CME

Welding-related parkinsonism

Clinical features, treatment, and pathophysiology

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Article abstract—*Objective:* To determine whether welding-related parkinsonism differs from idiopathic PD. *Background:* Welding is considered a cause of parkinsonism, but little information is available about the clinical features exhibited by patients or whether this is a distinct disorder. *Methods:* The authors performed a case-control study that compared the clinical features of 15 career welders, who were ascertained through an academic movement disorders center and compared to two control groups with idiopathic PD. One control group was ascertained sequentially to compare the frequency of clinical features, and the second control group was sex- and age-matched to compare the frequency of motor fluctuations. *Results:* Welders were exposed to a mean of 47,144 welding hours. Welders had a younger age at onset (46 years) of PD compared with sequentially ascertained controls (63 years; $p < 0.0001$). There was no difference in frequency of tremor, bradykinesia, rigidity, asymmetric onset, postural instability, family history, clinical depression, dementia, or drug-induced psychosis between the welders and the two control groups. All treated welders responded to levodopa. Motor fluctuations and dyskinesias occurred at a similar frequency in welders and the two control groups. PET with 6-[^{18}F]fluorodopa obtained in two of the welders showed findings typical of idiopathic PD, with greatest loss in posterior putamen. *Conclusions:* Parkinsonism in welders is distinguished clinically only by age at onset, suggesting welding may be a risk factor for PD. These preliminary data cannot exclude a genetic contribution to susceptibility in these exposed individuals.

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Welding is the process of joining metals by electric arc or flame with a filler material.[1] The filler material, also called the consumable, is usually a coated electrode or wire that contributes metal to the joint. The four most common welds are the tungsten inert gas (TIG), metal inert gas (MIG), metal active gas (MAG), and manual metal arc (MMA).[2] The process of melting the parent metal and the consumable produces concentrated particulate fumes and gases; the consumable produces 80 to 95% of the fume. These fumes contain a number of elements, including F, Mn, Zn, Pb, As, Ca, S, Cr, and Ni. Gases released include CO, CO_2, F, and HF.[3,4]

A number of health problems are attributed to welding fumes. Welding may cause acute upper respiratory symptoms,[5] pulmonary edema,[6] pulmonary fibrosis,[7] and lung cancer.[8] Welding has also been associated with genitourinary[9] and laryngeal[10] cancers. Actinic keratoconjuctivitis (welder's flash)[11] and cataract formation[12] from ultraviolet radiation may be produced by the arc if eye protection is not worn. Neurologic complications of welding exposures include encephalopathy, probably from exposure to the fume (fume fever),[13] and lead poisoning caused by heating lead-based paint.[14]

The materials safety data sheet (MSDS) for welding consumables lists parkinsonism as a potential hazard of welding. Evidence supporting these claims consists of several case reports[15-18]; however, no established relationship between welding exposure and development of symptoms has been shown. Most reported patients had atypical features, including cognitive abnormalities, disturbances of sleep, peripheral nerve complaints, and mild motor slowing.[15,19] Manganese may be the toxic agent in welding fumes,[19,20] but welders exposed to manganese fumes in one study did not have

See also page 4

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higher blood concentrations of manganese than controls.[19] We have studied welders who developed parkinsonism to determine whether the symptoms and disease course in these individuals were different from those in controls with idiopathic PD.

Methods. We identified 15 career welders with parkinsonism from the Movement Disorders Center at Washington University School of Medicine (St. Louis, MO) from a group of 953 new parkinsonian patients seen between 1996 and 2000. Each welder reported the average number of hours per day worked, the years worked, exposure before symptom onset, and the percentage of time spent welding. We calculated cumulative hours of welding exposure before symptom onset (cumulative exposure = hours worked per week × days worked per year × years welding × fraction of working hours spent welding). History was taken and physical examination performed in all patients. We defined disease severity with the modified Hoehn and Yahr scale[21] at the most recent rating; positive family history as having one or more first- or second-degree relatives with a history of parkinsonism; dementia as previously described,[22] depression as that requiring treatment, psychosis as one or more episodes of visual or auditory hallucinations; asymmetry was determined by examination.

The first control group of 100 patients diagnosed with idiopathic PD[23] was sequentially ascertained from the Movement Disorders Center. The second control group from the same center included six patients with PD age- and gender-matched to each of the welders with parkinsonism.

