Culprit hidden in plain sight in Alzheimer disease development

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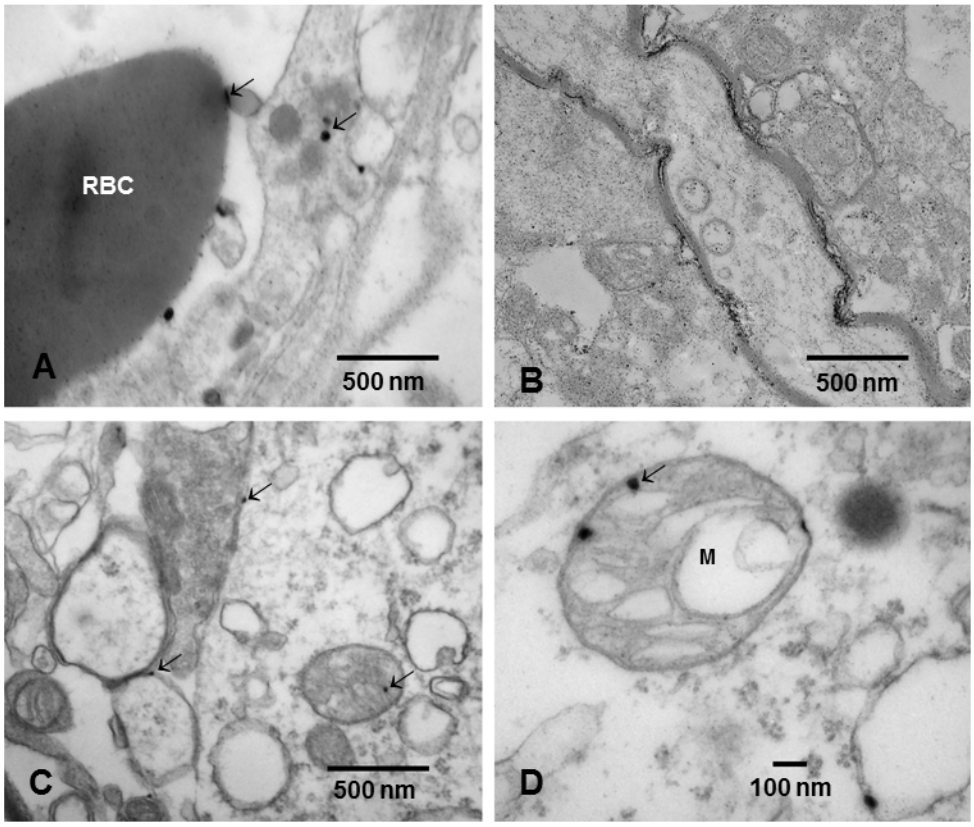

Exposure chamber in Mexico. Credit: Dr. Lilian Calderone

A new study by researchers at the University of Montana, Universidad

del Valle de México, Instituto Nacional de Pediatría, Boise State, and Universidad Nacional Autónoma de México, heightens concerns over the detrimental short- and long-term impact of airborne iron-rich strongly magnetic combustion-derived nanoparticles (CDNPs) present in young urbanites' brains. Using transmission electron microscopy, the researchers documented by abundant combustion nanoparticles in neurons, glial cells, choroid plexus, and neurovascular units of Mexico City children, teens and young adults chronically exposed to concentrations above the US-EPA standards for fine particulate matter. Residents in Mexico City are exposed from conception to harmful neurotoxic air pollutants. These findings are published in the *Journal of Alzheimer's Disease*.

The detrimental impact of these tiny particles getting into the brain through the nasal and olfactory epithelium, the lungs and the gastrointestinal system is quickly recognized by extensive alterations in critical neuronal organelles including mitochondria, as well as axons and dendrites. Since these nanoparticles are in close contact with neurofilaments, glial fibers and chromatin, the researchers are very concerned about their potential for altering microtubule dynamics, accumulation and aggregation of unfolded proteins, mitochondrial dysfunction, altered calcium homeostasis and insulin signaling, and epigenetic changes.

Mexico City children, teens and young adults have shown key markers of Alzheimer's disease (AD): hyperphosphorylated tau and amyloid plaques along with significant brain and intrathecal neuroinflammation, dysregulated immune responses, breakdown of epithelial and endothelial barriers, extensive damage to the neurovascular unit, and brain accumulation of metals associated with combustion. Moreover, these seemingly healthy young people have olfaction deficits, dysregulation of feeding hormones, deficiencies in attention and short-term memory, and below-average scores in Verbal and Full Scale IQ compared to age,

gender, and socioeconomic status-matched low air pollution residents. The cognitive problem is particularly serious for overweight female teens carrying an allele of the apolipoprotein E (APOE) ε4, the most prevalent genetic risk factor for AD.

"In the context of serious continuous exposures to high concentrations of fine particulate matter (PM 2.5) and ozone, our current electron microscopy findings and the extensive literature associating air pollutants with brain damage, the issue of who is at risk of neurodegeneration at an early age should be an urgent public health concern," said Dr. Lilian Calderon-Garcidueñas. "The effects of poverty, urban violence and urban stress on impaired cognitive skills are also very important for the developing brain and can't be ignored. We know gender, BMI, and APOE influence children's cognitive responses to air pollution."

According to the researchers, the problem of having combustion-derived nanoparticles in children's brains—developing brains—is very serious. These particles are ubiquitous and present in high concentrations in children as young as 3 years old. The particles contain transition neurotoxic metals and they are certainly causing extensive brain damage in key organelles. "The predominant combustion particles in young brains have properties that enable them to cause oxidative damage because these nanoparticles are capable of crossing all barriers. No barrier is spared," Dr. Calderón-Garcidueñas emphasized.

Angélica González-Maciel added, "People with children and teens struggling in school and facing a significant increase of violence in school, streets, parks, and public transportation are deeply concerned about the impact these particles have on children's behavioral patterns and academic performance and parents question what they can do to protect their families".

All involved researchers agreed that in spite of the driving restrictions policies [that are clearly ineffective (Davis LW. Sci Rep 7: 41652, 2017)], millions of Mexico City residents continue to be exposed to very unhealthy concentrations of both PM 2.5 and ozone, both known risk factors for AD.

"Our results," said Dr. Calderón-Garcidueñas, "highlight the urgent need for significantly decreasing the concentrations of fine particulate matter and ozone in Mexico City and the adjacent polluted states. Multidisciplinary intervention strategies could provide paths for prevention or amelioration of air pollution targeted cognitive deficits and possible long-term AD progression."

The combined effects of combustion-derived nanoparticles, residency in a highly-polluted city, poor nutrition, obesity, metabolic syndrome, urban stress, lower brain and cognitive reserves, and APOE ε4 could lead to an acceleration of neurodegenerative changes among precarious young brains.

The authors concluded: highly oxidative, combustion nanoparticles entering young developing brains—the culprit hidden in plain sight in Alzheimer's disease development—constitute a very serious public health issue, with grave social and economic consequences.

Efforts should also be aimed to identify and neuroprotect high risk young populations. Unfortunately, to date that is not happening.

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