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Neurodevelopmental status of HIV-exposed but uninfected children: A pilot study

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Introduction. HIV affects children both directly and indirectly, with evidence of increased infectious mortality and morbidity in the HIV-exposed but uninfected (HEU) infant. There is little published research on neurodevelopmental outcome of HEU infants in Africa. Following the introduction of successful prevention of mother-to-child transmission programmes, it has become important to determine whether differences exist between HEU infants and infants born to HIV-negative mothers in order to guide current management policies of this rapidly growing group of infants.

Objectives. To compare the developmental outcome of infants exposed to HIV *in utero* who remained uninfected (HEU) with that of infants unexposed to HIV *in utero* (HUU).

Methodology. This was a prospective, blinded, hospital-based study. Infants aged between 17 and 19 months were assessed on the Griffiths Mental Developmental Scales (GMDS). Birth history, previous hospitalisation, maternal and infant characteristics, antiretroviral exposure, anthropometric measurements and abnormal clinical findings were documented.

Results. Of the original 55 infants enrolled at 2 weeks of age, 37 (17 HEU and 20 HUU) underwent neurological and developmental assessment. There were no significant differences between the groups with regard to the GMDS general quotient or other subscales, apart from the Personal/social subscale, where the HEU group performed significantly more poorly than the HUU participants (p=0.026). This difference is probably a result of cultural differences between the groups, as 76% of HEU and only 15% of HUU participants were of Xhosa origin.

Discussion. There was no difference in neurodevelopmental outcome at 18 months between the HEU and HUU groups.

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Successful prevention of mother-to-child transmission (PMTCT) programmes have resulted in a decrease in vertical transmission of HIV to below 5%.[1] In South Africa, with an antenatal HIV prevalence rate of around 30%, about a quarter of infants born are therefore classified as HIV exposed but uninfected (HEU). HIV affects children both directly and indirectly, and there is evidence of increased infectious mortality and morbidity in the HEU infant.[2] There remains uncertainty regarding possible mechanisms of increased susceptibility and also the preventive measures to reduce these effects. Potential factors include increased exposure to infections and immune abnormalities in the infant, socio-economic difficulties, poor maternal health (including mental health), lack of parental care, reduced breastfeeding and unsuitable feeding practices.[3] Conflicting data have been published about toxicity to the fetus of antiretroviral drugs (ARVs) and their effects on neurodevelopment.[4-6] All these factors could potentially affect child development.

Of the published research on HEU children in Africa, only a few studies have high methodological quality using control groups and systematic validated measures of cognitive function.[7] Msellati *et al.* in Rwanda demonstrated no difference in neurodevelopmental outcome between HEU and HIV-unexposed children (HUU), i.e. infants born to HIV-uninfected mothers.[8] A Ugandan study also showed no significant difference between a group of HEU and HUU infants.[9,10] On the other hand, Boivin *et al.* demonstrated deficits in cognitive performance in HEU children in Zaire compared with HUU controls,[11] while Van Rie *et al.* found that HEU preschool children in the Democratic Republic of the Congo had poorer motor development and expressive language than HIV-unexposed controls.[12] The authors argued that socio-economic differences between these groups rather than the inherent consequences of *in utero* HIV exposure may have accounted for the poorer outcome.

In South Africa the availability of ARVs and PMTCT, while decreasing the number of HIV-infected infants, has significantly increased the number of HEU infants born to HIV-infected mothers.[1] It is important to determine whether any neurodevelopmental differences exist between HEU and HUU children, in order to facilitate the development and implementation of appropriate interventions for this growing population of infants.

Aims and objectives

The primary objective was to compare the neurodevelopmental outcome of infants who were exposed to HIV *in utero* but were uninfected (HEU) with that of infants born to HIV-uninfected mothers (HUU). A secondary objective was to identify markers for poor neurodevelopmental outcome in either group.

