Challenges for Epidemiological Research of Pesticide Exposure and Parkinson's Disease

a report by

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Parkinson's disease (PD), a neurodegenerative disease affecting at least one million individuals in the US, is characterized by a progressive loss of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies (inclusions composed of aggregated proteins) in the surviving neurons. Once approximately 70% of the dopaminergic neurons have been lost, the clinical signs of PD become apparent; these include resting tremor, muscular rigidity, and bradykinesia, among many other motor and non-motor manifestations. Increasing age is a major risk factor for PD, and as a consequence the disease prevalence and ensuing societal impact of the disease are expected to increase as the population ages in coming years. Despite this, the factors that trigger the pathological changes leading to PD remain unknown for the vast majority of cases.

A slow progressive loss of dopaminergic neurons accompanies normal aging, and exposure to harmful environmental factors may cause PD by accelerating the rate of neuronal depletion. Alternatively, environmental exposures in early life may reduce the number of dopaminergic neurons to levels below those needed to maintain function upon age-related neuronal depletion in later life. In either case, the environmental impact may not be immediately evident, and the disease may appear years later when dopamine levels drop below the threshold required for normal function.[1]

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Investigators have long sought to identify harmful environmental factors leading to PD, particularly since the 1983 identification of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as a causal agent.[2] MPTP contaminated a synthetic narcotic, leading to severe parkinsonism with features of classic PD in several young drug users. MPTP was later shown to act selectively on dopaminergic neurons in the substantia nigra. Since then, much epidemiological research has focused on the pathways leading to MPTP-induced parkinsonism.

Structural and functional similarities exist between the active metabolite of MPTP (MPP+) and some pesticide chemicals, particularly paraquat. Given this, pesticide exposure has been examined in many epidemiological studies as a risk factor for PD, but some uncertainty remains. A meta-analysis of case-control studies conducted prior to 2001 showed that individuals with PD were 85% more likely to report being directly exposed to pesticides compared with unaffected individuals.[3] Lifestyle factors thought to correlate with pesticide exposure, including rural living, well-water consumption, and farming, have also been implicated in PD, adding support to the association between pesticide exposure and PD. However, rural living, well-water consumption, and farming are poorly defined, highly variable, and inter-related factors likely reflecting several environmental exposures, which may or may not include pesticide exposure. Furthermore, the lack of significant association between direct pesticide exposure and PD in several studies and the inconsistent reporting of specific pesticide chemicals as risk factors for PD have disputed the role of pesticide exposure in PD.[4] In this article, we present the major challenges of examining the complex relationship between pesticide exposure and PD and suggest future directions for the research field.

Study Design Considerations

Different observational study designs have contributed valuable information on the relationship between pesticide exposure and PD, but the drawbacks of each design must be considered when interpreting the findings. Descriptive ecological studies have suggested a relationship between pesticide exposure and an increased prevalence of PD at the population level,[5,6] but individual characteristics of exposure and disease cannot be inferred from these measures. Individual-level measures have been provided by other epidemiological study designs.

The case-control study design, which ascertains individuals based on their disease status and retrospectively assesses their exposures, has been employed most often to examine the association between pesticide exposure and PD, with at least 40 studies published since 1983.[4] As reviewed by Brown et al., the

studies of cases and unrelated controls have mostly supported a significant positive association, but inconsistent findings have been reported.[4] The association has been further supported by a study of cases and related controls in which confounding by unmeasured genetic and environmental factors is reduced since cases are generally well-matched to their relatives.[7] Nonetheless, all case-control studies are subject to inherent biases due to inaccurate recall of pesticide exposures, problems in temporal inference (i.e. whether exposure precedes disease), and selection of cases and controls that may not be from the same base population.

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A few cohort studies that ascertain healthy individuals based on their exposures and prospectively follow them to assess their disease status have also examined the association of pesticide exposure with PD. Cohort studies are robust to recall, temporal inference, and selection biases, but the evidence supporting the association from cohort studies is preliminary.[8–10] As most cohorts were not designed to study pesticide exposures or PD, inadequate exposure assessment and variable case definitions—including self-reporting, which introduces the potential for disease misclassification bias—have also complicated the interpretation of findings from some studies.

Studies often obtain detailed pesticide exposure assessments at the expense of reliable PD diagnoses based on clinical examinations. The Farming and Movement Evaluation (FAME) Study, a nested case-control study taken from the Agricultural Health Study cohort of pesticide applicators and their spouses, is an example of an ongoing study that achieves both detailed exposure and clinical assessments.[11] However, its relatively small sample size is problematic, as is the case for most case-control studies examining pesticide exposure in PD.

Complex Assessment of Pesticide Exposure

The complex nature of pesticide exposure poses a major obstacle for obtaining reliable pesticide exposure assessments. Most individuals exposed to pesticides experience unique exposures that vary in a multitude of ways. The duration, frequency, route of uptake (i.e. inhalation, ingestion, or dermal absorption), and pesticide agents often vary across time in irregular patterns for the same individual. For instance, some people may report chronic low doses of the same pesticide chemical, while others may report acute high doses of different pesticide chemicals. Furthermore, individuals may report occupational, residential, and/or environmental exposures, and integration of the different types of exposure is challenging.

The impact of pesticide exposure in neurodegeneration may depend on a critical window of time. A single exposure in childhood or adulthood may be a sufficient predisposition to PD in later life. Alternatively, a multiple hit hypothesis has been proposed, whereby pesticide exposures at multiple time-points may influence the risk for disease.[12] Ideally, a large prospective cohort study following children through adulthood and measuring their pesticide exposure and PD incidence over different periods of their life would be needed to address many of these questions, but today minimal evidence is available to identify the critical window of time for exposure. Until then, exposures must be recalled throughout the lifespan, but reliability of exposure reports may vary from childhood to adulthood.

