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Neuroinflammation and Air Pollution: Investigating the Link between Particulate Matter and Neurodegeneration

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ABSTRACT

The emergence of ambient air pollution and especially fine particulate matter PM2.5 has taken a centre stage as a key environmental risk factor in neurodegenerative disorders. To provide evidence about the complex relationships between neuroinflammation and air pollution, our analysis is based on the empirical research carried out during the last few years. Recent evidence shows that PM2.5 enters the central nervous system (CNS) through the olfactory bulb and the systemic circulation, which leads to the cascade of nitro-oxidative stress and microglia hyper activation. These incidences damage the blood-brain barrier (BBB) and promote the misfolding of hallmark proteins including amyloid-beta and alpha-synuclein, thus playing a role in the pathogenesis of Alzheimer and Parkinson diseases. The molecular processes and pathways that are observed, the current research limitations, which are primarily the complexity of multi-pollutant interactions and future opportunities, such as epigenetic biomarkers, AI-based predictive modelling have been outlined in the present paper. The findings highlight the importance of the fact that air pollution is not just an issue related to respiration it is a major changeable threatening condition to brain health on a global scale.

KEYWORDS: *AI, Biomarkers, Neurodegeneration, Oxidative Stress, Pollution*

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INTRODUCTION

The neurodegenerative disease pandemic is a silent pandemic currently facing the global public-health environment. With the ageing of the world population, the prevalence rates of the Alzheimer disease (AD), Parkinson diseases (PD) and amyotrophic lateral diseases (ALS) are expected to grow exponentially. Traditionally genetic mutations and inherent biological aging have been recognized as the major causes of such conditions in the scientific community, but paradigm shift has been experienced in the past decade making it evident that such pathogenesis and cognitive decline are instigated by environmental factors, especially air pollution (ambient).1

Air pollution is a heterogeneous mixture of gaseous pollutants, liquid droplets and solid particles. Particulate matter (PM) is one of them further separated into PM10 (coarse), PM2.5 (fine) and PM0.1 (ultrafine) based on the aerodynamic diameter. Though upper respiratory tract has a significant capacity to retain PM10, PM2.5 and PM0.1 have the special ability to reach deepest alveolar surfaces and reach the systemic circulation.2 The past few years research have now provided the same kind of molecular evidence that these particles are not localized to the respiratory or cardiovascular systems. They are instead, neurotoxicants which are able to penetrate the CNS via various physiological pathways.3

The primary chronic neuroinflammatory stage between air pollution and cerebral damage is the central one. Contrary to acute inflammation, a protective response to an injury, neuroinflammation caused by PM2.5 is characterized by a low-grade and chronic immune response in the brain. The key characteristics of this process are chronic microglia and astrocyte switching on which is a generic feature of the brain macrophages, microglia.4 The recent longitudinal research shows that the level of pro-inflammatory markers in cerebral-spinal fluid and brain tissue are significantly higher in people living in the areas of high pollution compared to the rural areas.[5] In addition the problem of multiple-hit hypothesis introduction argues that air pollution is one of the main stress factors that reduce the brain threshold to other pathological demands including genetic tendency or metabolic stressors.[6]

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Mechanisms of Neurotoxicity

Entry Pathways to the CNS: The entry of the brain by PM2.5 is observed to take three major pathways that have different regional exposures:

- The Olfactory-Nigrostriatal Pathway: Ultrafine particles (PM0.1) do not have to circumvent the BBB. On inhalation, the particles settle on the olfactory mucosa are taken inside the olfactory sensory neurons by endocytosis and then conveyed along the axon by the olfactory nerve, cribriform plate and directly to the olfactory bulb and frontal cortex.7
- The Systemic/Vascular Pathway: PM2.5 spreads to the circulatory system and causes an inflammatory reaction in the body.

This cytokine storm raises the amount of IL1-2, IL-6 and TNF- alpha which subsequently destroy endothelial cells in the BBB, block tight-junctional proteins like claudin-5 and occludin, and thus predisposes the addition of neurotoxic elements into the brain parenchymal.[8]

- The Gut-Brain Axis Pathway: Introduced in terms of gastric content, the particles trigger gut dysbiosis, which causes a significant rise in the proportion of Firmicutes to Bacteroidetes. This imbalance of the microbes increases the intestinal permeability (leaky gut) and allows the bacteria endotoxins such as lipopolysaccharide (LPS) to be absorbed by circulation and stimulate the brain through the vagus nerve.[9]

Super-Spreader Proteins Molecular catalysts

One of the most notable studies published in 2025 found out that PM2.5 was a molecular catalyst of protein misfolding. The misfolding of α-synuclein into a super-spreader strain is triggered by traffic-related PM in models of Parkinson disease.10 This strain is highly aggressive, neurotoxic and resistant to the endogenous clearance processes (autophagy) of the brain in comparison to aggregates that are only formed due to aging. These aggregates serve as templates to which healthy proteins are recruited to a pathological form, which carries on through the entire brain prion-like fashion.[11]

Nitroosylation Nitro-oxidative Stress and S-Nitrosylation

Nitro-oxidative stress has now been recognized as a cascaded process in which generation of nitric oxide (NO) comes before the hereditary oxidative injury. One of the landmark seminal findings in 2025 aberrant S-nitrosylation in which surplus NO caused by inflammation-related pollution is bound to proteins like CRTC1.11 This alteration prevents the CRTC1 nuclear translocation and the activation of genes necessary to make a long-term memory and synaptic plasticity thus, establishing a first-order molecular connection between urban smog and cognitive impairment.[12]