Statistical analysis. Age at onset in the two groups and duration of disease was compared with a two-tailed, unpaired Student's *t*-test. The distributions of the Hoehn and Yahr in the three groups were compared using a Mann–Whitney *U* test. We used a χ^2 analysis to compare the frequency of individual clinical features between controls and welders. The Bonferroni correction was applied to correct for multiple comparisons; all *p* values obtained from comparison of clinical features were multiplied by 12, corresponding to the number of comparisons made between the welders and two control groups. All *p* values reported are corrected values.

6-[^{18}F]fluorodopa ([^{18}F]FDOPA) PET studies. [^{18}F]FDOPA PET scans were performed in two welders (aged 44 and 46 years at time of scan) and in 13 subjects (mean age, 49 years; range, 41 to 55 years) with typical idiopathic PD. These "control" subjects with PD had an average duration of symptoms of 2 years, closely matching the two welders. Similarly, they had asymmetric symptoms including bradykinesia, rigidity, and resting tremor (only one did not have resting tremor). Patients fasted overnight, with no PD medications taken for 12 hours before the study. PET scans were acquired by using a Siemens/CTI 953B scanner (Knoxville, TN) in 3D mode.[24] Each subject took carbidopa 200 mg 1 to 2 hours before the study. A lateral skull radiograph recorded the position of each subject's skull with respect to the PET images.[25] Attenuation factors were measured by using a transmission scan made with rotating rod sources of ^{68}Ge. [^{18}F]FDOPA was prepared as previously reported.[26] After injection of [^{18}F]FDOPA (4.65 to 5.00 mCi with a specific activity of approximately 365 Ci/mol), we collected 30 sequential PET images, beginning with 2-minute frames and increasing to 5 minutes. Reconstructed resolution of the images was approximately 5 mm full width at half maximum in the transverse plane. All frames were realigned to correct for head movement during the study, with reference to the first frame in which counts filled the brain. Each sequential frame was aligned to its preceding frame by use of automatic image registration.[27] Before alignment, frames were resampled to remove bias caused by pixelization.[28] Resampled frames were then smoothed (by AIR, 5-mm 3D blur) and the mean bidirectional fit was computed. Each frame was resliced exactly once by use of the combination of transformation matrices of all preceding frames plus the inverse of the resampling matrix.

Regions of interest, including caudate (10 × 10 × 13.5 mm), anterior putamen (10 × 10 × 13.5 mm), posterior putamen (10 × 10 × 13.5 mm), and occipital region (27 × 13 × 4.5 mm), were identified by a blinded rater who used a stereotactic method independent of the appearance of the images.[25] The striatal regions included four contiguous PET slices. An influx constant K_i was calculated,[29,30] with the occipital region as the input. We calculated K_i by using data from 24 to 94 minutes after injection. These PET studies were approved by the Human Studies committee and the radioactive drug research committee of Washington University School of Medicine. All participants gave written informed consent.

Results. All welders were men, whereas our sequentially ascertained controls were 52 men and 48 women. The welders identified welding as a substantial occupational time commitment and had an average cumulative exposure of 47,144 welding hours. Welders were younger at symptom onset (46 years; range 29 to 68) compared with sequentially ascertained controls (63 years; range, 30 to 81; $p < 0.0001$) who had a typical age at onset.[31] Duration of disease was 8.5 years in the welders, 6.6 years in sequentially ascertained controls, and 9.5 years in age-matched controls; the differences between the welders and these two control groups was not significant. Disease severities, as measured by the modified Hoehn and Yahr scale, were similar when comparing the welders to each of the control groups (Mann–Whitney *U* test; welders versus sequential controls: $p = 0.15$; welders versus age-matched controls: $p = 0.12$). The clinical features of the welders are summarized in table 1.

Family history was positive in 53% of welders, 32% of the sequentially ascertained controls, and 41% of age-matched controls (welders versus sequential controls, $p = 0.11$; and welders versus age-matched controls: $p = 0.33$). There was no significant difference between the frequency of cardinal PD signs when comparing welders with the two control groups (table 2). There was a trend toward a greater frequency of tremor when comparing the age-matched controls with the welders, but this difference was not significant when correcting for multiple comparisons.

