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Editorial

Welding and Parkinson disease

Is there a bond?

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The cause of Parkinson disease (PD) remains unknown. Progress has been made on the genetic front with the identification of specific gene mutations (e.g., α-synuclein) associated with familial Parkinson syndromes. Because of their clinical heterogeneity there remains debate as to whether these genetic syndromes are representative of what has been considered classical PD. The identification of mutations in the parkin and LRRK2 genes in both familial and sporadic PD[1,2] suggest that genetic mutations may be more common than previously estimated. Despite these advances, at least 80% of PD cases do not have a clear genetic or familial basis. The knowledge that different genetic mutations can produce the PD phenotype suggests that perhaps there is no single clinical entity PD, but rather that PD is an amalgamation of many different conditions that simply have a greater or lesser degree of phenotypic overlap. However, most clinicians and scientists still endorse the classical concept of idiopathic PD.

For the condition generally referred to as idiopathic PD and characterized by asymmetric onset of rest tremor, bradykinesia and rigidity, responsiveness to dopaminergic treatment, and the classic pathology of nigral degeneration with Lewy bodies, the cause remains unknown. Because genetic causes appear identifiable in only a minority of cases, there has been an extensive search for potential environmental causes. This search has been fueled by the identification of individuals who developed parkinsonism following exposure to MPTP through injection drug use and epidemiologic links between PD and environmental exposure to agricultural chemicals. Another environmental topic of recent interest has been the potential relationship between occupational welding fume exposure and PD. Welding fume is the cloud of smoke that is produced when welding metals. This fume, like cigarette smoke, is a combination of many different chemicals in a complex interaction. The fume contains manganese, iron, aluminum, chromium, nickel, and ozone. The health effects of welding have been the subject of clinical investigation for over 50 years. Recognition that manganese, one of the metals found in welding fume, is a neurotoxicant and can lead to a neurologic syndrome with parkinsonian features has led to speculation that manganese exposure through welding fumes might result in PD. Speculation around this question has been sufficient to prompt extensive litigation throughout the United States. Many experts researching and writing on this topic have been involved on one side or the other of this litigation, providing expert testimony, research data, or both. Hence this is an area where the reader (and the writer) need to be careful about recognition and disclosure of potential conflicts of interest (see ours).

Two *Neurology* articles by Racette and others have described a potential relationship between welding and PD. In this issue of *Neurology*, two additional articles address this topic. The original Racette et al. article[3] examined the clinical features of 15 out of approximately 1,000 patients with PD in a tertiary referral practice who reported welding as their occupation. When age matched with patients with PD of other occupations, the clinical features and demographics of the welders were the same. The age at onset of the welders was lower than a different control group that was not age matched, but this may have represented an age effect of sampling individuals still employed compared to those who were largely retired. The second Racette et al.[4] article explored whether there is a higher than expected rate of parkinsonism in welders from Alabama. This study used an acceptable definition of parkinsonism, but one that was not sufficiently rigorous to define PD. A comparison was made to historical data derived from a PD epidemiologic survey done in Copiah County, Mississippi. The observed prevalence of parkinsonism in the studied welders was high, but it is not clear that the rate was higher than an appropriate control population.

The current articles expand this inquiry. The re-

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view article by Jankovic[5] (partially funded by defendants in the national litigation) lays out the historical perspective of manganese as a neurotoxicant and data regarding the association of manganese with PD. He concludes that manganese, usually in the form of dust from mining or grinding operations, can cause an intoxication resulting in a neurologic syndrome associated with dystonia, dysphonia, cognitive impairment, emotional disturbances, and some features of parkinsonism. He finds no convincing evidence in the published literature for an association between welding and PD. However, the absence of finding a relationship does not prove the absence of relationship. Many of the past studies have not used careful definitions of welding exposure or of case definitions of parkinsonism or PD. That said, the case-control studies in population-based samples published to date have indeed failed to find any meaningful association between PD and manganese exposure. To date, there have been no well-designed case-control studies assessing the relationship between welding exposure per se and PD.

