Insulin-like Growth Factors and Stunting in African Infants Exposed to HIV and Uninfected

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Brenda C. Kakayi[1], Patricia DeMarrais[2], Kristin Baltrusaitis[2], Lynda Stranix-Chibanda[3], Clemensia Nakabiito[1], Vivian Rexroad[4], Maxensia Owor[1], Sufia Dadabhai[5], Dhayendre Moodley[6], Friday Saidi[7], Avy Violari[8], Gerhard Theron[9], Takara Leah Stanley[10] and Mary Glenn Fowler[11]

[1]Makerere University- Johns Hopkins University Research Collaboration | MU-JHU CARE LTD, Kampala, Uganda, [2]Havard T.H. Chan School of Public Health, Boston, MA, USA, [3]University of Zimbabwe Clinical Trials Research Centre, Harare, Zimbabwe, [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [5]Johns Hopkins Research Project, Blantyre, Malawi, [6]Umlazi CRS School of Clinical Medicine University of KwaZulu Natal, Durban, South Africa, [7]UNC Project Malawi, Lilongwe, Malawi, [8]PHRU University of the Witwatersrand, Johannesburg, South Africa, [9]Department of Obstetrics and Gynaecology Faculty of Medicine and Health Sciences Stellenbosch University, Cape Town, South Africa,, [10]Mass General Hospital for Children, Boston, MA, USA, [11]Johns Hopkins University School of Medicine, Baltimore, MD, USA

BACKGROUND

The biological mechanism underlying the increased risk of stunting in infants/children who are HIV-exposed and uninfected (CHEU) is not fully understood.

We assessed whether insulin-like growth factors (IGFs) that are known to be associated with infant growth, are associated with high rates of stunting observed among CHEU.

We leveraged stored samples from infants in the P1084s sub-study of the IMPAACT PROMISE Trial: pregnant women living with HIV and their infants were enrolled and randomized to different PMTCT regimens. P1084s was the bone and kidney observational sub-study of PROMISE.

METHODS

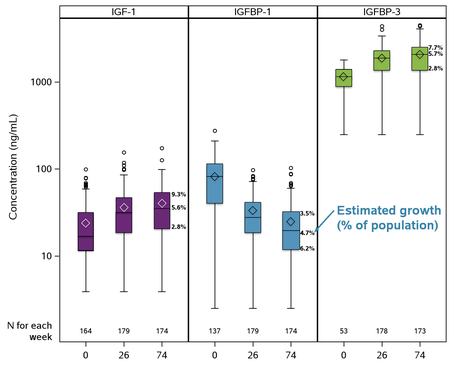
- A random sample of 213 out of 268 infants from the antepartum part of the P1084s sub-study was selected. These infants had at least one serum sample from the birth visit, week 26 or week 74 visits in Uganda (n= 106), Malawi (n=55), and South Africa (n=52)
- Stored serum samples were analysed for IGF-1, IGF Binding Protein (IGFBP)-1 and IGFBP-3 by Quest Diagnostics using in-house assays validated in accordance with CLIA regulations.
- IGF-1 was measured using liquid chromatography/mass spectrometry, IGFBP-1 using radioimmunoassay and IGFBP-3 using immunoassay.
- Risk ratios (RRs) for stunting (i.e., length-for-age z (LAZ) -score<-2 standard deviations(SDs)) at birth, weeks 26 and 74 were estimated using log-binomial regression models with $\log_{10}$ transformed growth factors at birth as predictors.
- Cross-sectional associations between LAZ-scores and $\log_{10}$ transformed growth factors at birth, weeks 26 and 74 were evaluated using adjusted linear regression models.

Growth factor concentrations were significantly related to LAZ-scores at 26 weeks and 74 weeks of age.
Higher IGF-1 levels at birth were associated with a reduced risk of stunting at 26 weeks of age, but not for IGFBP-1 and IGFBP-3 at birth.

RESULTS

- The study included 213 infant participants with 47% being male. The median (Q1, Q3) weight within 5 days of birth was 2.9 kg (2.6, 3.2) and length was 48 cm (46, 50) representing a median LAZ-score of -1 (-2, 0).
- Overall, 24% of the participants were stunted at birth, 26% at week 26 and 38% at week 74.
- Although higher IGF-1 at birth was significantly associated with reduced risk of stunting at week 26 (RR: 0.4 per $\log_{10}$ increase; 95% confidence interval (CI): 0.19, 0.86), IGFBP-1 or IGFBP-3 at birth were not associated with future stunting (Table 1, Analysis 1).

Fig 1: Growth factors by age



- Table 1, Analysis 2 shows that, at 74 weeks, LAZ-scores increase per $\log_{10}$ increase in IGF-1 (1.60; 95% CI: 1.5, 2.04), decreased per $\log_{10}$ increase in IGFBP-1 (-0.62; 95% CI -1.21, -0.02), and increased per $\log_{10}$ increase in IGFBP-3 (2.08; 95%CI: 1.26, 2.91). Similar observations were made at week 26.

CONCLUSIONS

- Growth factor levels were significantly associated with LAZ-scores at 26 weeks and 74 weeks of age.
- However, only modest associations between IGF-1 at birth and future stunting were shown in this population.
- Therefore, variations in IGF levels may not be the main determinant for stunting in CHEU. Other mechanisms independent of the growth hormones/IGF axis should be explored.
- Further research is needed to elucidate the mechanisms involved and develop effective interventions to address stunting in CHEU.

Table 1. Stunting and infant LAZ-score as functions of growth factors

Growth Factor[1]	Visit Week	Analysis 1: Risk of stunting at each visit with growth factor concentration (per $\log_{10}$ increase) at birth		Analysis 2: Cross-sectional association between Infant length-for-age z (LAZ)-score and growth factor concentration (per $\log_{10}$ increase) at each visit	
		n	Relative Risk (95% CI); p-value	n	Adjusted[2] Coefficient (95% CI); p-value
IGF-1 ($\log_{10}$ ng/mL)	0	164	0.80 (0.39, 1.65); 0.55	164	0.21 (-0.32, 0.73); 0.44
	26	133	0.40 (0.19, 0.86); 0.018[3]	179	1.19 (0.62, 1.75); < 0.001
	74	136	0.63 (0.36, 1.09); 0.10[3]	174	1.60 (1.15, 2.04); < 0.001
IGFBP-1 ($\log_{10}$ ng/mL)	0	137	0.69 (0.39, 1.24); 0.21	137	0.42 (-0.09, 0.93); 0.11
	26	116	1.32 (0.54, 3.22); 0.55	179	-0.78 (-1.41, -0.16); 0.014
	74	117	1.54 (0.76, 3.12); 0.23	174	-0.62 (-1.21, -0.02); 0.042
IGFBP-3 ($\log_{10}$ ng/mL)	0	53	5.16 (0.06, 480.20); 0.48	53	1.04 (-0.75, 2.83); 0.25
	26	48	1.14 (0.03, 47.05); 0.95	178	1.81 (0.92, 2.71); < 0.001
	74	43	1.66 (0.11, 24.19); 0.71	173	2.08 (1.26, 2.91); < 0.001

[1]Priority of growth factor measurement was 1) IGF-1; 2) IGFBP-1; 3) IGFBP-3
[2]Adjusted for treatment, entry CD4, WHO stage, age, time between entry and delivery, breastfeeding duration censored at analysis week and gestational age at birth.
[3]Similar estimated were observed for adjusted model, other adjusted models did not converge.

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