Exposure to Pesticides Predicts Prodromal Feature of Parkinson’s Disease: Public Health Implications

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The pathological processes underlying Parkinson’s disease (PD) begin in the prodromal phase of the disease, which may well span more than 2 decades.1,2 During that period, pathology spreads throughout the nervous system.3 The most specific prodromal feature of PD is the presence of rapid eye movement sleep behavior disorder (RBD).4-6 When PD finally becomes clinically manifest, 60% to 80% of dopaminergic neurons in the nigrostriatal pathway are already depleted.7 This advanced stage of pathology likely explains why disease modification has proven to be difficult in individuals with manifest PD.7 Therefore, there is growing interest in preventing or slowing the progression of PD at an earlier stage by targeting risk factors that drive the earliest pathological processes, that is, at a time when individuals have either no or only prodromal symptoms.

Epidemiological studies, mostly in the occupational setting, have demonstrated that exposure to pesticides is a risk factor for PD,8,9 but it has thus far remained unclear at which stage of pathology their detrimental effects are exerted. The study by Yuan and colleagues in this month’s edition of Movement Disorders addressed that important gap in knowledge by demonstrating an association between high pesticide exposure events and the subsequent presence of RBD symptoms in otherwise clinically unaffected individuals.10 Here, we reflect on these findings and discuss the public health implications, including recommendations for future work.

The study by Yuan and colleagues involved 11,248 middle-aged farmers enrolled in the US Agricultural Health Study. At baseline, between the years 1993 and 1997, participants were asked whether they had a history of at least one high pesticide exposure event. Subsequently, at a follow-up interview between the years 2013 and 2015, participants were asked about dream enactment behavior (DEB), which are symptoms suggestive of RBD.11 The prevalence of DEB was 9.3% (n = 939). The key finding was that farmers who had reported a history of high pesticide exposure events at baseline had an elevated risk of subsequent presence of DEB. Several carefully designed sensitivity analyses provided support for the robustness of the main results. The authors also explored which specific pesticides were implicated. They observed univariable associations of two organochlorine insecticides (Dichlorodiphenyltrichloroethane [DDT] and lindane), four organophosphate insecticides (phorate, ethoprop, terbufos, and parathion), two chloroacetanilide herbicides (alachlor and paraquat), and fungicides (as a group) with the subsequent presence of DEB. Of these pesticides, organochlorines have been linked to PD risk, whereas the evidence is mixed for organophosphates12 and chloroacetanilide herbicides.13,14 Overall, the study strengthens the current evidence base of possible linkages between pesticides and PD and points toward high exposure events and exposures in early adulthood as possible important exposure events.

The study had several strengths, including the prospective design with a long follow-up duration, the detailed baseline interview of high pesticide exposure events that included questions on specific pesticides and the assessment for DEB using a validated questionnaire. The study also had some limitations. First, the assessment of pesticide exposure was based on self-report, which is prone to misclassification.15,16 Self-report may have introduced some recall bias, as the baseline prevalence of motor or nonmotor symptoms was slightly higher in individuals who later developed DEB (58%)
than in those who did not (45%). Second, the presence of DEB was not assessed at baseline. This means that, in some individuals, the presence of DEB may have preceded the high pesticide exposure event they reported at baseline.

The findings by Yuan and colleagues shed light on two important issues for the design of public health interventions to prevent PD. The first issue is that some of the pesticides implicated in the etiology of PD are still in use today. Of the pesticides univariately associated with DEB in this study, many are still in use in the United States (parathion, phorate, ethoprop, terbufos, alachlor, paraquat). However, these individual results should be interpreted with some caution as they do not come from a multipollutant or mixture model and no formal multiple comparison correction was applied. Although this precluded this study to pinpoint which individual pesticides are independently associated with DEB, the findings by Yuan and colleagues suggest that pesticides in general continue to contribute to the onset of the pathological processes of PD today.

