The development and convergence of co-pathologies associated with Tau, Ab, 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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Session 5: Health and Toxicity
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Consumption of > 40 million liters of petroleum fuels per day

> 50,000 industries and > 6 million cars

Valley with obstruction of air movement, at 7350 feet

An involuntary, very effective exposure chamber for 21.8 million people
Metropolitan Mexico City 21.8 million people.

Typical Day ozone and PM
Hallmarks of Alzheimer disease are evolving relentlessly in Metropolitan Mexico City infants, children and young adults. APOE4 carriers have higher suicide risk and higher odds of reaching NFT stage V at ≤ 40 years of age.

203 consecutive autopsies age $25.36 \pm 9.23$ years, including 44 children age $12.9\pm4.9$ years

Quadruple abnormal protein aggregates in brainstem pathology and exogenous metal-rich magnetic nanoparticles (and engineered Ti-rich nanorods). ER 2020

Neuropath golden markers for Alzheimer, Parkinson and TDP-43 (frontotemporal dementia and ALS)
Primary outcomes: staging of Htau and beta amyloid (Braak et al.,) per decade and cumulative PM$_{2.5}$ (CPM$_{2.5}$) above standard. Apolipoprotein E allele 4 (APOE4), age and cause of death were secondary outcomes.
203 FORENSIC AUTOPSIES AVERAGE AGE:
25.36 ± 9.23 years, 44 children age 12.9±4.9 years

HYPERPHOSPHORYLATED TAU
FORENSIC AUTOPSIES

Extracellular deposits of insoluble amyloid-beta (Abeta)
Tau per decades

Age: 0–20 years

Age: 21–40 years

- NFT stage V
- NFT stages III–IV
- NFT stages I–II
- Pretangle stages 1a, 1b
- Pretangle stages a–c
- Htau 0
Beta amyloid per decades

Age: 0–20 years

Age: 21–40 years

Legend:
- Aβ Phase 5
- Aβ Phase 4
- Aβ Phase 3
- Aβ Phase 2
- Aβ Phase 1
- Aβ Phase 0
ACCUMULATIVE SUICIDE RISK

For APOE 3 Subjects

For APOE 4 Subjects
Immunohistochemistry and Electron Microscopy. First decade of life
Immunohistochemistry and Electron Microscopy. Second decade of life
Electron Microscopy. First decade of life
Electron Microscopy and Toluidine 1µm sections. 1st and 2nd decades of life
Neurofibrillar tangles (NFT) Stages I-II, amyloid phases 1-2, Htau in substantia nigrae, auditory, oculomotor, trigeminal and autonomic systems in the 2nd decade.

NFT stages III-V was present in 24.8% of 30-40 y old subjects.
Immunohistochemistry
3rd and 4th decades of life
Quadruple pathology overlap
ALZHEIMER (99.5%), PARKINSON (23%) AND TDP-43 PATHOLOGY (18%) (FRONTOTEMPORAL DEMENTIA AND ALS).

Quadruple abnormal protein aggregates in brainstem pathology and exogenous metal-rich magnetic nanoparticles (and engineered Ti-rich nanorods). The substantia nigrae is a very early target in young urbanites and the gastrointestinal tract a key brainstem portal.
The Montreal Cognitive Assessment (MoCA) was administered to 517 urbanites, age 21.60±5.88 years, with 13.69±1.28 formal education years, in Mexican PM2.5 polluted cities.
MoCA Normal scores

• NORMAL COGNITION 26-30

• MILD COGNITIVE IMPAIRMENT 24-25

• DEMENTIA SCORES ≤23
RESULTS

Residency in polluted cities is associated with progression of multi-domain cognitive impairment affecting 55% of Mexican seemingly healthy youth age $21.60\pm 5.88$ years, with $13.69\pm 1.28$ y of formal education.

MoCA score was $23.92\pm 2.82$, and 24.7% and 30.3% scored $\leq 24$ and $\leq 22$, respectively (MCI$\leq 24$, AD$\leq 22$).

Average age for dementia MoCA scores was $22.38\pm 7.7$ years.
Pie Chart of Mexico City subjects of age less than or equal to 30 years.

- Normal (>=26)
- MCI (24-25)
- AD (<=23)
MoCA total scores
517 urbanites, age 21.60±5.88 years
A major impediment in early diagnosis of Alzheimer's disease (AD) is the lack of robust non-invasive biomarkers of early brain dysfunction.

We measured brainstem auditory evoked potentials in MMC clinically healthy children (8.52±3.3 years) and adults (21.08±3.0 years, 42.48±8.5 years, and 71.2±6.4 years) compared to clean air controls.
MMC children had decreased latency to wave I, delays in waves III and V, and longer latencies for interwave intervals, consistent with delayed central conduction time of brainstem neural transmission.

