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Distinct Neuroimaging Features Define Parkinsons Disease and Welding-Related Neurotoxicity

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Editorial

Neurobehavioral disorders are a significant and growing health, economic and social problem worldwide. Age-related neurodegenerative disorders contribute significantly to this growing problem because of increased longevity in the population. Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting 1% of the population over 60 yrs [1]. It is marked clinically by motor dysfunctions, e.g., resting tremor, bradykinesia and rigidity and pathologically by α-synuclein-positive Lewy bodies and nigrostriatal dopamine neuron loss in the substantia nigra pars compacta (SNpc) of the basal ganglia (BG) [2]. Despite a growing number of associated genetic factors, the exact cause(s) for PD are unknown [3]. Because the majority of PD patients do not have a family history and identical twins are often discordant for the disease, there is increased interest in the role that environmental and occupational toxicant exposure may play in PD aetiology [4-8]. For example, previous studies reported that exposure to well water, pesticides, herbicides and certain metals such as manganese (Mn), iron (Fe), lead (Pb) and mercury (Hg), or occupations like welding and farming, were associated with developing Parkinsonian symptoms [6], a clinical syndrome that presents both in PD and a number of look-a-like disorders.

Since Couper [7] first reported Mn-induced Parkinsonism in 1837, significant effort has been exerted to determine potential links between Mn-induced neurotoxicity and PD. Recent studies reported that Mn-exposed workers had a higher prevalence of Parkinsonian features compared to unexposed workers [9,10] and the Parkinsonian motor symptoms exacerbated with cumulative long-term Mn-exposure [11]. Welders have been among the most studied occupational groups since Mn is one of the major elements in many types of welding fumes [12] but several metals including Mn, Fe and Cu also may be at high concentrations and may co-influence the exposure-related neurotoxicity [13]. Both PD and welding-related neurotoxicity share common motor symptoms such as bradykinesia and rigidity, but they present distinguishable clinical features as well, e.g., welders display rapid postural rather than resting tremor, early development of gait and balance problems and a lack of response to levodopa therapy (the most common drug therapy for PD [5,7]. Thus, welding- (or Mn-) related Parkinsonian symptoms actually are not similar to idiopathic PD.

Recent studies using both neuroimaging and neuropathology have suggested some possible underlying neural mechanisms. For example, in PD, PET and SPECT imaging shows lower dopamine neuron function (i.e., lower flurodopa uptake and dopamine release) and terminal density (i.e., DAT) in key pathological areas like the dorsal striatum, but preserved or even increased postsynaptic D_2 receptor raclopride binding [14,15]. Mn-exposed workers and animals, however, presented opposite imaging patterns. There are normal flurodopa uptake and DAT density, decreased dopamine release and D_2 receptor raclopride binding in the striatum [16-18] and no decrease in numbers of SNpc neurons [19]. Such data suggest that welding-related neurotoxicity may be associated with a dysfunctional dopamine system, rather than degeneration in nigrostriatal neurons, although further investigation is needed to determine if the animal models are relevant to human exposure.

Over the past decade, MRI techniques have become invaluable tools in understanding Mn neurotoxicity due to its noninvasiveness. For example, Mn is paramagnetic and its brain accumulation is associated with higher T1-weighted intensity and/or T1 relaxation rate [R1: 1/T1] [20,21]. The T1 signal changes are greatest in the globus pallidus [GP; 22,23], whereas no increased T1 signal is seen in the GP of PD [24]. Elevated T1 signals, however, typically go back to baseline levels within 6 months after welding cessation, whereas welding-related neurobehavioral symptoms may persist [25-29]. This suggests T1 signals are less reliable as a long-term marker of welding-related neurotoxicity. Thus, there have been efforts to search for MRI markers that may reflect neuropathological processes more robustly.

Diffusion tensor imaging [DTI] measures the random translational motion of water molecules [30] and has shown promise as a tool for assessing tissue microstructural organization or potentially neuronal cell death. In the MPTP PD mouse model, DTI changes were correlated with dopamine neuron loss in the SN [31]. Furthermore, several human studies have demonstrated reduced DTI fractional anisotropy (FA) values in the SN of early PD patients, consistent with the exciting notion that DTI changes may detect microstructural changes due to cell loss [32-35].

Previous studies in welders reported altered overall diffusion magnitude in the GP. Moreover, a recent study demonstrated reduced DTI FA values in the GP of asymptomatic welders that were associated with a long-term welding exposure measure even in the absence of clear differences in T1 signals at the time of measurement. Although it is not clear whether the observed DTI changes in the GP reflect

microstructural changes due to compromised dopaminergic systems, this MRI modality may serve as a useful long-term marker to assess welding-induced microstructural changes and help further dissociate them from PD.

Overall, the current clinical, pathological and neuroimaging findings suggest that welding-related neurotoxicity is distinct from PD. It is possible; however, that Mn-exposure may contribute to an atypical presentation of idiopathic PD and further research can ultimately lead to better diagnoses and treatment.

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