Methods

Recruitment

Participants were recruited from the postnatal maternity wards of Tygerberg Hospital, Western Cape, for a pilot study of the innate immune abnormalities in HEU infants. Tygerberg Hospital is one of two tertiary academic hospitals servicing the city and surrounds of Cape Town, Western Cape province, South Africa. It serves as the teaching hospital for Stellenbosch University. Patients accessing care are generally from lower socio-economic communities and are predominantly Afrikaans- or Xhosa-speaking. Participants were recruited consecutively over a 16-week period from March to June 2009. Mothers' HIV infection status was confirmed on presentation in labour using standard HIV testing algorithms.[13]

The study protocol was approved by the Human Research Ethics Committee, Faculty of Health Sciences, Stellenbosch University (N08/10/289).

Inclusion and exclusion criteria

All infants who tested HIV negative (HIV-DNA-PCR) at 2, 6 and 12 weeks of age were included. Participants had to be between 17 and 19 months of age and physically healthy on the day of neurodevelopmental assessment. HIV-infected infants were excluded from the study.

Data collection

Information regarding pregnancy, birth history, weight gain, previous illnesses and hospitalisation, maternal characteristics and family history was obtained from the caregiver, hospital medical records and the child's Road-to-Health card (immunisation record). Head circumference, weight and length were plotted on charts from the Centers for Disease Control and Prevention (USA), and a developmental and neurological examination was performed.

Instruments

The Griffiths Mental Developmental Scales (GMDS) 0 - 2 years[14] were administered. There are 5 subscales: Locomotor, Personal/social, Hearing and speech, Eye and hand co-ordination, and Performance. The GMDS have been adapted for South African children. Standard instructions and questions are available in English, Afrikaans and Xhosa. Although this tool has been widely used in South Africa,[15-17] it has yet to be validated and standardised on South African children. The mother or a primary caregiver was present during the assessment, which was carried out in the child's home language by one of two developmental paediatricians. An interpreter, also a trained GMDS administrator, helped the paediatricians to complete the scales with Xhosa-speaking patients. The paediatricians initially assessed a participant together and reached consensus on discrepant pass or fail test items, until it was felt that scoring was of a similar standard. The testers were blinded to the child's HIV exposure status.

Data analysis

Statistica (Release version) 10 (Statsoft, Inc Tulsa, OK, USA) was used for analysis. Categorical data were analysed using either Fisher's two-tailed analysis or Pearson's chi-square analysis. The differences in numerical data (i.e. gestational age, birth weight, maternal age, weight, length, head circumference, chronological age and hospitalisation) among the two groups were analysed using *t*-tests. A Mann-Whitney U-test was used to determine differences in the GMDS scores.

Results

Twenty-five HIV-infected and 28 HIV-uninfected mothers were recruited from the postnatal wards at Tygerberg Hospital and their infants (27 HEU and 28 HUU) were enrolled 2 weeks after delivery. Of the original 55 infants enrolled, 39 presented for the visit at 18 months. Fifteen infants (6 HUU and 9 HEU) were lost to follow-up and 1 infant (HUU) died before 12 months. Thirty-seven of the remaining 39 infants underwent neurodevelopmental assessment, as one parent declined consent and one missed the appointment.

Among the 37 participants, there were 17 children who were HEU and 20 who were HUU. There was no significant difference between the groups with regard to gender, gestation, birth weight, mode of delivery or maternal age and education (Table 1). However, the HUU participants were predominantly Afrikaans language speakers (85%) while the HEU participants were predominantly Xhosa (76%).

There was no significant difference between HEU and HUU participants with regard to the general quotient and 4 of the 5 GMDS subscales, although both HEU and HUU group means were lower than the standardised mean (Table 2). However, the HEU group performed significantly more poorly than the HUU participants on the Personal/social subscale of the GMDS (Fig. 1). Specific items on the Personal/social scale which differentiated the groups included:

