A Comment on the Role of Environmental Factors in Parkinson's Disease

The paper in this issue by Sanyal et al[1], provides intriguing data from a case control survey study that assessed environmental and familial risk factors for Parkinson's disease (PD). This report confirms in an Eastern Indian population previous epidemiological findings concerning mainly Caucasian populations showing that exposure to various pesticides was associated with an increased incidence of PD. This important finding is consistent with numerous experimental reports demonstrating that administration of pesticides that are correlated with PD (e.g. paraquat) induce PD-like changes in rodents, including a loss of midbrain dopamine neurons, coupled with inflammatory and oxidative distress[2,3].

The fact that exposure to other potential toxins assessed in the current study, such as heavy metals, laboratory chemicals and chemical fertilizers, were also correlated with a greater incidence of PD suggests the possibility of some common mechanism of action of these insults. Based on animal studies[4], it is tempting to speculate that activation of inflammatory and oxidative stress pathways as one such culprit. Indeed, pesticides, heavy metal and industrial chemicals have well known pro-inflammatory and pro-oxidative effects. Many of these same agents have also been implicated in other neurological conditions, particularly those of a neurodevlopmental nature.

Whatever the case, the current findings are in line with the "multi-hit" hypothesis for PD, wherein exposure to multiple agents (e.g. chemical, immunological) over ones lifetime gradually results in accumulating pathological processes occurring leading to neuronal demise and eventually clinical signs of disability. Indeed, emerging evidence is beginning to reveal that exposure to several pesticides (e.g. maneb, paraquat), as well as heavy metals (e.g. iron), can synergistically provoke the degeneration of dopamine neurons[5]. These are important data considering that individuals are likely to be exposed to a mixture of chemicals and other insults over time. Indeed, agricultural areas that routinely use paraquat and maneb have especially high rates of PD[6]. Yet, the fact that not everyone exposed to combinations of these agents develops PD begs the question as to what other factors might be at play.

It is likely that only certain individuals develop toxin induced PD because of certain inherent vulnerabilities. Indeed, the same can be said for psychological disorders, such as depression, wherein some individuals appear to be somewhat "stressor hardy" whereas others are "stressor sensitive" and a prone to developing illness. In the case of PD, it is conceivable that the first "hit" could result from an inherited genetic vulnerability. Although it is unclear what genes might be involved, a safe bet would be to consider those that are critical for anti-oxidant defenses, protein folding as well as those associated with dopaminergic neurotransmission. In fact, recent reports suggest that mutations in the gene, DJ-1, or the dopamine transporter might enhance vulnerability of dopamine neurons to toxin exposure[7]. In effect, "vulnerability genes" might set the stage, but disease is not fully realized until sufficient environmental "hits" have occurred.

The present finding indicating a positive correlation between family history of PD and current diagnosis further supports a role for genetics in the disease. However, since it is highly likely the separate generations of individuals with PD were exposed to similar environments, it is impossible for this study to distinguish between the impact of heritable and environmental factors. Moreover, it is unknown from the present study as to whether some of the PD diagnosed subjects acquired the disease through mutations of autosomal dominant or recessive familial alleles (such as Parkin, LRRK2 and DJ-1, which give rise to familial forms of PD[8], as opposed to "vulnerability genes" (which convey increased susceptibility but disease only arises in the presence of appropriate eliciting factors).

Perhaps the most intriguing aspect of this study is the finding of an increased prevalence of PD among those with a prior history of depression. Within recent years, a few scattered reports have suggested a link between depression and PD[9], but the exact relationship has been unclear. Although unlikely to be a primary predisposing factor, depression might occur prior to the appearance of motor symptoms owing to changes in neuro-transmission and other pathology in limbic brain regions that occur during early stages of PD. Indeed, accumulation of abnormal Lewy body plaques has been posited to early occur in brainstem regions before midbrain dopamine neurons are affected[10]. Likewise, norepinephrine neurons of the brainstem locus coruleus are known to substantially degenerate in PD[11], thereby depriving emotional regulatory limbic regions of critical noradrenergic input. Furthermore, once the disease takes hold the distress caused by motor disability and the many social and other stressors could augment depressive symptoms and conversely, depression could magnify motor disability creating a vicious loop.

In summary, a plethora of data now supports a role for environmental agents in the genesis of PD and these findings should hopefully help inform guidelines and policies for dealing with potentially toxic agents. Similarly, the confluence of reports showing several important mechanisms (e.g. inflammatory and oxidative) through which environmental toxins can have deleterious consequences on dopamine neurons should guide the search for new therapeutic targets to exploit. This latter point deserves special attention, as the track record for translating findings from animal models of PD into the clinical domain has been less than adequate. To this end, it is reasonable to suppose that better animal models more closely mimicking the human

condition are required. At the very least, this requires a better understanding of the causal factors (both environmental and genetic) that shape the evolution of the disease. A further understanding at the biological level is also critical to disentangling how the myriad of signaling pathways can be manipulated to not only stop neural loss in the first place, but also stabilize and promote some degree of recovery in the surviving neurons in PD patients. Although we are still a long way off from having such viable clinical agents, we should remain optimistic given the steady progress is being made on this front.

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