Impact of Environmental Exposure, Risk factors, Biomarkers in Parkinson's Disease: A Brief and Comprehensive review

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Abstract. Parkinson's disease (PD) is defined by the progressive death of nigrostriatal dopaminergic neurons, which is accompanied with intracellular Lewy bodies. The condition is influenced not only by genetic predispositions but also by environmental factors. This paper reviews the pivotal role of environmental exposure risk factors-such as pesticides, heavy metals, solvents, and air pollutants in the development and progression of parkinsonism. It delves into the mechanisms through which these environmental toxins instigate neurodegeneration, exacerbating the underlying pathology. Moreover, the review discusses the emerging significance of biomarkers in assessing environmental exposure levels and predicting individual susceptibility to parkinsonism. Biomarkers offer promise in unravelling the intricate biological processes involved in disease onset and evolution, potentially enabling early detection and intervention strategies. Understanding the intricate interplay between environmental exposures, biomarkers, and parkinsonism is paramount for devising preventive measures and targeted therapeutic interventions.

Keywords: Parkinson's disease; heavy metals; pesticides; mptp.

1. Introduction

Parkinson's disease is a neurodegenerative condition that worsens with time and is marked by motor symptoms like stiffness and tremors. The disease is caused by a reduction in dopamine levels brought on by the death of dopaminergic neurons in the brain. Parkinson's disease encompasses more than just shaky movements, non-motor symptoms such as sleep disturbances, digestive disorders, and exhaustion also play a key role. Recognizing and addressing these non-motor components is critical for successfully managing the illness.[1]

Parkinson's disease, a neurological movement illness, affects more than a million Americans and four million worldwide. While some cases begin before 50 (early onset), the typical onset age is around 60. This demonstrates the wide-ranging impact of Parkinson's disease across age groups.[2] Parkinson's disease is classified into two types: familial, which is inherited through certain genetic patterns, and sporadic (idiopathic), which is believed to be caused by gene-

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environment interactions. This shows the condition's various manifestations, which combine hereditary and environmental influences. [3]

The genesis of Parkinson's disease has been difficult to understand and appears to involve a complicated interaction of hereditary and environmental variables. Alpha-synuclein gene (SNCA) mutations that produce autosomal dominant disease are linked to early cognitive impairment and in rare cases even induce dementia from the beginning. This is consistent with a diagnosis of dementia with Lewy bodies (DLB).[4]

MPTP, a neurotoxin, transforms to MPP^+ in the brain, altering dopamine neurons, weakening mitochondria, and leading to Parkinson's disease. The Environmental Hypothesis links Parkinson's disease to toxins such as MPTP, which is present in IV drug users, emphasizing the role of the environment in disease.[5] This narrative review investigates how environmental and lifestyle factors, such as smoking, coffee, pesticides and heavy metals affect Parkinson's disease through epigenetic changes, focusing on their well-studied involvement in PD. While smoking and physical activity provide protection against Parkinson's disease, environmental variables such as pesticide exposure and traumatic brain damage increase the disease's risk. Gene mutations are the cause of familial Parkinson's disease (PD), although environmental variables, neuroinflammation, and mitochondrial dysfunction also play a role in PD.[6]

Parkinson's disease is significantly correlated with the SNCA, LRRK2, MAPT, and low-frequency GBA variations, according to GWAS and candidate gene studies, highlighting their critical roles in the pathophysiology of the disease.[7]

Parkinsonism, like Parkinson's disease, causes movement impairments and has several risk factors. Increasing age is a major role, with older persons being more vulnerable. Genetic predispositions also play a role, with certain cases exhibiting genetic characteristics. Environmental factors, such as exposure to poisons or pollutants, add to the risk, as do head traumas, particularly repeated concussions. Long-term use of some medications, particularly antipsychotics and nausea meds, can cause symptoms similar to Parkinsonism.[8] In addition, underlying medical problems like stroke or multiple system atrophy, as well as vascular variables like high blood pressure or diabetes, increase risk. While smoking may lessen the risk of Parkinson's disease, its effect on Parkinsonism is unknown. However, strong alcohol use may increase susceptibility.[9]