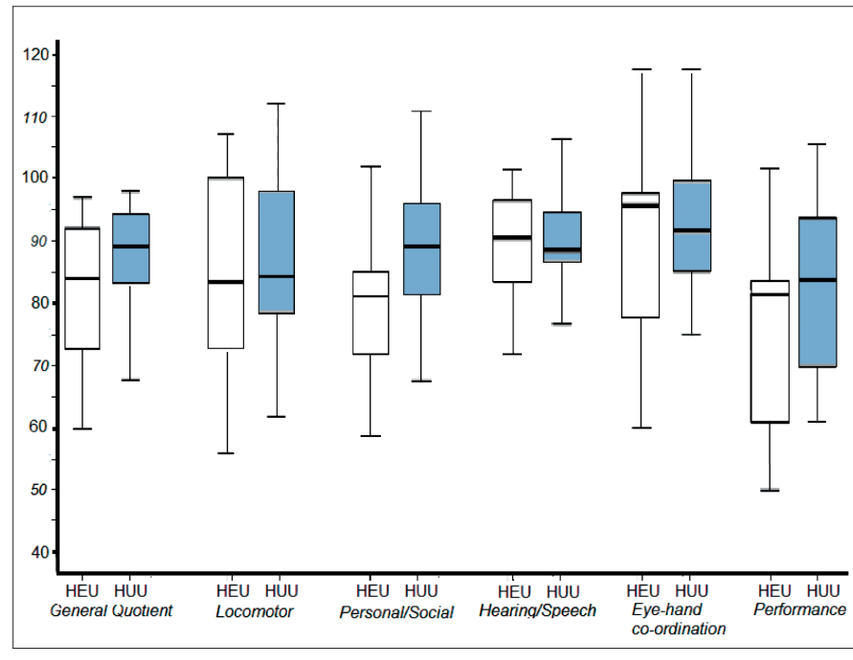

Fig. 1. Mean general quotients and subquotients obtained on the Griffiths Mental Development Scales: comparison of HIV-exposed but uninfected (HEU) and HIV-unexposed and uninfected (HUU) infants.

- Item 42: 'shows shoes on request' – correctly indicated by 85% of the HUU but only 47% of HEU participants
- Item 43: 'mother reports that child uses spoon himself but spills some' – passed by 85% of the HUU versus 59% of HEU participants
- Item 45: 'shows one part of a doll's body on request, e.g. hands, hair, feet, eyes, nose' – passed by 65% of HUU versus 41% of HEU participants.

Five of the HEU and 2 of the HUU infants required at least one hospital admission for acute infection during their first 18 months of life, while 3 of the 5 HEU infants had two hospital admissions (Table 3). However there was no statistically significant difference between the groups with regard to the number of infants with one or more hospitalisations (p=0.21). An unexpected finding was the anthropometric differences between the groups. More children in the HUU group were stunted (Fig. 2). Two HUU participants had height-for-age z-scores (HAZ) scores more than 2 standard deviations (SD) below the mean, and 5 HUU participants had HAZ scores that fell between 1 and 2 SD below the mean. Only 1 HEU participant had a HAZ score between 1 and 2 SD below the mean, and none was greater than 2 SD. There were no infants in either group with weight-for-length z-scores (WLZ) more than 2 SD below the mean at 18 months. Although there was no statistically significant difference in head circumference between groups (0.21), 3 of the HEU infants had head circumferences above the 97th centile and 3 of the HUU infants had head circumferences below the 3rd centile.

The groups differed significantly in feeding patterns. All but 1 of the HEU infants were formula-fed, while all HUU infants were breastfed for a median of 12 weeks.

A significantly greater percentage of mothers in the HUU group (45%) versus the HEU group (11%) admitted to smoking during pregnancy (p=0.036).

Discussion

There was no significant difference in the General quotients of HEU and HUU participants, which correlates with findings of previous studies in Africa.[8-10] However, the Personal/social subquotient was significantly lower in the HEU group. It is difficult to ascertain whether the lower mean Personal/social score was due to the biological and environmental exposures associated with having an HIV-positive mother or to a

Table 1. Maternal and infant characteristics: comparison of HIV-exposed but uninfected (HEU) with HIV-unexposed uninfected (HUU) infants

