2 ARE THERE ANY CONSISTENT ENVIRONMENTAL RISK FACTORS FOR PARKINSON'S DISEASE?

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Parkinson's disease (PD) is a debilitating neurodegenerative disorder that affects ~2 percent of the population over age 65. The cardinal signs of PD – muscle rigidity, bradykinesia, gait disturbance, postural instability – occur much more frequently, either singly or in combination. Despite decades of extensive toxicological and epidemiological research into the causes of PD, there are very few established risk (or protective) factors, apart from increasing age and male gender. Mendelian inheritance accounts for roughly 5–10 percent of cases. This suggests that the vast majority of PD is attributable to the "environment," which includes air and water contaminants in the workplace and ambient environment, and lifestyle factors, such as diet, smoking, and medications. Notably, of all the environmental factors, cigarette smoking bears the strongest, most consistent relation to PD risk. In fact, smoking appears to be "protective" for reasons that remain poorly understood. Workplace and ambient environmental exposures that have received the greatest attention are pesticides and metals. Toxicological support, including reasonably convincing animal models for some pesticides (paraquat, rotenone) and clinical similarities between some occupational poisoning and parkinsonian features – manganism is the classic example – provide rationale for the focus on these exposures. Unfortunately, findings for nearly all environmental risk factors, other than cigarette smoking, have been very inconsistent for broad classes of exposures, and also for specific agents. This pattern is exemplified by results for pesticides, which have been considered as broad functional categories (insecticides, herbicides, fungicides, etc), as groupings based on shared chemical properties (eg, organophosphates), or as specific compounds (eg, paraquat). A very similar pattern of etiologic findings has been seen for metals. Gene/environment interactions, whereby persons harbouring specific genetic variants may be especially susceptible to environmentally-induced neurotoxicity, has also been of considerable recent interest. However, despite the conceptual promise of the gene/environment approach, the results to date have seldom been reproduced. Low population frequencies of exposures of interest in the population-at-large and imprecise exposure assessments are the main limitations of most PD epidemiological research because the population-based case-control study has been by far the most commonly applied design. Case-control studies continue to dominate owing to their efficiency of case accrual and opportunity to explore a wide spectrum of exposures. Cohort studies, especially of well characterised occupational groups, offer an attractive alternative study design. The cohort design, in theory, can remedy problems of rare exposures of interest and inaccurate exposure assessment. However, very large cohort studies are needed in order to provide adequate statistical power, and the logistical difficulties verifying diagnoses based on accepted clinical definitions can severely compromise validity. Disappointingly, results from occupational cohort studies have been as inconsistent as those generated from case-control studies. The literature on PD among welders offers a vivid illustration. Why have the environmental signals been so few and so inconsistent? One possible explanation is that PD is simply not an "environmentally-related" disease. Alternatively, PD may represent multiple diseases that share some common features, but have divergent risk factor profiles. If, in fact, the latter is the case, which is quite plausible, then considerable improvements to epidemiological research will be needed. These include: rigorous clinical classification of PD features; clinical follow-up to identify phenotypic changes and disease progression; and, enhancements to environmental exposure assessment, such as MRI which can characterise toxicant uptakes and burdens, and reveal early pathological effects. Pooling of epidemiological data among studies is also recommended when studies have similar methods of exposure and outcome assessments. These concepts will be illustrated with selected examples from the epidemiological literature.