-1.1)*	1 (0.9-1)	4.7 (0.3-58.8)	10.3 (2.0-52.1)*	8.6 (1.8-41.5)*
stunting 18 months	2.7 (0.2-25.9)	0.9 (0.9-1)	0.9 (0.9-1)	7 (0.8-58.9)	6.1 (1.3-29.3)*
wasting 21 months	1.1 (1-1.1)*	1 (0.9-1)	1 (0.9-1)	1 (0.9-1)	2.6 (0.2-26.9)
wasting 24 months	1 (1-1.1)*	1 (0.9-1)	1 (0.9-1)	1 (0.9-1)	1 (0.9-1)

*statistical significance

Table 3. Odds ratios and 95%CI by age (in months) between malnutrition indices and achievement of specific motor milestone achievements.
Tabella 3. Odds ratios e limiti di confidenza al 95% per età (mesi) tra indici di malnutrizione e mesi di raggiungimento delle specifiche *motor milestones*.

ran African settings. The present study demonstrates that malnutrition as manifested by specific indices, such as underweight status, stunting, and wasting, decreased the odds of attaining motor milestones, particularly the four milestones assessed at 9 months of age, standing with assistance, walking with assistance, standing alone, and walking alone.

When we compared motor milestone achievements in our population with results from different studies of non-HIV-exposed children, we saw that the median age of achievement of specific motor milestones in our cohort was delayed as compared to the ages reported in the WHO multicenter study,[14] as well as studies conducted in Malawi,[18] Italy,[19] and Indonesia.[20] Our study had similar findings to studies conducted in Vietnam[21] and Zanzibar,[22] where the median age of achievement for the four motor milestones was similar to that observed in our cohort. It is important to note, however, that most studies in the literature to date evaluated motor development in malnourished non HIV-exposed children, who are distinct from our own population of HIV-exposed infants. A study in Brazil[23] described motor development in HIV-exposed children in Sao Paulo and demonstrated a 10% delay in the achievement of motor milestones, which was not related to environmental or maternal parameters using the Alberta Infant Motor Scale (AIMS). The study had a sample size of 30 subjects, less than half of the present analysis, and the population differed significantly from ours in the fact that HIV-exposed children in Brazil are not breastfed and use formula since infancy. In addition, our malnutrition indices were very high, with more than 60% of our cohort having evidence of stunting with LAZ of <-2 and nearly 40% having WAZ <-2 at 18

Parameters	Age (months)						
	9	11	12	15	18	21	24
mean weight (kg±SD)	7.56±1.08	7.8±1.2	8.0±1.2	8.5±1.3	9.0±1.3	9.6±1.3	10.3±1.4
mean length (cm±SD)	67.4±3.5	68.5±3.2	69.9±3.4	72.6±3.6	75.2±3.5	77.6±3.6	80.0±3.7
WAZ	-1.2±1.2	-1.5±1.3	-1.4±1.3	-1.5±1.3	-1.5±1.2	-1.4±1.1	-1.3±1.1
LAZ	-1.8 ±1.2	-2.2 ±1.4	-2.2±1.4	-2.3 ±1.4	-2.4±1.3	-2.4±1.3	-2.0± 1.2
WLZ	-0.2 ±1.2	-0.3 ±1.2	-0.4 ±1.1	-0.5 ±1.1	-0.5 ±1.1	-0.3 ±1.1	-0.3±1.1
underweight [N (%)]	19 (33.3%)	31 (44.2%)	31 (40.7%)	28 (36.8%)	28 (36.8%)	25 (32.8%)	24 (32%)
wasted [N (%)]	2 (3.5%)	3(4.2%)	8 (10.5 %)	6 (7.9%)	8 (10.5%)	7 (9.2%)	3 (4%)
stunted [N (%)]	26 (45.6%)	39 (55.7%)	41 (53.9%)	43 (56.5%)	46 (60.5%)	46 (60.5%)	44 (58.6%)
sitting without support [N (%)]	57 (100%)	70 (100%)	76 (100%)	76 (100%)	76 (100%)	76 (100%)	76 (100%)
crawling [N (%)]	33 (57%)	60 (85%)	68 (89.5%)	69 (90.7%)*	71 (93.4%)*	70 (92.1%)*	71 (93.4%)*
standing with assistance [N (%)]	28 (49%)	66 (94%)	73 (96%)	75 (98.6%)	75 (98.7%)	75 (98.6%)	75 (98.6%)
walking with assistance [N (%)]	3 (5.2%)	28 (40%)*	49 (64.4%)*	70 (92.1%)*	73 (96.1%)	75 (98.6%)	75 (98.6%)
standing alone [N (%)]	1 (1.7%)	8 (11.4%)[§]*	18 (23.6%)	52 (68.4%)[#§]	66 (86.8%)[#]*	74 (97.3%)	75 (98.6%)
walking alone [N (%)]	0	4 (5.7%)[#*§]	9 (11.8%)	41 (53.9%)[#§]	60 (78.9%)[#§]*	71 (93.4%)	75 (98.6%)

SD: standard deviation
statistical significant association (p <0.05) between: *wasting, [§]stunting, [#]underweight, and developmental milestones

Table 4. Growth and developmental milestones in our cohort between 9 to 24 months of age.
Tabella 4. Crescita e raggiungimento delle *motor milestones* nella nostra coorte da 9 a 24 mesi di età.

months of age. Low birth weight was present in 21% of our cohort, which demonstrates that malnutrition is already present at birth and worsens over time, as reported in prior assessments of our paediatric cohorts.[17]

Our findings likely underestimate the degree of the problem in similar settings in Sub-Saharan Africa, as our patients received nutritional supplementation and were followed very closely in a study setting. Nevertheless, even in more optimal conditions the impact of food insecurity was still tangible in this cohort. One of the study limitations was that we were unable to assess earlier developmental milestones in many subjects and, for this reason, we focused our analysis on later periods which coincide with a time of higher food insecurity in an infant's life, after the introduction of solids, when breastfeeding is no longer a source of full sustenance. It is likely that delayed developmental milestones would have worsened over time, paralleling growth faltering, which is more prevalent in the second semester of life, following the interruption of breastfeeding. Nevertheless, the ability to evaluate developmental milestones between 9 and 18 months of age allowed us to assess a critical window period of both growth and development.

In summary, in order for health care programs to address the negative impact of food insecurity, intrauterine retardation, and reduced exposure to breastfeeding, a holistic approach to management needs to be supported. Routine evaluation of gross motor milestones should be included in programs as a surrogate for nutritional assessment in order to optimize the care of malnourished HIV-exposed children.

Conflicts of interest: none declared

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