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Effects of HIV exposure on metabolite levels in Midfrontal Gray Matter in children: at 5 and 7 years

Study

Single voxel ^{1}H-MRS (SVS) data were acquired in twenty-one 5-year old (mean age ± standard deviation = 5.5 ± 0.4 years;15 Xhosa/6 Cape Coloured; 13 HIV-exposed, uninfected (HEU)/8 HIV-unexposed, uninfected (HUU)) and thirty-one 7-year old children (7.3 ± 0.1 years; 24 Xhosa/7 Cape Coloured; 8 HEU/23 HUU) on a Siemens 3T Allegra Head Scanner (Siemens, Erlangen, Germany) in Cape Town, South Africa. Nine children were imaged at both ages. All HEU children were exposed to treatment for prevention of mother-to-child transmission (MTCT).

MRS data were acquired using a real-time motion and B_0 corrected [1] point resolved spectroscopy (PRESS) sequence (TR 2000 ms, TE 30 ms, 64 averages, Scan Time: 2:16 min). We collected spectra in the midfrontal gray matter (MFGM). Water reference scans were acquired in the voxel for eddy current compensation, frequency/phase correction, and to compute absolute metabolite levels. Spectra were analyzed with LCModel. R was used for all statistical analyses. A mixed effect linear regression model was used to account for repeated measures for some children.

Background

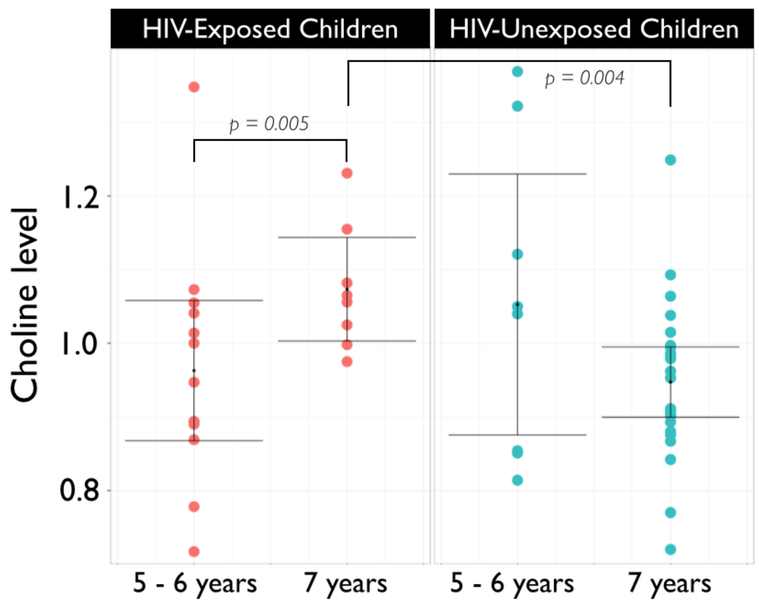
In South Africa, 95% of HIV-positive pregnant women and 68% of HIV-exposed infants have been receiving antiretroviral therapy (ART) [2,3]. Several studies [4,5,6] suggest that *in utero* ART exposure is associated with long-term neurological effects, motivating additional study of HIV-exposed uninfected (HEU) children. These studies suggest HEU children have an increased risk of neurological symptoms such as cognitive delay and motor abnormalities [5,7]. The increased risks may involve exposure to HIV antibodies, antiretroviral (ARV) drugs and environmental factors [8].

MR spectroscopy (MRS) is used for the non-invasive investigation of neuro-development in children. Many childhood neurological processes are accompanied by metabolite changes that sometimes correlate with age [9,10]. NAA is associated with neuronal density and has been shown to increase with age in childhood [9,10]. Choline remains relatively constant throughout childhood [10]. Glutamate is a neurotransmitter involved in normal cell function and neurotransmission, and is constant in childhood [10,11].

Hypothesis - From age 5 to 7 we expect to observe an increase in NAA levels as well as constant choline and glutamate levels.

