Adults with Significant Childhood Lead Exposure Evaluated with Proton MR Spectroscopy

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Introduction: Despite numerous studies demonstrating an inverse association between blood lead levels and cognitive functioning, academic performance, and social behaviors, structural neuroimaging evaluations of children and adults with elevated lead exposure (US EPA action level 10 μg/dL) are generally unremarkable. However, magnetic resonance spectroscopy (MRS) evaluations of lead exposed populations may provide distinct metabolic information useful for refining the mechanistic models of lead induced brain injury. We hypothesized that adults with childhood lead exposure would demonstrate evidence of irreversibly altered neural metabolism, specifically via reductions of N-acetyl aspartate (NAA).

Methods: One hundred fifty nine adult participants of a longitudinal birth cohort studying the effects of lead exposure completed a quantitative, short echo PRESS spectroscopy protocol evaluating seven regions within the brain. Table 1 highlights the demographics of the study cohort. Table 2 details the regions of interest. Metabolite concentrations were determined with LCModel analyses, and corrected for CSF contribution to the voxel. Correlation and multiple regression analyses were used to investigate the relationship between regional metabolite concentrations and mean childhood blood lead levels. Blood lead levels were measured in this cohort every three months for the first five years of life and every six months from 5 - 6.5 years of age with a mean value determined for childhood. For comparison with the metabolite concentrations, the individual mean of the twenty-three childhood blood lead assessments was employed in the analyses. Potential confounders and covariates were included in analytical models.

Table 1. Demographics for Imaging Cohort (N=159)

Age	20.8 ± 0.91 years
Race	148 black (93%), 11 white (7%),
Sex	83 male (52 %), 76 female (48%)
Mean childhood blood lead level (μg/dL)	13.3 ± 6.1, range 4.65 - 37.2
Gestational age (weeks)	39.4 ± 1.7, range 35-43
Birth weight (grams)	3106 ± 467, range 1814-4260
SES, 20 years	21.4 ± 7.1, range 10-40
IQ-FSIQ, 7 years	86.8 ± 11.9, range 50-116
Marijuana Usage	76 positive (48%)

Abbreviations: SES-Hollingshead Socioeconomic status, FSIQ-full scale intelligence quotient

Table 2. Regions of Interest Sampled

Frontal Gray Matter (w/anterior cingulate)
Left Hemisphere Prefrontal White Matter
Left Hemisphere Basal Ganglia
Right Hemisphere Superior Temporal Gyrus
Left Hemisphere Centrum Semiovale
Cerebellar Vermis
Left Cerebellar Hemisphere (Mixed tissues)

Results: Higher mean childhood blood lead levels were associated with reduced metabolite concentrations in the left frontal white matter, left centrum semiovale, left basal ganglia, left cerebellar hemisphere and vermis. After adjusting for the impact of age and FSIQ in all the models, increases in the mean childhood blood level correlated with a reduction of the NAA concentration level ($p=0.02$) and the Creatine (Cr) concentration level ($p=0.01$) in the basal ganglia, a marginal reduction of NAA ($p=0.05$) and Choline (Cho) ($p=0.04$) concentration levels in the cerebellar hemisphere, and a reduction of glutamate and glutamine composite (GLX) ($p=0.02$) concentration level in the vermis. Reductions of Cho ($p=0.02$) and GLX ($p=0.02$) concentration levels in parietal white matter and Cho ($p=0.02$) in frontal white matter were observed with increasing mean lifetime blood lead concentrations.

Conclusions: This study of young adults with low-to-moderate childhood lead exposure demonstrates a significant association between mean childhood blood lead levels and regional brain metabolite concentration levels. These findings indicate a diffuse reduction of metabolite concentration levels in the cerebellum, deep gray matter, and white matter, respectively. The gray matter reduction of N-acetyl aspartate is consistent with the concept that sustained childhood lead exposure results an irreversible, pattern of injury consistent with an insult from childhood and/or possibly neurodegenerative pathologies. The white matter choline changes suggest an alteration to the myelin structure. These neural alterations may be responsible for the cognitive and behavioral changes attributed to lead exposure.