Biomarkers for Parkinsonism, including Parkinson's disease, offer valuable tools for early detection and tracking disease progression. Key candidates include alpha-synuclein aggregates detected in cerebrospinal fluid or through imaging, alongside measures of dopamine levels using PET scans.[10]Neuroimaging techniques like MRI reveal structural and functional brain changes, while peripheral markers in blood or saliva provide insights into inflammation and oxidative stress. Olfactory dysfunction and REM sleep behaviour disorder serve as early indicators, with quantitative gait and movement analysis offering objective measures of motor function. Though promising, these biomarkers require further validation and standardization before widespread clinical use, with potential for enhanced accuracy through combination approaches.[11]

2. Impact Of Environmental Exposure

Research on the potential link between Parkinson's disease and environmental toxins such as pesticides and industrial chemicals is lacking, demanding further research into occupational exposure risks and protective measures.[12]Research on Parkinson's disease (PD) and the workplace has shown that there are a variety of risks. For example, exposure to pesticides and heavy metals in agriculture and electrical vocations raise risk, but there are no consequences in these fields. It is debatable if living in a rural area increases the incidence of Parkinson's disease (PD); pollution from industry and transportation may be a factor.[13]

2.1 Heavy Metals

Metal elements demonstrating significant biological toxicity and concentrations greater than 5 g/cm3 are referred to as heavy metals (HMs). Examples include cadmium (Cd), chromium (Cr), mercury (Hg) iron (Fe), manganese (Mn), copper (Cu), and lead (pb).[14] The pathophysiology of numerous neurodegenerative disorders is influenced by the aberrant distribution of metals in susceptible regions of the brain, demonstrating similar molecular processes involving metal dys homeostasis. In the brain, neurotoxins have the ability to cause oxidative stress and interfere with neurotransmission, especially affecting the basal ganglia. These harmful consequences are exacerbated by reactive oxygen species, which are produced via the Fenton Haber-Weiss reaction.[15]

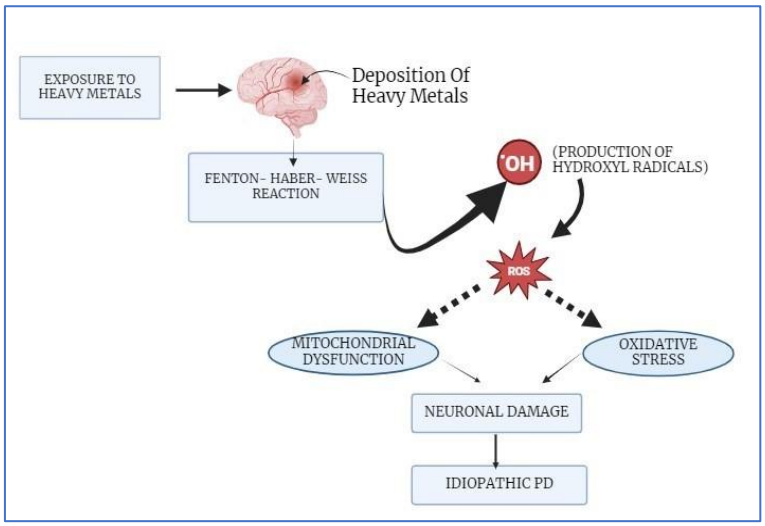

Fig. 1 Influence of Heavy Metals in Parkinson's Disease.