Thirteen welders experienced symptomatic improvement with levodopa therapy. One subject had adequate control of his symptoms with pramipexole monotherapy. Another subject was lost to follow-up and at the time of his last visit did not require symptomatic treatment. There was no significant difference between the frequency of motor fluctuations and dyskinesias when comparing the welders with the two control groups. There was a trend toward a greater frequency of motor fluctuations in age-matched

Table 1 *Clinical features of 15 welders with parkinsonism*

Patient no.	Age at onset, y	Welding, h	Cardinal signs	Family history	Neuropsychiatric complications	Complications of therapy
1	39	55,200	T, R, B	Y	Depression	MF, D
2	34	24,000	T, R, B	Y	Psychosis	MF
3	43	52,800	T, R, B	Y	None	None
4	47	60,000	T, R, B	Y	Depression	None
5	29	Unknown	T, R, B, P	N	None	MF, D
6*	45	54,000	T, R, B	N	None	None
7*	41	48,300	T, R, B	Y	Depression	None
8	55	72,000	T, R, B, P	Y	None	None
9	34	45,000	T, R, B, P	N	None	None
10	50	8,300	T, R, B, P	N	None	MF, D
11	56	24,000	T, R, B, P	Y	None	MF, D
12	44	48,000	R, B, P	N	None	MF, D
13	50	24,000	T, R, B, P	Y	None	MF, D
14	54	60,000	R, B, P	N	Depression	D
15	68	84,000	T, R, B, P	N	Psychosis	MF, D

* These patients underwent PET with 6-[^{18}F]fluorodopa.

T = tremor; R = rigidity; B = bradykinesia; PI = postural instability; MF = motor fluctuations; D = dyskinesias.

controls compared with welders, but this difference was not significant after correcting for multiple comparisons. There was no significant difference between the frequency of clinical depression, dementia, or psychosis comparing the welders with the two control groups (table 3).

Eight welders had T1- and T2-weighted MRI scans of the brain; seven were normal, and one 78-year-old welder (Welder 15) had nonspecific white matter changes on T2-weighted images. [^{18}F]FDOPA PET obtained in two of the welders (Welders 6 and 7) showed findings typical of idiopathic PD with asymmetrically reduced striatal uptake, with greatest loss of uptake in posterior putamen (table 4). Although limited to only two welders, the degree of [^{18}F]FDOPA PET asymmetry in putamen corresponded with the degree of clinical asymmetry. Welder 6 had greater asymmetry of [^{18}F]FDOPA PET uptake compared with Welder 7. The degree of clinical asymmetry was defined by comparing the left and right scores for bradykinesia, rigidity, and tremor on the motor subscale of the Unified PD Rating Scale (UPDRS)[21] (maximum score = 32 on each side). Welder 6 had motor subscale scores of 7 versus 1, compared with Welder 7, who had motor subscale scores of 10.5 versus 5.

Discussion. Parkinsonism associated with welding is not clinically different from idiopathic PD, with the exception of a younger age at onset. Comparison of 15 welders with sequentially ascertained controls with idiopathic PD showed no significant differences except for younger age at onset. Subsequent comparisons of the welders with age-matched controls showed no significant differences. We found a high prevalence of familial PD in the welders and controls; this is likely due to the inclusion of second-degree relatives with PD in our definition of familial PD. There was no preponderance of psychosis, dementia, or clinical depression to suggest a predisposition to neuropsychiatric symptoms, as described previously.[32] Furthermore, levodopa provided similar benefits in welders, and they developed typical motor fluctuations after long-term treatment.

Our clinical observations and PET findings suggest that the pathophysiology of welding-related parkinsonism is similar to idiopathic PD, but we do not have pathologic confirmation of the diagnoses. Nev-

Table 2 *Frequency of cardinal PD features*

Study group	Asymmetry	Bradykinesia	Tremor	Rigidity	Postural instability
Welders	93	100	87	100	60
Sequentially ascertained controls	98	98	91	98	73
Age-matched controls	99	100	98	100	50

All values are percentages.

All p values >0.3 when comparing welders to the two control groups.

Table 3 *Frequency of complications of therapy*

Study group	Motor fluctuations	Dyskinesias	Depression	Dementia	Psychosis
Welders	53	47	26	7	20
Sequentially ascertained controls	42	38	15	9	16
Age-matched controls	80	61	26	9	21

All values are percentages.

All p values >0.3 when comparing welders to the two control groups.

ertheless, we speculate that the younger age at onset may be attributable to the effects of an accelerating agent from welding in a potentially "at-risk" patient who might otherwise develop PD with a later age at onset. Alternatively, *parkin*-associated parkinsonism could cause this phenotype in either familial or sporadic young-onset parkinsonism.[33] Expression of a genetic parkinsonism could be mediated by an environmental modifier. If welding contributes to the parkinsonism in these patients, presumably the accelerant would be inhaled, and the element in the inhalant most consistently associated with an extrapyramidal syndrome is manganese.

