

Toxicological Perspective on a Stealth Threat: The Link Between Pesticide Exposure and Neurodegenerative Diseases

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Abstract

Mounting research implicates pesticide exposure as a major environmental trigger in the etiology of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Pesticides, known for their neurotoxic potential, can cross the blood-brain barrier, persist in the environment, and trigger cellular damage through mechanisms including oxidative stress, microglial activation, and protein aggregation. Notably, these effects may remain clinically silent for years, a phenomenon termed "silent neurotoxicity." This review explores the toxicological basis of pesticide-induced neurodegeneration, supported by epidemiological data showing a growing global burden and economic impact of these diseases. It further underscores the need for preventive toxicological strategies such as restricting high-risk pesticide use, enhancing safety regulations, promoting biopesticides, and developing early diagnostic biomarkers to mitigate long-term neurological outcomes and support sustainable public health policy.

Keywords: Pesticide exposure, neurotoxicity, neurodegenerative diseases, silent neurotoxicity

Introduction

Recent advances in diagnostics and therapeutics have significantly reduced mortality from leading causes, thereby increasing global life expectancy. While this is a major public health achievement, it has also led to a rise in age-related disorders, particularly neurodegenerative diseases.

In light of this growing burden, the scientific community has intensified efforts to identify modifiable risk factors. One area of increasing interest is the role of environmental exposures particularly pesticides in the pathogenesis of neurodegenerative diseases.

Pesticides, widely introduced in the 1970s to enhance agricultural productivity, are toxic chemical and biological agents¹. Their neurotoxic effects have attracted the attention of both toxicologists and neurologists. A growing body of evidence supports their role as environmental risk factors in Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS)². These diseases share pathological features such as progressive cognitive and motor decline, ultimately leading to loss of independence and the need for long-term care.

This review aims to (1) evaluate the current toxicological evidence linking pesticide exposure to neurodegenerative diseases, (2) summarize the epidemiological burden and economic impact, and (3) propose preventive strategies and future research directions to mitigate risks.

By integrating toxicological mechanisms with clinical and epidemiological data, this work offers a comprehensive overview of how pesticide exposure may silently contribute to neurodegeneration.

Pesticide Neurotoxicity in the Context of Neurodegenerative Disease Etiopathogenesis

AD, PD, and ALS are progressive central nervous system disorders characterized by neuronal loss. They can exhibit a rapidly advancing course and significantly reduce life expectancy. Although the exact pathogenesis of neurodegenerative diseases is not fully understood, it is well recognized that an interplay between genetic predisposition and environmental factors plays a substantial role³.

In the pathogenesis of AD, the accumulation of extracellular amyloid plaques in the cortex and limbic system, along with the

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aggregation of hyperphosphorylated tau protein within neurons, play a significant role. In PD, the accumulation of intraneuronal α -synuclein proteins in the substantia nigra leads to the loss of dopaminergic neurons. In ALS, amyloid aggregates derived from various proteins such as TDP-43, C9ORF72 dipeptide repeats, and FUS have been reported, with protein aggregation being a distinctive feature of the disease⁴.

Oligogenic and polygenic inheritance models have been proposed to explain the pathogenesis of neurodegenerative diseases. In addition, complex gene environment interactions play a significant role in the etiopathogenesis of these disorders. Environmental factors such as metals, pesticides, and air pollution have been suggested as potential risk factors for these diseases⁵⁻⁷.

Pesticides are toxic chemical or biological agents developed to target harmful organisms. Increasing evidence has linked these agents to neurodegenerative diseases². Specific compounds such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat, maneb, rotenone, and organochlorine pesticides have been shown to damage dopaminergic neurons, leading to cellular injury within the substantia nigra, a key pathological hallmark in PD⁸. Furthermore, these substances have been implicated in promoting amyloid- β accumulation and tau hyperphosphorylation, thereby increasing the risk of AD⁹. Moreover, several meta-analyses have found a significant association between pesticide exposure and increased ALS risk^{10,11}. These findings suggest that pesticide exposure may not only initiate but also accelerate disease progression.

Due to their environmental persistence and lipophilic nature, pesticides accumulate in soil, water, and air and ultimately in human tissues. These compounds are capable of crossing the blood-brain barrier and may induce morphological damage and biochemical alterations in neural tissue¹². The central nervous system (CNS) is notably sensitive to neuroinflammation and reactive oxygen species (ROS) induced by metals, pesticides, and air pollutants¹³. Following toxic exposure, increased activation of glial cells is observed, and this process leads to enhanced ROS production alongside neuroinflammation. These inflammatory processes trigger the production of various pro-inflammatory cytokines, including TNF α , IL-6, and IL-1 β , as well as chemokines, cyclooxygenase-2, and inducible nitric oxide synthase^{14,15}. Studies in the literature have shown increased expression levels of these molecules in several brain regions, such as the hippocampus, striatum, and cortex^{16,17}. Additionally, it is noted that neuroinflammation may lead to endothelial dysfunction, resulting in increased permeability of the blood-brain barrier¹⁸. All these processes can trigger not only inflammation but also pathological events such as protein aggregation and DNA damage¹⁹.

Beyond these mechanisms, another important pathway involved in environmentally induced neurodegeneration is mitochondrial dysfunction. Oxidative stress caused by

exposure to toxic agents particularly targets mitochondria and leads to impairment in ATP production²⁰. This disruption in energy balance may eventually predispose to the loss of neuronal functions²¹.