The second issue is that the detrimental effects of pesticides on the onset of PD pathology may sustain for many years after new restrictions on the use of pesticides have been implemented. Although the exact interval between exposure to pesticides and the clinical manifestation of PD could not be determined in the study by Yuan and colleagues, the study did provide some clues. Specifically, the odds of developing DEB were similar in people with a high exposure incident in the 1960s, which preceded the baseline interview by 3 decades, as in people with a high exposure incident in the 1990s. If we assume that the onset of DEB occurred on average 10 years after the baseline interview (ie, at the midpoint of the follow-up period) and that there was an additional latency period of 10 years before PD became clinically manifest, then that study participant would have a 5-decade span between a high pesticide exposure incident and onset of manifest PD. Because of this long latency, it may take decades before new restrictions on the use of pesticides translate to the prevention of clinically manifest PD.

The work by Yuan and colleagues also sets the agenda for future studies with a complementary design. Specifically, this study can be built on in several ways. The first is to study high exposure events to other chemical pollutants that may also elicit prodromal features of PD. Recent studies have suggested that long-term exposure to particulate matter, heavy metals, and trichloroethylene may be associated with an increased risk of PD, although results have varied across studies. In the study by Yuan and colleagues, associations of high pesticide exposure incidents with DEB remained after adjustment for long-term exposure to pesticides, and the observed associations of high pesticide exposure incidents with DEB in this study were generally stronger than the previously reported associations of long-term exposure to pesticides with incident DEB in this cohort. Hence the findings by Yuan and colleagues could inspire future studies to assess associations between other high occupational exposure events (eg, spills in factories) and the onset of DEB and PD. Furthermore, the results of Yuan and colleagues indicate that the relevant high exposure events would have mostly occurred between the ages of 30 and 40. This provides additional evidence that early adulthood might be an etiologically relevant risk window for PD. Future studies should therefore not only address lifetime exposures but also apply a life course approach with an emphasis on early adulthood (or even earlier) as the etiological window of particular interest.

The second way is by addressing the important question of whether results from occupational studies on the associations of pesticides with DEB and manifest PD apply to the general population, which is exposed to much lower levels of pesticides and has a much lower probability of high exposure events, although exposure extends for long periods spanning decades. It is challenging to quantify the risk of pesticide exposure in a general population because multiple exposure routes and sources need to be accounted for. For example, pesticides can be found in measurable concentrations in commercially available food products and in the living environments of individuals living in proximity of agricultural fields. Studies in the general population have given mixed results, with some studies reporting that individuals who live in agricultural regions have an increased risk of PD, suggesting that exposure to pesticides may contribute to the etiology of PD not only in farmers but also in a considerably larger proportion of PD cases. Furthermore, previous studies show that people are rarely exposed to a single pesticide but, rather, to “cocktails” (mixtures) of different pesticides. Mixtures of pesticides may well be associated with additive toxicity and possibly even have a synergistic effect. To date, insight remains scarce on how exposure to such combinations of pesticides affects the risk of DEB or manifest PD, and this crucial topic deserves further study.

Still, assessing exposure in the general population remains challenging. Although objective methods exist to measure pesticide exposure—such as biomonitoring, air (outdoor, indoor, personal), house dust, and dermal sampling—they are not well suited for assessing exposure in large population studies and have limited value in retrospective case-control studies as they do not address historical exposures. However, recent progress has been made in developing deterministic exposure models for residential exposure to pesticides that arise
as a result of living near agricultural fields. Residual exposure can be estimated in areas where detailed (historical) information is available on land use (ie, crops), pesticides use, and atmospheric conditions. This provides the opportunity to follow-up occupational studies such as Yuan and colleagues in the general population by modeling long-term exposure to specific pesticides and high exposure events that could occur after pesticide spraying under unfavorable atmospheric conditions (ie, drift).

Overall, the work by Yuan and colleagues suggests that pesticides elicit the earliest stages of pathology of PD, that some of the implicated pesticides are still in use today, that high exposure events and early adulthood exposures may be of particular interest, and that the detrimental effects of pesticides on PD may sustain for an extended period of time (ie, drift).

Data Availability Statement
Not applicable.

References