Demographics	HEU (n=17)	HUU (n=20)	p-value
Gender, male (n (%))	6 (35)	10 (50)	0.093
Gestation (wks) (n)			
<37	4	4	0.65
≥37	13	16	
Birth weight (g) (median (range))	2 980 (1 900 - 3 820)	3 068 (2 080 - 3 600)	0.78
Mode of delivery (n (%))			
Vertex delivery	16 (94)	19 (95)	0.362
Breech delivery	0	1 (5)	
Caesarean section	1 (6)	0	
Maternal age at delivery (yrs) (median (range))	27 (19 - 41)	28 (19 - 44)	0.51
Maternal education (final grade attained in formal schooling) (n (%))			
≤7	3 (17)	3 (15)	0.745
8 - 10	8 (47)	11 (55)	
>10	6 (35)	6 (30)	
Language (n (%))			
Afrikaans	4 (23)	17 (85)	0.026
Xhosa	11 (64)	3 (15)	
Mixed Xhosa/Eng/French	2 (11)		

Table 2. Mean quotients and subquotients on the Griffiths Mental Development Scales: comparison of HIV-exposed but uninfected (HEU) with HIV-unexposed (HUU) infants

Griffiths quotients	Group	Mean	Median	Minimum	Maximum	SD	p-value
General quotient	HEU	83.05	84	60	97	11.31	0.190
	HUU	87.45	89	68	98	8.65	
Locomotor	HEU	82.76	83	56	107	16.33	0.433
	HUU	86.75	84	62	112	14.25	
Personal/social	HEU	79.35	81	59	102	11.20	0.026
	HUU	88.45	89	68	111	11.41	
Hearing and language	HEU	89.11	91	72	102	9.37	0.968
	HUU	89.25	89	64	107	10.70	
Eye-hand co-ordination	HEU	89.52	96	60	118	18.16	0.451
	HUU	93.25	92	75	118	11.26	
Performance	HEU	76	82	50	102	13.71	0.139
	HUU	83.4	84	61	106	16.01	

Table 3. Possible confounders: comparison of HIV-exposed but uninfected (HEU) with HIV-unexposed (HUU) infants

Variable	HEU (*n*=17)	HUU (*n*=20)	*p*-value
Low birth weight (<2 500 g) (*n* (%))	2 (11)	1 (5)	
Head circumference (cm) (mean)	46.92 Macrocephaly (*n*=3)	46.09 cm Microcephaly (*n*=2)	0.21
Weight for age (mean *z*-scores)	0.2773	-0.3985	0.016
Length for age (mean *z*-scores)	0.2272	-0.6266	0.045
Weight for length (mean *z*-scores)	0.6105	-0.1419	0.040
Physical and neurological findings	No major neurological or physical abnormalities	Achilles tendon contractures (*n*=1) Fetal alcohol spectrum disorder (*n*=1) Strabismus (*n*=1) Serous otitis media (*n*=1)	

SD = standard deviation.