Furthermore, there is evidence that exposure to toxic environmental factors during pregnancy may have adverse neurotoxic effects in utero and lead to various neurodevelopmental disorders²². Animal studies have shown that in utero exposure to neurotoxic agents such as metals and pesticides may contribute to the development of biological processes involved in AD and PD, such as amyloid plaque accumulation and dopaminergic dysfunction²³.

Neurotoxicity is often observed shortly after exposure during sensitive periods such as pregnancy, lactation, or early childhood. Nevertheless, clinical manifestations may remain latent for extended periods following pesticide exposure²⁴. This phenomenon has led to the emergence of the concept of silent neurotoxicity in the field of toxicology. Silent neurotoxicity refers to biochemical or morphological alterations in the nervous system that occur without overt clinical symptoms. Although subclinical, these changes may result in irreversible neuronal damage at the molecular level and potentially serve as a precursor to progressive neurodegenerative disorders. Over time, subclinical changes may evolve into a prodromal phase, eventually leading to measurable declines in motor and cognitive function¹².

Epidemiological Trends and Economic Burden

The global rise in neurodegenerative diseases has intensified interest in understanding their root causes. According to the World Health Organization, approximately 47 million individuals were diagnosed with AD in 2015; this number increased to 55 million by 2022, and it is projected to reach 132 million by 2050²⁵. The global economic burden of dementia was \$604 billion in 2010. It increased by 35% to \$818 billion in 2015, and it is estimated to exceed \$2 trillion by 2030. The elderly population is expected to grow from 703 million in 2015 to 1.5 billion by 2050. This projection places dementia among the priority neurodegenerative diseases requiring close monitoring in healthcare services²⁶.

Between 1990 and 2016, the number of PD cases more than doubled, reaching over six million. Age-standardized prevalence also increased by 22%. Projections indicate that by 2040, 12–17 million individuals may be affected. The indirect costs of PD stemming from long-term disability, premature retirement, and productivity loss represent a significant socioeconomic burden²⁷⁻²⁹.

ALS, although a relatively rare disorder with global incidence rates ranging from 0.5 to 3.6 per 100,000 people, presents considerable clinical and economic challenges³⁰. The progressive nature of ALS often requires intensive care and mechanical ventilation in advanced stages. This causes severe functional decline and dependence. It results in substantial direct healthcare costs and productivity losses³¹.

The cumulative effects of early retirement, caregiver dependency, and healthcare expenses highlight the need for public health policies aimed at minimizing environmental risk exposures.

Conclusion and Toxicological Approaches

The rising prevalence of neurodegenerative diseases underscores the growing importance of scientific and clinical investigations in this field. While only a small proportion of these diseases are attributable to purely genetic factors, the majority arise from complex interactions between environmental exposures and genetic susceptibility. In this context, pesticide exposure emerges as a critical environmental determinant.

Global population growth and the increasing demand for food sources have made pesticide use almost inevitable. Although pesticides have become indispensable tools in agricultural productivity and crop preservation, their neurotoxic potential has placed them at the center of toxicological research. Given that a significant portion of neurodegenerative disorders is believed to result from exposure to environmental neurotoxins, toxicological strategies aimed at preventing such exposures must be prioritized.

Considering the insidious and often latent nature of pesticide-related health effects, implementing preventive measures to reduce human exposure is of utmost importance. These measures include:

- Clearly defining the toxicological safety profiles of pesticides and ensuring proper hazard labeling on packaging;
- Restricting the use of pesticides known to pose risks to non-target organisms and human health;
- Avoiding the use of aerially dispersed gaseous or fog-form pesticides;
- Ensuring that pesticide applicators are properly trained in the use of personal protective equipment and safe handling protocols.

Additionally, minimizing pesticide residues in food and water supplies represents a critical public health strategy. Monitoring and reducing pesticide contamination in these sources can substantially lower population-level exposure to neurotoxic agents. As a sustainable alternative, the use of biopesticides naturally derived and environmentally friendly compounds offers the potential to minimize neurotoxic risks while reducing residual accumulation in ecosystems. These agents are increasingly being integrated into sustainable agricultural practices³².

Another major challenge is the lack of specific biomarkers for the early diagnosis and management of neurodegenerative diseases. Currently, in AD, molecular and imaging-based biomarkers such as amyloid PET, tau

PET, and cerebrospinal fluid (CSF) levels of A β 42, total tau, and phosphorylated tau are being used. In addition, in PD, dopamine transporter (DAT) imaging and α -synuclein-based biomarkers are also being utilized. Early diagnosis through these markers may enable timely intervention before irreversible neurodegeneration occurs.

The presence of a latent clinical phase following pesticide exposure highlights the need to identify novel biomarkers capable of detecting subclinical neurotoxicity. Developing such indicators could enable timely intervention and improve long-term outcomes. Biomarker-based early diagnostic strategies would thus create opportunities to act during the silent neurotoxicity window, potentially altering the disease trajectory.

Future research should focus on longitudinal human studies to confirm causality, identify at-risk populations, and develop sensitive screening tools. Cross-disciplinary collaboration combining toxicology, epidemiology, neurology, and public health will be key in crafting effective, sustainable solutions.

In conclusion, this review provides a toxicological framework for understanding how pesticide exposure contributes to neurodegeneration. It highlights actionable steps for prevention and calls for continued research to support safer agricultural practices and better neurological health outcomes.

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