Metals And Parkinson's Disease

Parkinson's disease is mainly triggered by metal depletion and exposure (PD). For example, iron shortage is associated with neurological impairment, whereas iron buildup in particular brain regions is linked to the onset of Parkinson's disease. PD and exposure to several metals are linked in epidemiological studies, which raises the risk in specific employment.[16]

i. Iron and Parkinson's Disease:

For several biological processes, including the generation of neurotransmitters, iron (Fe) is essential. Parkinson's disease (PD) and other motor-associated disorders are correlated with higher concentrations of Fe in brain areas relevant to motor function. Dopaminergic neurons may be harmed by unbalanced Fe levels .[17]Antioxidant-rich neuromelanin guards against low iron-induced dopamine toxicity, but in the presence of increased iron, it becomes a pro-oxidant. It stores iron, and oxidative stress in Parkinson's disease may be accelerated by its breakdown.[18]

ii. Manganese and Parkinson's Disease:

Manganese is essential for the activity of enzymes and physiological processes. Although excessive exposure can cause neurotoxicity and may be linked to Parkinson's disease, Exposure to manganese, either from industrial or environmental sources, has been linked to Parkinson's disease, hence drawing attention to occupational dangers and environmental health problems.[19]Overexposure to manganese (Mn) can exacerbate neurodegenerative illnesses by increasing iron (Fe) accumulation and disrupting mitochondrial function, which can result in oxidative stress. Glutamate receptor sensitivity is increased by excess manganese in basal ganglia, which can result in oxidative damage and motor dysfunction.[20]

iii. Mercury and Parkinson's Disease:

Mercury is extremely hazardous, especially methylmercury, which enters the brain effectively across the blood-brain barrier and the Hg-L-cysteine complex. Mercury affects endoplasmic reticulum function and ribosomal activity, which alters protein synthesis and brain development. Manganese mimics the etiology and symptoms of Parkinson's disease (PD), including oxidative stress and mitochondrial dysfunction, by inducing ROS, dopamine cell death, and dopamine dysregulation.[21]

iv. Copper and Parkinson's Disease

Reduced amounts of Cu in the substantia nigra accelerated the α-Syn aggregation, according to biochemical investigations conducted on PD brains. In mouse models, increasing Cu enhanced motor performance, whereas exposure to Cu and Fe caused α-Syn aggregation.[22] In order to produce dangerous species like dopamine quinones and radicals, copper (Cu) stimulates the oxidation of dopamine. Cu may have a role in dopamine oxidation and the synthesis of neuromelanin, as indicated by the highest quantities of Cu in the substantia nigra.[23]

v. Lead and Parkinson's Disease

In Parkinson's disease, Pb damages dopaminergic neurons, causing an imbalance in extracellular dopamine levels and potential neurotoxicity in the CNS. Lead poisoning inhibits ALAD, resulting in a buildup of ALA -ALA oxidizes, producing free radicals and triggering lipid peroxidation through ferrous ions, worsening cellular damage.[24]

2.2 Pesticides: Pesticides used for pest management offer health risks to both people and non-target animals. They've been connected to cancer, neurological illnesses including Parkinson's, and fertility difficulties.[25]

A study of young-onset Parkinson's disease patients discovered links with insecticide or herbicide exposure, previous residency in fumigated buildings, and rural residency. While some research employing self-reported pesticide use found no link, others indicate a dose-dependent relationship with PD prevalence.[26]

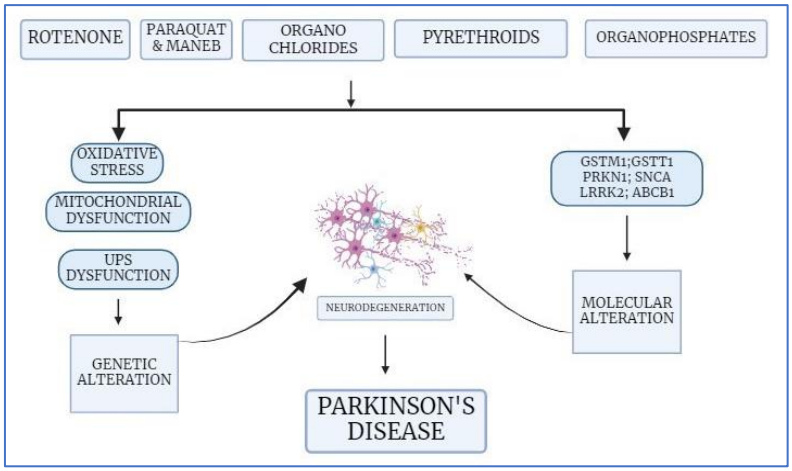

Fig. 2 Role of Pesticides in Progression of Parkinson's Disease.