Most studies examining pesticide exposures have been retrospective studies that rely on self-report, thus incurring the potential for inaccurate recall. Among the several types of pesticides (e.g. insecticides, herbicides, fungicides, and fumigants) there are hundreds of specific pesticide chemicals. The continuous flow of available products into and out of the market and the existence of commercial products containing multiple pesticide chemicals further complicates the recollection of specific pesticide exposures. Given this, broad categories of pesticides are often assessed. It is debatable whether self-reporting is a reliable assessment for occupational exposure to broad categories of pesticides, and there is even less confidence in self-reporting for assessment of specific pesticide chemicals and for assessment of residential exposures.[13–15]

Some insecticide classes (organochlorines, organophosphates, rotenoids, and pyrethroids), the herbicide class of chlorophenoxy acids/esters, the herbicide paraquat, and the fungicide maneb have been implicated in PD.[4,7,16] However, studies moving beyond the broad assessment of pesticides and examining classes or specific chemicals for an increased risk for PD are limited, and no single chemical has been consistently implicated. Factors that may influence the level of exposure to any pesticide, such as protective gear, are usually not examined. The broad and variable assessment of pesticide exposure in many retrospective studies introduces the potential for exposure misclassification bias, possibly explaining the inconsistency of pesticide associations in PD. Not all pesticides are equal, not even pesticides in the same class, so the quality of pesticide exposure assessment when summarizing evidence for specific chemicals is vital to the validity of association findings.

Insufficient Biological Evidence

Even though epidemiological studies have implicated the broad spectrum of pesticides in PD, only select pesticide chemicals have been investigated for biological function relating to PD. Thus, limited biological evidence is available to authenticate the epidemiological implication of pesticide exposure in PD. High levels of organochlorine chemicals, notably dieldrin, have been found in the brains of individuals with PD compared with controls,[17,18] and cases of organophosphorus-induced acute parkinsonism have been reported.[19,20] Furthermore, rodents display symptoms and pathological features characteristic of PD when exposed to high doses of several pesticide chemicals, specifically rotenone,[21] paraquat alone,[22] and paraquat with maneb[23] and other dithiocarbamates.[24]

There are several proposed biological mechanisms for pesticide exposure leading to PD. Impaired mitochondrial complex I activity is a commonly suggested mechanism, given that MPTP exerts its toxic effects by inhibiting mitochondrial complex I and deficiency at this site has been observed in PD. Alternatively, pesticides may interfere with dopamine transmission, inhibit xenobiotic-metabolizing enzymes, exacerbate oxidative stress, initiate inflammatory processes, or promote α-synuclein fibrillation, a known cause

of PD. No biological mechanism has been consistently shown to mediate the effect of pesticide exposure on dopaminergic neurons in the substantia nigra and lead to PD.

Future Directions

Pesticide exposure has been suspected for many years to increase risk for PD, but progress has been slow toward identifying the truly causal pesticide agents among the numerous possibilities and their biological mechanisms of action.

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The complexity of obtaining a reliable pesticide exposure assessment over the lifespan poses a major challenge. Ideally, long-term biomarkers of pesticide exposure could provide objective, reliable assessments in large-scale epidemiologic studies. However, such a biomarker is available only for the organochlorine insecticide class.[16] Further research is needed to identify other long-term biomarkers for pesticide exposure. This research would be guided by epidemiological findings since biomarkers would likely only indicate exposure to relevant pesticides instead of overall pesticide exposure.

Until the elusive long-term biomarkers are identified, more extensive questionnaires are needed for pesticide exposure assessment. Pesticide exposure is generally thought to be a risk factor for PD, even though the challenges presented here have shown that many questions remain. Most studies have only considered exposure to any pesticide in classifying individuals as exposed or unexposed. The next step in deciphering the role of pesticides on PD is to refine the broad assessment toward a more specific categorization of pesticide exposures and to examine the role of specific pesticides on risk of PD. Consistency in assessment measures would also ease the integration of interview data and biological samples for large-scale collaborations. Exposure to different pesticides may contribute to PD in different individuals, and this heterogeneity may only be detectable with large-scale studies with adequate exposure assessments.

Some cases of PD are entirely attributable to a genetic or environmental cause, but the vast majority of cases likely result from an intricate interplay of susceptibility genes and environmental triggers, such as pesticide exposure. Despite the potential for gene–environment interactions, few studies have reported examining joint effects of pesticide exposure and genetic factors on risk for PD. The candidate genes that have been reported for interaction with pesticide exposure in PD include genes involved in dopamine transmission (SLC6A3[25]), xenobiotic metabolism (CYP2D6,[26,27] GSTP1,[28] and NQO1[29]), and oxidation reduction (NOS1[30] and SOD2[29]). These initial gene–environment interaction reports merit replication, and many biologically plausible interactions between candidate genes and pesticide exposure in PD remain unexplored. Studies of environmental associations not accounting for interacting genetic factors and studies of genetic associations not accounting for environmental factors may explain the inconsistencies in both genetic and environmental association findings. Identification of genetic interactions with pesticide exposure is therefore a vital step towards unifying the pesticide studies in PD and understanding the relevant biological pathways. ■

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American Parkinson Disease Association

The American Parkinson Disease Association (APDA) is the largest grassroots organization serving the country's 1.5 million people with Parkinson's disease and their caregivers through a national network of 56 chapters, 64 Information & Referral Centers and 800 support groups.

APDA has been a funding partner in every PD research breakthrough and has been providing support to persons with Parkinson's disease and their caregivers for 47 years making it easier to remain as independant as possible for as long as possible.

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