Results

1

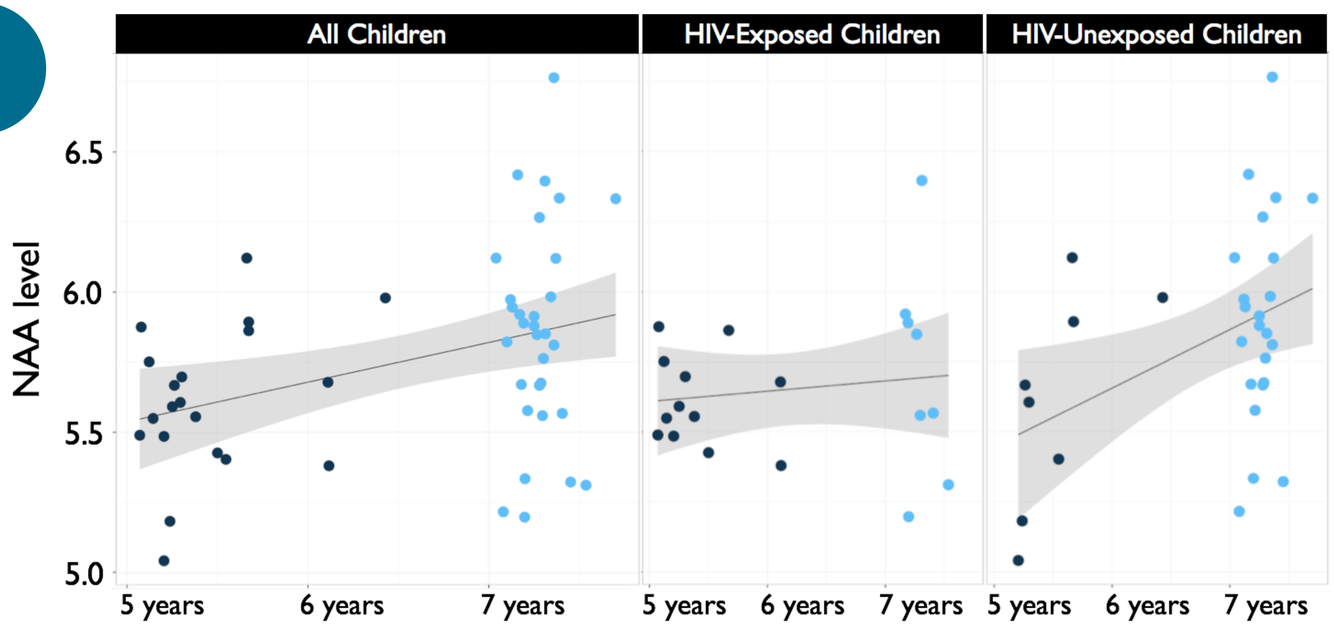


HEU children have HIGHER mean choline levels at age 7

Result: HEU children have HIGHER choline levels at age 7 compared to age 5 (*t-test: HEU (5yrs) vs HEU (7yrs) - p = 0.005)*. In addition, HEU children have HIGHER choline levels at 7 years compared to HUU children (*t-test at age 7: HEU vs HUU - p = 0.004)*. Bars represent confidence intervals.

Interpretation: Both the increased choline levels among HEU children from age 5 to 7, and the higher mean choline level at age 7 compared to HUU children, suggest a developmental difference among HEU children at age 7. Increased choline levels may imply glial proliferation/inflammation or increased cellular density.

2

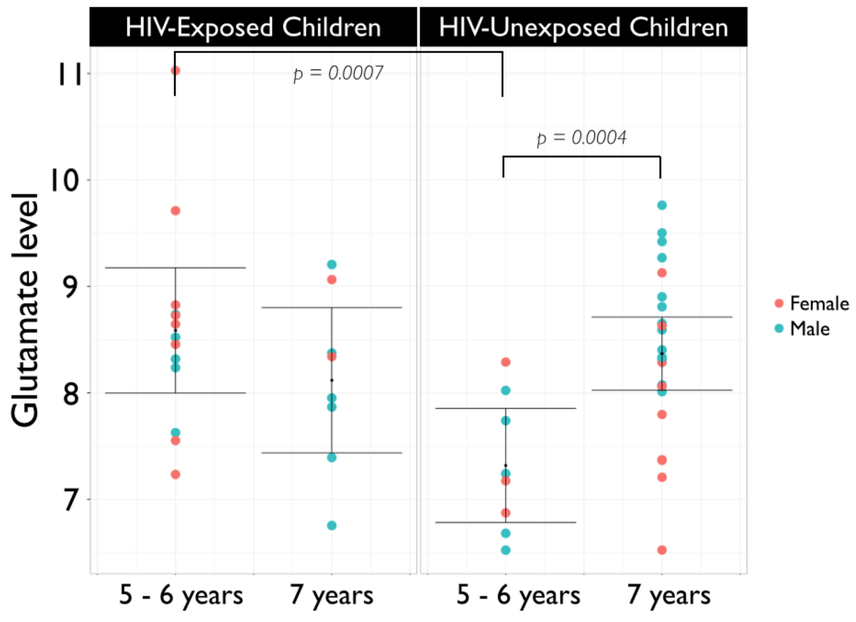


NAA increases from age 5 to 7 in HUU children *only*

Result: We found an increase in NAA with age - from age 5 to age 7 (slope = 0.15; p = 0.02) across all children. The relationship is driven by HIV-unexposed children (slope = 0.23, p = 0.02). Gray represents confidence intervals.

Interpretation: The increased NAA levels may be due to increased neuronal populations and synaptic connections with age [8]. We find the increase is driven by HUU children; NAA increases with age among HUU children, however the metabolite level increase with age disappears (slope = 0.04, p = 0.6) in HEU children. The lack of age related NAA growth suggests a possible long-term effect of HIV exposure and/or ARV treatment on neuron populations, axons, dendrites and synaptic terminals.

3



HUU children have LOWER mean glutamate levels at age 5

Result: Glutamate levels at age 5 are LOWER in HUU compared to HEU children (p = 0.0007). Among HUU children, we found lower glutamate levels at age 5, compared to age 7 (p = 0.0004). The significant difference among HUU children in glutamate levels with age is driven by male children (p = 0.001). Bars represent confidence intervals.

Interpretation: The low mean glutamate level at age 5 among HUU children is unexpected as glutamate levels are expected to remain constant in childhood in healthy children. However, due to the small number of 5 year old children included in MRS studies of metabolite levels in childhood, age and gender related variability has not been examined in depth. This result suggests metabolite levels are influenced by both gender and age variability, suggesting that a more detailed understanding of the normal age and gender dependent variability is critical to interpreting MRS results across pediatric populations.

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Acknowledgements

Support for this study was provided by NRF/DST South African Research Chairs Initiative; US National Institute of Allergy and Infectious Diseases (NIAID) through the CIPRA network, Grant U19 AI53217; NIH grants R01HD071664 and R21MH096559; NRF grant CPR20110614000019421, and the Medical Research Council (MRC). We thank the CUBIC radiographers Marie-Louise de Villiers and Nailah Maroof, our research staff Thandiwe Hamana and Rosy Khethelo, and Shabir A. Madhi for access to control participants on the CIPRA-SA04 trial.