a) Rotenone: Initially thought to be safe due to its organic nature, the chemical inhibits Complex I of the electron transport chain, resulting in neurodegeneration and oxidative damage, implicating it in neurodegenerative illnesses such as Parkinson's. Rotenone causes alpha-synuclein and polyubiquitin positive clumps in dopamine neurons, similar to Parkinson's disease. It also promotes tau and amyloid protein aggregation. Motor decline may not be caused primarily by dopaminergic malfunction, indicating a broader mitochondrial influence.[27]

b) Paraquat & Maneb: Paraquat, an oxidative stressor, is linked to Parkinson's disease (PD) in human studies, with synergistic effects alongside maneb. It induces tissue damage via superoxide free radicals, alpha synuclein upregulation, and dopaminergic neuronal cell death. Prenatal exposure may heighten susceptibility to neurotoxicants, supported by human epidemiological studies.[28]

c) Organophosphates: Organophosphates, which cause acute neurotoxicity, represent long-term exposure concerns associated with Parkinson's disease. Animal studies suggest that neonatal exposure to chlorpyrifos results in long-term dopaminergic cell loss and microglial activation. Variations in paraoxonase activity influence vulnerability to neurotoxic effects, hence increasing the incidence of Parkinson's disease.[29]

d) Organochlorines: Organochlorine pesticides, which are now banned due to neurotoxicity concerns, have been linked to Parkinson's disease. Dieldrin and HCH decrease mitochondrial activity and disturb calcium homeostasis in dopaminergic cells, thereby leading to Parkinson's disease development. Serum and postmortem studies support the link to Parkinson's disease.[30]

e) Pyrethroids: Pyrethroids, which are prevalent in household pesticides, may indirectly increase dopamine transporter mediated dopamine absorption, resulting in death of dopaminergic cells in animal experiments .Limited human data suggests a general link between pesticide exposure, notably pyrethroids, and Parkinson's disease (PD), requiring further examination.[31]

f) 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): MPTP transforms to MPP^+ and inhibits Complex I, causing dopaminergic neurons to be damaged while leaving non-dopaminergic regions unaffected. Postmortem investigations indicate long-latency neurotoxicity in conjunction with continuing inflammation. MPTP research helps to build animal models and investigate neuroinflammation-targeted PD therapies.[32]

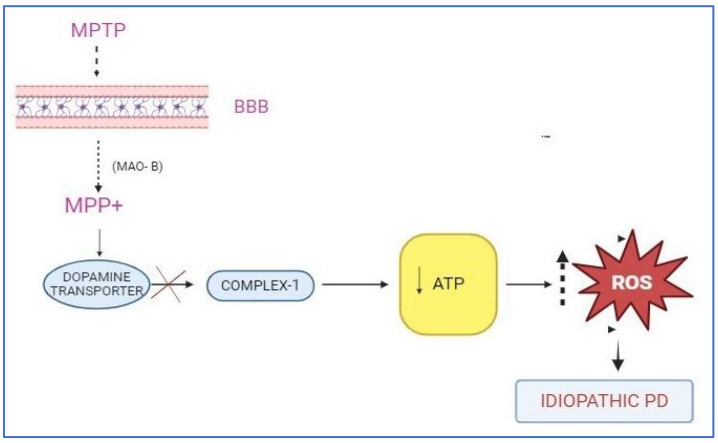

Fig. 3 Role of MPTP in Progression of Parkinson's Disease.

