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Editorial

CME

Environmental toxins accelerate Parkinson's disease onset

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Several pathologic entities manifest as Parkinson syndrome (PS). The most common is the Lewy body disease also known as idiopathic PD.[1]

Most PD cases are sporadic and are believed to be caused by exogenous environmental factors.[2,3] Autosomal dominant PD with α-synuclein gene mutation[4] and autosomal recessive parkinsonism with parkin gene mutation[5] have been reported in some families, but in general, genetic mutation is an extremely rare cause of PD.[6]

von Economo encephalitis, neuroleptics, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine are well-known environmental causes of PS; however, the pathology in these disease entities is different from that in PD. If an environmental agent caused PD, every patient would have evidence of exposure to the offending agent—obligate association. There are several epidemiologic reports on environmental factors associated with PD, but no exogenous factor has been consistently linked to PD. Sorting out true causally linked associations in PD is a major challenge. Metals such as aluminum, copper, iron, and manganese (Mn) have been implicated in PD. Manganese is a widely used metal, and miners exposed to Mn fumes develop PS. In this issue of *Neurology*, Racette et al.[7] report 15 parkinsonian patients who were professional welders. Compared with unselected PD patients, the welders had an earlier onset of symptoms. However, the clinical features, PET scan results, and pharmacotherapy profile were similar between the two groups. If welding is indeed responsible for parkinsonism in these patients, it resulted in PD and not PS associated with globus pallidus or striatal pathology.

In the normal human brain, Mn concentrations are the highest in the globus pallidus, striatum, thalamus, and substantia nigra (SN). In the few pathologic reports on Mn-induced parkinsonism, the abnormality was characterized by neuronal loss and gliosis in the globus pallidus and striatum, although one autopsy also revealed a significant depigmentation and neuronal loss in the SN.[8]

There are other indicators that the SN is vulnerable to Mn toxicity. Sethi et al. assessed a welder who developed PS. He had bilateral high T1 signal intensities in the globus pallidus and SN on MRI (personal communication). The MRI abnormalities subsequently resolved, but the patient continued to have dopa-responsive PS. Reduced PET fluorodopa uptake has been reported in another welder who had parkinsonism.[9] In primates exposed to Mn for 18 months, marked degeneration of the SN has been reported.[10] Together, these indicate that SN damage resulting in PS can be a feature of chronic Mn toxicity. It should be noted that the loss of SN neurons alone is not indicative of Lewy body PD because SN loss is also a feature of MPTP toxicity and several other degenerative disorders.[1,5]

Did the patients of Racette et al.[7] have Mn-induced SN pathology, or did they have preclinical PD that was unmasked by Mn? The even more important issue is whether Mn alone can produce Lewy body pathology. In the absence of reliable biological markers to identify Lewy body PD during life, these questions cannot be answered.[1]

Average age at onset of PD is 62 years. The preclinical interval is uncertain and probably varies widely. Thus, all of the environmental factors to which a patient is exposed prior to the clinical manifestations of PD are etiologic candidates. An epidemiologic search for the cause of PD based on community population or on clinic-based cases is akin to looking for needle in a haystack. By narrowing the focus to one occupational group, Racette et al.[7] have chosen a smaller stack and, therefore, have a greater chance of finding

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whether there is a needle (cause) or not. PD occurs in all races and in all geographic locations. The search for an environmental cause, therefore, requires ingenuity. In addition to the focus on one occupational group, as Racette et al.[7] have done, other strategies, such as studies restricted early-onset cases and geographic clusters of PD, may have better chance of success than the large, all-inclusive epidemiologic studies using environmental surveys for the entire life-span of patients. The observations by Racette et al.[7] should spark interest in carefully planned and focused environmental studies to determine the cause of PD.

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