A different approach to exploring the possible relationship between welding and PD is reported by Goldman et al.[6] (again the authors disclose connections to the defendants in the litigation) by comparing the prevalence of welders in clinical populations of patients with PD with the prevalence of welding in the general population from which these patients were drawn. This study looked not only at welding, but also considered other occupations that have previously been associated with an increased risk of PD (farming, healthcare workers). The authors acknowledge methodologic shortcomings, including their assumption that subjects in the clinics were drawn from the same populations used to establish the frequency of welding as an occupation. The definition of parkinsonism was relatively broad, although the majority of the subjects in the investigation had idiopathic PD. The authors failed to find an association between parkinsonism and welding, although they did identify an association with farming, healthcare occupations, and some other jobs. This study is not definitive given the potential referral biases involved and the fairly small sample studied.

The article by Josephs et al.[7] describes neurologic syndromes in welders who had evidence of hyperintensity in the pallidum on T1-weighted MR images. Such imaging abnormalities have been seen in individuals with presumed manganese intoxication, including those whose exposure has been through mining and hyperalimentation. The authors make the tentative assumption that the welders with MR abnormalities have manganese intoxication. This assumption warrants further investigation and substantiation. However, the authors found a broad spectrum of clinical disturbances in the subjects, including parkinsonism, isolated cognitive impairment, myoclonus, and vestibular dysfunction. The difficulty in interpreting the results of such a small case series is that the coexistence of welding with these phenomena does not demonstrate a causal relationship.

Where does current information leave the clinical and research community? It is now broadly accepted that manganese is a potential neurotoxicant and that excessive exposure can lead to neurologic disease. Hence, limiting excess exposure to manganese through any route (nutritional, inhalation, hyperalimentation) is warranted. Occupational workplace exposure guidelines have been set with this risk in mind. However, given the overall picture of pathologic disruption in the globus pallidus with sparing of the dopaminergic nigrostriatal pathway and clinical features that are dominated by dystonia and myoclonus, manganese-induced brain toxicity does not appear to be a good model for an environmental cause of PD.

There are reasons to believe that welding fumes may have different neurotoxicant effects than the largely pure manganese exposures studied so far, since welding fume includes not only manganese but a complex mix of other heavy metals and substances. Iron, a major component of fumes, increases oxidative stress through the formation of free radicals and its effects on mitochondrial function.[8] Iron promotes aggregation of α-synuclein[9] and provokes neuroinflammation.[10] In addition, welding fumes are associated with more aerosolized and smaller (ultrafine) particles than seen in mining or other exposures. This particle size might facilitate entry into the brain, and perhaps into the deep structures pathologically disturbed in PD. Metal particles generated in experimental welding fume exposures have been shown to be taken up by olfactory neurons and transynaptically transported in the brain.[11] Despite these theoretical concerns, as pointed out by Jankovic, there are currently insufficient data to support an association between welding fume exposure and the development of PD. It is also unknown whether welding fume exposure might lead to a broader set of clinical manifestations that may or may not include parkinsonism, as suggested in the work of Josephs et al.

Given the lingering scientific uncertainty and swirling litigation about this topic, further research is needed. Such investigations should avoid the pitfalls of the past. Specifically, rigorous case definitions of parkinsonism and PD should be adopted by consensus. However, other neurologic disturbances, such as cognitive impairment, sensory abnormalities, and other movement disorders, should also be assessed. Blinded, rigorous assessment of occupational and non-occupational exposure to welding fumes should be implemented. Finally, rigorous research designs that are capable of allowing inferences about causal relationships must be used, specifically case-control and cohort designs. The latter design might be most convincing, for example, following individuals beginning welding and nonwelding occupations and systematically determining rates of parkinsonism and PD over time. Such cohort studies are by their nature long-term and expensive.

Settings that lend themselves to the identification of specific populations, complete access to medical records, and long-term follow-up of individuals would be appropriate for such studies. Large health maintenance organizations or government and military populations are potential study groups. Unfortunately, since there is litigation in process, there may be little patience for the appropriate, scientifically sound accumulation of such data. In the meantime, the associations of neurologic syndromes with welding fume exposure must be considered speculative and tentative.

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