2.3 Air pollutants: Airborne contaminants can cause α-synuclein neuropathology in the olfactory system, breaking the bloodbrain barrier. Although epidemiological evidence is insufficient, it suggests that air pollution is linked to Parkinson's disease. Air pollution have also been linked to olfactory impairment and neuroinflammation, highlighting the need for more research into the underlying biological mechanisms.[33]

2.4 Cigarette smoking: According to studies, there is an inverse link between cigarette smoking and Parkinson's disease (PD) risk, which persists even after quitting. This calls into question the concept that habits change during the premotor period. While some studies demonstrate neuroprotective effects, the evidence is based on non-representative models of PD disease. Smoking is associated to rapid eye movement sleep behaviour problem but not to Parkinson's disease conversion.[34]

2.5 Coffee and Tea: Consuming caffeine reduces the risk of Parkinson's disease (PD) by 25%, which is due to caffeine's A2A antagonist characteristics. However, the research is based on preclinical models using toxins. Regular tea use is also associated with a lower incidence of Parkinson's disease, while a Chinese study showed no link with green tea, implying variance across populations and tea kinds.[35]

2.6 Urbanization: Surveys on ALS and place of residence show varied results, with some indicating a higher risk in urban regions and others finding no association. Agricultural

chemicals and diesel exhaust in rural regions, as well as air pollution in cities, may all contribute. Pesticides, especially glyphosate, are implicated, however evidence for electromagnetic field involvement is equivocal. More study involving geographical data and pollution measurements is required.[36]

2.7 Water pollution: Residents of Reggio Emilia, Italy, who were exposed to high levels of selenium in their drinking water were more likely to develop ALS, particularly females. Heavy metals such as manganese in contaminated water sources may also contribute to neurological disorders.[37]

2.8 Climate change: The outcomes, revealed that there is significant correlations between epidemiological and climate data in PD patients. but no significant correlations in AD/D and ALS/MND patients, could be attributed to the fact that AD/D and ALS/MND patient's neurons are less vulnerable to heat-related degeneration effects than PD patients. PD patients' SNpc DA neurons, which are naturally fragile due to their structure and function, fail under extreme oxidative stress caused by climate change.[38]

3. Risk Factors

The current risk factors for Parkinson's disease (PD) are:

3.1 Age: Aging damages substantia nigra neurons, diminishing their ability to withstand assaults such as mitochondrial malfunction and protein degradation changes, resulting in Parkinson's disease symptoms. Aging raises the risk of oxidative damage, which contributes to Alzheimer's disease and dementia, as well as reduced motor coordination and muscle tone in Parkinson's disease.[39]

3.2 Genetics: While most cases of Parkinson's disease are sporadic, meaning they occur at random and have no apparent hereditary origin, some genetic mutations and variations can enhance vulnerability to the disease. A family history of Parkinson's disease or kindred movement disorders may increase risk. Genome-wide association studies (GWAS) identifies genetic risk factors in sporadic Parkinson's. Microarrays detect SNPs, highlighting genes associated with Parkinson's disease. Sporadic instances are influenced by SNCA and LRRK2.[40]

3.3 Head Trauma: Traumatic brain injuries, particularly repeated concussions, are linked to an increased chance of acquiring Parkinson's disease later in life. Oxidative stress, proteostasis dysregulation and neuroinflammation are among the mechanistic linkages between TBI and dementia. disease-specific associations include TAR DNA binding protein 43 in ALS/FTD, alphasynuclein in PD.[41]

3.4 Sex: Men are slightly more likely than women to develop Parkinson's disease, but the reasons for this gender difference are unclear. Sex variations influence Parkinson's disease neuroinflammation, as evidenced by differing serum immunopurified and cerebrospinal fluid marker levels. Animal models exhibit varying inflammation patterns, underlining oestrogen’s therapeutic promise for sex-specific neuroinflammation therapies.[42]

3.5 Lifestyle: Nutrition and lifestyle adjustments, such as eating a Mediterranean diet, exercising, and managing stress, have shown promise in treating Parkinson's disease

symptoms. Probiotics and CoQ10 supplements may also be beneficial. Changes in dietary habits, physical activity levels, and sleep patterns may all have an impact on Parkinson's disease risk. Adopting unhealthy habits, such as sedentary activity, poor food, and persistent sleep deprivation, may raise the likelihood of developing Parkinson's disease in the future.[43]

