

The development and convergence of co-pathologies associated with Tau, A β , α -synuclein and TDP-43 proteinopathies in Metropolitan Mexico City children and young adults: a health crisis is in progress. Nanoparticles a common denominator?

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Complex interacting pathways play key roles in Alzheimer's disease and other fatal neurodegenerative diseases, wherein we have multiple misfolded proteins causing a range of neuropathological changes and contributing strongly to clinical symptoms, including cognition deficits as well as brain MRI, gait and equilibrium, olfaction and brainstem auditory evoked potentials (BAEPs) alterations.

Quadruple misfolded proteins (tau pre-tangles and neurofibrillary tangles, amyloid- β [A β], α -synuclein, and transactive response DNA-binding protein 43 [TDP-43]) in the same brain are common in children and young residents in Metropolitan Mexico City (MMC) exposed to high concentrations of fine particulate matter PM_{2.5} and nanoparticles. Indeed, 99.5% of 203 consecutive forensic autopsies in subjects younger than 40y, exhibit AD hallmarks, 20% Parkinson's disease and 18.7% TDP-43 pathology. Cortical tau pre-tangles, neurofibrillary tangles (NFT) Stages I-II, and amyloid phases 1-2 are documented by the 2nd decade. Of critical importance is the documentation of NFT stages III-V in 24.8% in 30-40 y old subjects.

Cognitive changes in subjects age 21.6 \pm 5.8 years are likely an indication of the neuropathology seen in forensic young cases. The Montreal Cognitive Assessment (MoCA) administered to 517 urbanites, showed an overall MoCA score of 23.92 \pm 2.82 (normal 26-30), with 24.7% and 30.3% individuals scoring \leq 24 and \leq 22, respectively (Mild Cognitive Impairment MCI \leq 24, Dementia scores D \leq 22). Cognitive deficits progressively targeted Visuospatial, Executive, Language, and Memory domains.

Alzheimer Continuum subjects have higher numbers of brain NPs versus clean air controls with normal brains. Iron rich NPs and transitional metals and non-metals are identified in neural cells and endothelium's mitochondria, Golgi, and endoplasmic reticulum and are associated with significant structural organelle damage.

We strongly support combustion and industrial NPs are key players in early ROS generation, neurovascular unit, mitochondria, endoplasmic reticulum and endolysosomal dysfunction, and catalysts for protein misfolding, aggregation and fibrillation. Fe-rich NPs respond to external magnetic fields and thus might be involved in cellular damage by agglomeration/clustering, magnetic rotation and/or hyperthermia.

Nanoparticle exposure regardless of sources carries a high risk for the developing brain homeostasis and ought to be included in the AD, PD and TDP-43 research framework. The ultimate neural damage and neuropathology could depend on NP characteristics and the differential access and targets achieved via their portals of entry. Control of NP sources becomes critical.

Neurodegenerative fatal diseases are likely the result of complex interactions between environmental and genetic factors. A more complete understanding of NPs as plausible and modifiable environmental risk factors for the development of diseases such as Alzheimer and Parkinson's, Frontal-Temporal Dementia and Amyotrophic Lateral Sclerosis evolving from childhood will help guide their early detection and prevention. We are in the midst of a devastating crisis too big to ignore, with profound health, social and economic consequences.