Contribution of NLRP3 Inflammasome

PM2.5 can be used as a strong activator of NLRP3 inflammasome in microglia. And microglial ingestion of particulate matter results in intracellular stress which leads to the assembly of the NLRP3 protein complex which activates caspase-1. The processing of pro-IL-1-beta into the active highly inflammatory form occurs through caspase-1. This type of neuroinflammation, which is caused by inflammasomes, is especially detrimental since it leads to pyroptosis which is a form of cell death that releases toxic cellular components into the brain space.[13,14]

Impact of Specific Particulate Constituents

The more recent speciation studies reveal that the chemical composition of PM is even more significant than its size. Specifically, the potency of transition metals such as iron, copper and manganese in brake-wear and industrial emissions is high. The metals induce the Fenton reaction in the brain which produces highly reactive hydroxyl radicals which lead to the lipid peroxidation of neuronal membranes.15 Also the adsorption of polycyclic aromatic hydrocarbons (PAHs) onto the soot particles can activate the aryl hydrocarbon receptor (AhR) in astrocytes which interferes with the lymphatic system that forms a part of the brain waste-clearance system and thus inhibits the drainage of amyloid.[16]

Challenges in Current Research

There are various significant challenges pursuing the research of the air pollution and neurodegeneration:

- Heterogeneity in the pollutant: PM2.5 is a toxic cocktail the composition of which changes depending on the source. The issue facing research is that the toxicity of a particle is not directly related to its mass but on its chemical composition. It is also highly challenging to bring such mixtures to the laboratory and standardize them.[12,17]
- The Time Lag Effect: The neurodegeneration process is progressive, thus it is hard to determine the dose of life-course that an individual has received. The majority of the research is based on the existing residential addresses which fails to consider the previous mobility or indoor air quality.[18]
- Translational Model Limitations: Majority of research studies are based on rodent models. But relative to the size of the brain, human beings possess much smaller olfactory surfaces than rodents, which implies that the olfactory route may receive overrepresentation in animal research, as compared to the systemic vascular route which is under-researched.[13,19]
- Co-Pollution Interactions: Human beings are not exposed to PM2.5 alone. The interaction between PM and gaseous air pollutants, such as Nitrogen Dioxide (NO2) or ground-level Ozone (O3) is poorly comprehended and probably increases the inflammatory process.[20]

Future Aspects and Perspectives

- The following decade of research will lean more towards individualised prevention and hi-tech diagnostics:
- Exposomics and AI: The application of AI to simulate the exposome, the cumulative environmental exposures through all of lifetime history in an individual in predicting disease risk depending on residential history and genetic predisposition.[15]
- Liquid Biopsies and Epigenetics: The detection of DNA methylation or histone modification as the early warning biomarker in blood-derived extracellular vesicles.16 These time pieces might inform a medic of the precise amount of air pollution that has affected the brain of a patient on a molecular level.
- Pharmacological Shields: The development of specific drugs that inhibit the NLRP3 inflammasome or the use of antioxidants including Astaxanthin, to counteract the effects of pollution in the production of ROS.[17] Chelators are also under investigation that can bind the metals in the nose and prevent their entry into the brain.
- Smart Urban Planning: With this information, it is possible to design low-pollution buffers around educational establishments and hospitals, namely, covering children and the older generation with the most neurotoxic streets.

DISCUSSION

These studies validate the fact that air pollution is a powerful contributor of neuroinflammation. Surprisingly, the effect is not just on the elderly, but even children in the most polluted cities have shown the signs of Alzheimer like A 42 deposition implying that pollution in young children predisposes the brain to the disease.[18] This results in a synergy of vulnerability in which with bad air quality, socioeconomic stress and unantioxidant-rich diet, the load of dementia becomes heavier in marginalised communities.[1,19]

A new learning curve in the discourse is the propagation of the protein aggregates caused by pollution in a prion-like manner. When air pollution can cause a certain type of alpha-synuclein

(a more resilient form as compared to the incurable one) to develop it means that the current clinical trials of Parkinson can be only unsuccessful since they are being tested with an entirely different strain of the protein in question.[10,11] This indicates that environmental neurology must be a sub-discipline on its own, dealing with the causes of various clinical phenotypes of the disease in response to various chemical fingerprints of pollution.

Moreover, there are far reaching economic consequences. Since long-term care incurs exponentially in the world because PM2.5 leads to the occurrence of dementia. As per the economic models, the subsequent savings of trillions of healthcare costs could be achieved through achievement of the 2021, WHO air quality standards by simply postponing the average onset of AD by at least two years.20 Multiple-hit is the most popular model now, in which air pollution is a cumulative stressor which decreases neurodegeneration threshold in genetically predisposed persons.

CONCLUSION

The ultimate interface between PM2.5 and neurodegeneration are neuroinflammation. Persistent exposure initiates a vicious loop of microglial stimulation, nitro-oxidative damaging and protein misfolding. Although the problem of assessing mixed-pollutant toxicity is still unresolved, there is a way forward to the prevention of future through the introduction of AI-driven exposomics and epigenetic biomarkers. To safeguard the neurological health, it is necessary to consider air quality control as one of the major measures of preventing the global epidemic of dementia and Parkinson disease.20

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