3.6 Certain medications: Long-term use of some pharmaceuticals, such as antipsychotics and anti-nausea treatments, has been linked to an increased chance of acquiring Parkinson's disease-like symptoms, a condition known as drug-induced Parkinsonism. Persistent gait impairment in Parkinson's disease, despite treatment, was associated with motor decline. Nondopaminergic variables also play a role. Over the course of 18 months, there was a gradual deterioration.[44]

3.7 Other Health Conditions: Diabetes and heart disease may be linked to an increased risk of Parkinson's disease, while the exact association is complex and unknown. Neurogenic orthostatic hypotension and supine hypertension are common in Parkinson's disease. Managing both requires balancing risks, considering short-term fall and cognitive risks versus long-term stroke and heart risks.[45]

3.8 Environmental Changes: Continued environmental deterioration, such as air and water pollution, deforestation, and climate change, may expose people to additional poisons and pollutants, increasing their risk of Parkinson's disease. Efforts to reduce environmental contamination and encourage sustainable behaviors are critical for lowering future dangers.

3.9 Rapid urbanization and industrial: expansion in developing countries may expose people to more environmental toxins and pollutants, potentially increasing the incidence of Parkinson's disease. Efforts to regulate industrial activity and raise environmental standards are critical to reducing these dangers.[46]

3.10 Technological Advancements: As technology advances, new electronic devices and materials may introduce novel environmental contaminants and chemicals that might harm brain health. Exploring the possible neurotoxic impacts of developing technology will be critical for understanding and minimizing future dangers.[47]

3.11 Socioeconomic inequities: such as unequal access to healthcare, education, and resources, may increase the risk of Parkinson's disease (PD). To reduce future inequities in Parkinson's disease, it is critical to address social determinants of health and promote fair access to healthcare and resources.[48]

3.12 Demographic Shifts: Aging populations and changing demographic patterns, such as rising life expectancy and shifting population demographics, may have an impact on PD prevalence and risk factors in the future. Understanding the impact of demographic changes on PD risk is critical for planning healthcare services and therapies.[49]

3.13 Advances in genetics and epigenetics: Reveals novel gene-environment interactions that influence Parkinson's disease risk. Understanding how genetic predispositions interact with environmental factors to influence Parkinson's risk will be critical for creating.[50]

3.14 Global Health risks: Emerging infectious illnesses, pandemics, and other global health risks may have an indirect impact on PD risk by affecting healthcare systems, social and economic stability, and the environment. Strengthening global health infrastructure and preparedness initiatives is critical for reducing the impact of these risks on the PD risk.

To address these potential future risk factors for Parkinson's disease, a holistic approach is required, encompassing environmental, social, economic, and technical components. Research, policy interventions, and public health activities focused at lowering environmental pollution, promoting healthy lifestyles, addressing socioeconomic inequities, and improving healthcare access and infrastructure are crucial for minimizing future Parkinson's disease risks.[51]

4. Conclusion

Parkinson's disease (PD) is complex neurodegenerative disorder, influenced by unique gene-environment interactions. Understanding these epigenetic mechanisms could lead to personalized treatments for this multifactorial disorder. Present Parkinson's disease (PD) biomarkers aid diagnosis and monitoring. They include alpha-synuclein levels, dopamine imaging, olfactory dysfunction, REM sleep behaviour disorder, and gait analysis. Future biomarkers aim to enhance early detection and tracking through blood-based indicators, neuroimaging, biosensors, genomics, and inflammation markers. Metal ions like Fe, Cu, Pb, and Hg play pivotal roles in Parkinson's disease (PD) pathogenesis. Their dysregulation leads to neuronal toxicity via oxidative stress, inflammation, and apoptosis. Synergistic effects with pesticides exacerbate toxicity. Understanding these mechanisms informs therapeutic strategies including chelation and antioxidants to mitigate PD progression.

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