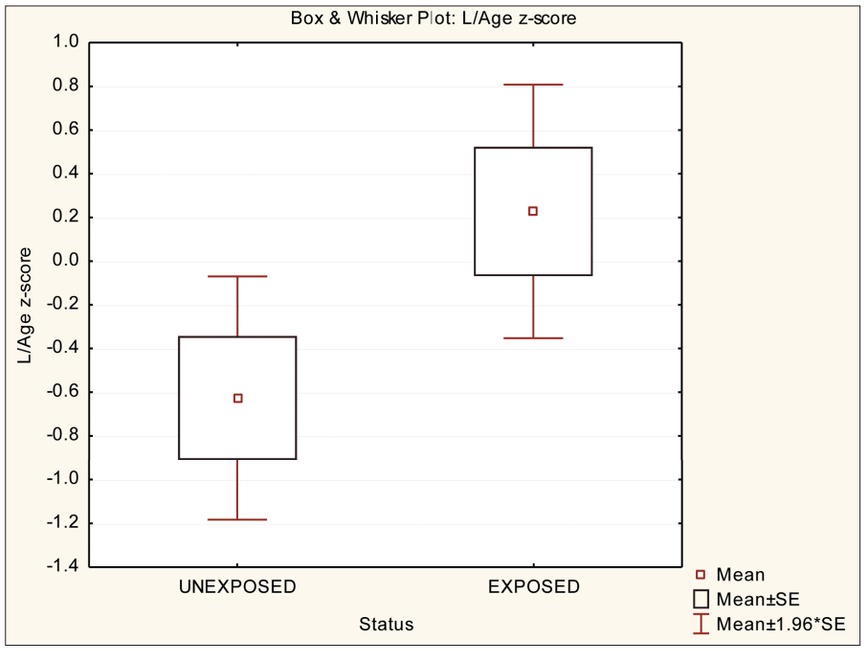

Fig. 2. Comparison of length-for-age z-scores between HIV-unexposed uninfected (HUU) and HIV-exposed but uninfected (HEU) infants.

confounding effect of cultural differences between the groups which manifested as different child-rearing practices. For example, items in the GMDS such as spoon feeding and exposure to dolls are not culturally universal activities. The HUU participants were predominantly Afrikaans speaking, while the HEU participants were largely Xhosa speaking. When Personal/social subquotients were grouped primarily by home language and not by HIV exposure, the difference in scores between the Afrikaans and Xhosa groups was even more significant (p=0.015). The influence of cultural differences has been supported by Cockcroft *et al*., who found that black South African infants aged between 13 and 16 months performed significantly more poorly on the Personal/social scale compared with a British sample.[15] Luiz also postulated that this subscale was the most culturally biased.[18]

Infant nutrition, specifically stunting, may also adversely affect development. Increased stunting among the HUU participants was an unexpected finding. Stunting has been found to be associated with poor neurodevelopmental outcome.[19] It could be postulated that stunting was a confounder that adversely affected the HUU developmental scores, thus minimising the difference between the HUU and HEU groups. A significantly greater percentage of mothers in the HUU group admitted to smoking during pregnancy, and 3 of the mothers, all HIV uninfected, admitted to drinking alcohol. The HUU group may therefore have had other risk factors that could potentially have lowered their developmental scores.

All but 1 of the HEU participants had been exposed to ARVs, either as a result of PMTCT prophylaxis or combination ARV therapy given to their mothers, but no neurological abnormalities attributable to ARVs were evident at 18 months.

The strengths of the GMDS are that the tool has been extensively used on this age group in South Africa with Xhosa and Afrikaans translations, and it does appear to be reliable in picking up differences between groups.[15-17]

Limitations

Limitations of the study include the number of children lost to follow-up from the original cohort. By the 18-month time point when development was assessed, a large number of infants had been lost from the study as a result of relocating or mothers returning to work. Secondly, the small sample size precluded multivariable analysis to adjust for the effects of confounding factors. In particular this meant that any effect of the cultural imbalance between the HEU and HUU groups could not be adequately adjusted for. Finally, the effects of ARVs on neurodevelopmental outcomes could not be ascertained as all but 1 of the HEU children had been exposed to ARVs at some point in time.

Conclusion

There was no difference in performance on the GMDS between HEU and HUU infants, except for the Personal/social scale, where the HEU participants did significantly worse. This was probably accounted for by cultural variations between the groups.

Recommendations

Studies with a larger sample size attempting to control for confounding factors through matching or adjustment are recommended. Evaluating children's development at 12 months of age may reduce attrition. It would be beneficial to review items on the Personal/social subscale for cultural bias.

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Author contributions. PS contributed to protocol design, carried out the interviews and neurodevelopmental assessments, contributed to the understanding of the results and drafted the initial article as well as revisions. BL contributed to the conceptualisation of the project, protocol design, carried out the interviews and neurodevelopmental assessments, contributed to the understanding of the results and assisted in the write-up and revision of the article. MT contributed to the understanding of the results and assisted in the write-up and revision of the article. JH provided data analysis support. ME was the supervisor, contributed to the conceptualisation of the project and assisted in the revision of the article. We gratefully acknowledge the data provided by co-workers Amy Slogrove, Shalena Naidoo, Kevin Ho and Gareth Mercer.

There is evidence of increased infectious mortality and morbidity in the HIV-exposed but uninfected infant.

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