

Metal toxicity and white matter in young urbanites exposed to fine particulate matter

Air pollution exposures are linked to cognitive and olfaction deficits, oxidative stress, neuroinflammation and neurodegeneration including frontal hyperphosphorylated tau and diffuse amyloid plaques in Mexico City (MC) children and young adults. Mexico City residents are chronically exposed to fine particulate matter (PM_{2.5}) concentrations (containing toxic combustion and industrial metals) above the annual standard (15 µg/m³) and to contaminated water and soil. We have shown that frontal metals correlate with olfactory bulb DNA repair genes and with frontal and hippocampal inflammatory genes. MC children have significantly higher serum actin IgG, occludin/zonulin 1 IgA, IgG, myelin oligodendrocyte glycoprotein IgG and IgM ($p < 0.01$), myelin basic protein IgA and IgG, S-100 IgG and IgM, and cerebellar IgG ($p < 0.001$). Concentrations of Ni and Cd are also significantly higher in exposed children ($p < 0.001$). CSF MBP antibodies and nickel concentrations are higher in MC children ($p = 0.03$). Air pollution exposure damages epithelial and endothelial barriers and is a robust trigger of tight junction and neural antibodies. Metals likely play a key role in the white matter pathology.

OBJECTIVE:

We are very interested in the white matter early changes in children and young adults residents in Mexico City and the association with the blood metal concentrations and APOE 4 genotype. We will do MRS, MRI and DTI (diffusion tensor imaging) in a cohort of 30 healthy individuals ages 18-40, 15F and 15 males and measure their levels of total blood metals and their lifetime exposures to PM_{2.5}.

The apolipoprotein E (APOE) ε4 allele is the most prevalent genetic risk for AD. N-acetylaspartate (NAA)/creatinine (Cr), choline (Cho)/Cr, myo-inositol (ml)/Cr, and NAA/ml will be calculated using proton magnetic resonance spectroscopy in the white matter of the frontal and parietal lobes, hippocampus, and pons. We propose to use high-resolution DTI novel image analysis tools to allow detailed regional analysis of WM microstructure properties. Measuring a local diffusivity of water constrained by neuronal environment (axons) provides insights into tissue microstructure and enables studying the brain connectivity *in vivo* non-invasively. The diffusion of water in WM is anisotropic and it is assumed that the apparent diffusivity is greater in the direction parallel to axon fibers than in the perpendicular direction. Thus, the magnitude, orientation and anisotropy of water diffusivity in WM can be used to study the organization and microstructure of the WM and the alterations related to severe exposures to air pollutants. The general finding is that diffusion anisotropy in WM increases from infancy to adulthood and subsequently decreases with aging most likely reflecting the status of WM myelination. Measurements on structural MRI data will include i. Whole brain tissue volumes of white matter, gray matter, CSF ii. Cortical regions and quantification of WM/GM/CSF, iii. Measurements of all major sub-cortical structures, including hippocampus, amygdala, caudate, putamen, globus pallidus and lateral ventricles, iv. Cortical thickness for whole brain and lobar parcellations, and v. Measurement of the WMH.

Expected results: Highly exposed children will have a significant reduction in white matter volumes and microstructural WM damage as shown by DTI FA alterations. Metals will be significantly higher in highly exposed children and the WM changes will have a strong correlation with age and metal concentrations.

AD pathogenesis may be influenced by the WM changes and combustion-related metals. We will be in the position of identifying potential anatomical targets associated with neurodegeneration in urban children, 50% of whom are showing the hallmarks of AD.

Exploring Mexican pediatric and young adult populations will help define key early biomarkers potentially related to the development of AD in later years and of utmost relevance, this knowledge will be applicable immediately to millions of people worldwide, 50 million Hispanics living in the USA, and 110 million people in Mexico. These efforts will contribute to the future development of pediatric and young adult Alzheimer's disease prevention strategies that could be applicable worldwide.