Young adults have significantly shortened interwave intervals I-III and I-V. By the 5th decade, wave V and interval I-V were significantly shorter, while the elderly cohort had significant delay in mean latencies and interwave intervals.

Compensatory plasticity, increased auditory gain, cochlear synaptopathy, neuroinflammation, and AD continuum likely play a role in the evolving distinct auditory pathology in megacity urbanites.
Gait and balance disturbances are common in young urbanites and associated with cognitive impairment. Air pollution and the historical development of Alzheimer’s disease in the young. ER 2020

We tested gait and balance with Tinetti and Berg tests in 575 clinically healthy subjects, age 21.0 ± 5.7 years who were residents in Metropolitan Mexico City, Villahermosa and Reynosa.

In the 575 cohort, 75.4% and 34.4% had abnormal total Tinetti and Berg scores and high risk of falls in 17.2% and 5.7% respectively.
Magnetic nanoparticles in targeted brain areas

![Graphs showing SIRM values in different brain areas over age]

**A** Substantia Nigra

**B** Tectum

**C** Cerebellum

**D** Box plots comparing SIRM values between Substantia Nigra (SN), Tectum (Tec), and Cerebellum (Cereb)
NP characterization by TEM and EDXS in human granular cell layer, cerebellum. (A) A cluster of NPs in granular cells observed by TEM and indicated by red square. (B) EDXS identifies the cluster composition: Fe and traces of Cu and Si. (C) A spherical ~80 nm NP (red square). (D) Typical rounded crystal morphologies and fused surface textures of combustion and friction derived nanoparticles (CFDNPs) are co-associated with other reactive metals including Ti and Al, as well as metalloid elements like Si. (B, D) Ni traces reflect the Ni TEM support grid.
HAADF-STEM neuroenteric sample Ti nanorods and Fe NPs. ER 2020
Metal and non-metal nanoparticles in mitochondria. ER 2020
Sources of nanoparticles in MMC

Emissions from internal combustion engines burning fossil fuels in motor vehicles—unregulated diesel engines and equipment—are responsible for total regional and urban MMC pollution.

Fixed sources

E-Waste

Food, cosmetic, pharmaceutical, and medical utilization

Nanoparticles as a sink for organic and inorganic co-contaminants.
NPs Damage to the brain

- Oxidative damage i.e., formation of free radicals
- Direct damage of membrane organelles
- Interference with metabolic processes
- *de novo* mutations of DNA
- Apoptosis, autophagy, immune-responses, neuroinflammation and brain-blood-barrier BBB damage
- Magnetic damage i.e., heat production, alignment and/or rotation in response to magnetic fields.
Neurodegenerative diseases

Exposure to air pollutants has been associated with the most common neurodegenerative fatal diseases affecting millions of people across the world:

Alzheimer and Parkinson’s diseases, Fronto-temporal dementia and ALS.
To date, NPs remain an underexplored environmental toxicant in the development of common neurodegenerative diseases.
Environmental NPs and body distribution

For health purposes, it is critical to understand entry routes and profiles of NPs capable of crossing different barriers. Toxic NPs are typically smaller, inorganic in nature and water insoluble and toxicity appears linked to exposure dose and frequency.
Neural damage and neuropathology could depend on NP characteristics, genetic susceptibility, comorbidities and the differential access and targets achieved via their portals of entry.
Human Brains exposed to NPs

10y old boy, IQ 111, several targeted cognitive deficits

45Y FEMALE, MoCA 21
NANOPARTICLES

We need to characterize UFP exposures in urban populations. We desperately need to quantify and characterize NPs concentrations, composition, size, shape and location in neural cells in specific brain target areas in exposed individuals.

We need working hypothesis establishing the association between nanoparticles and neuropathology hallmarks taking into account there is considerable overlap between misfolded protein pathologies.

We need support from multidisciplinary groups and resources to do the research.
Highly polluted city exposures consequences

1. OLFACTORY DEFICITS
2. COGNITIVE DEFICITS
3. VESTIBULAR AND AUDITORY ALTERATIONS
4. SYSTEMIC INFLAMMATION
5. BRAIN INFLAMMATION
6. HEART INFLAMMATION
7. RESPIRATORY AND CARDIOVASCULAR MORBILITY AND MORTALITY
8. NEURODEGENERATIVE DISEASES INCLUDING Alzheimer and Parkinson

• Etc., etc., etc.,

Detail of a Painting by Lilian Calderon-Garciduenas. The girl in blue