A variety of occupational manganese exposures are associated with a primarily extrapyramidal presentation called manganism.[34-38] The syndrome, best characterized in Moroccan manganese miners, includes progressive parkinsonism, dystonia, and neuropsychiatric symptoms.[34] Those exposed to manganese while working in the steel industry also may develop progressive parkinsonism.[35-37] Levodopa responsiveness in these parkinsonian subjects is transient and not associated with motor fluctuations.[39-41] Although our patients differ from the classic scenario of manganese exposures, this does not necessarily disprove the association. It is possible that our patients experienced a lower level of inhaled manganese exposure compared with occupations involving crushing of manganese ore (miners), because ore crushing produces higher air concentrations of manganese.[16] Low-level, long-term exposure over many years may be more analogous to unknown environmental triggers hypothesized to cause PD.[42]

Our two welders who had PET had asymmetric reduction of striatal [^{18}F]FDOPA uptake with greater reduction of uptake in posterior putamen, findings that are typical of idiopathic PD.[43] Although there are only two subjects, the welders did have greater asymmetry of caudate [^{18}F]FDOPA uptake than our 13 subjects with PD. An older study found normal striatal [^{18}F]FDOPA uptake in people with manganism; however, because of the relatively low resolution of the PET scanner in that study, the authors were only able to calculate uptake in left and right striatum and could not identify specific reductions in smaller regions such as posterior putamen.[44,45] It is also not clear whether the four subjects in that study had clinical manifestations similar to ours. They did report that all had bradykinesia, rigidity, and "gait abnormalities." Two had mild rest tremor, but the degree of asymmetry and response to levodopa were not addressed,[46] making it difficult to directly compare our results. Typical manganism may cause characteristic symmetric hyperintensities in the globus pallidus on T1-weighted MRI that resolve when the exposure is eliminated.[15,45,47,48] However, the sensitivity of the T1 signal changes for manganism is unknown. None of our welders had MRI-identified abnormalities in the basal ganglia, but the PET studies provided results typical of idiopathic PD. These findings suggest that our welders have a pathologic condition similar to idiopathic PD.

Table 4 *Findings in 6-[^{18}F]fluorodopa PET studies*

	Caudate		Anterior putamen		Posterior putamen	
Patient or group	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Welder 6	0.0120	0.0097	0.0122	0.0096	0.0114	0.0054
Welder 7	0.0105	0.0077	0.0096	0.0086	0.0040	0.0039
PD, n = 13*	0.0105 ± 0.0015	0.0104 ± 0.0011	0.0095 ± 0.0017	0.0081 ± 0.0021	0.0074 ± 0.0018	0.0053 ± 0.0029
PD, ipsilateral/ contralateral†	1.01 ± 0.10 (0.79–1.15)		1.21 ± 0.21 (0.96–1.67)		1.67 ± 0.74 (0.86–3.84)	

Values are Ki in min^{-1}.

* Represents 13 age-matched patients with idiopathic PD with mean values ± SD.
† Indicates ratios of the ipsilateral to contralateral Ki values found in the PD group. Values are mean ± SD (range).

Ipsilateral = the side of the brain ipsilateral to the more affected side of the body; contralateral = the contralateral side of the brain.

Our study suggests that welding may be a risk factor for a parkinsonism syndrome that is associated with reduced [^{18}F]FDOPA uptake and is clinically indistinguishable from idiopathic PD except for age at onset. We believe that welding exposure acts as an accelerant to cause PD. Our findings do not prove that manganese is the toxic agent, and other components of the fume could be responsible for parkinsonism in welders. Further studies are necessary to clarify this important issue. A detailed clinical evaluation of career welders compared with age-matched controls in a proper epidemiologic study will be essential to prove the relationship between welding and parkinsonism. If further studies prove an increased risk of parkinsonism in welders, welding may be the first example of an environmental risk factor for idiopathic PD.

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Relationship of substantia nigra echogenicity and motor function in elderly subjects

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Article abstract—*Background:* Patients with Parkinson's disease (PD) exhibit an increased echogenicity of the substantia nigra (SN) on transcranial sonography. Some healthy adults with the same echo characteristics showed a reduced ^{18}fluorodopa uptake on PET, indicating a subclinical alteration of the nigrostriatal system. *Objectives*: To determine whether the sonographic phenotype of hyperechogenic SN has any relevance for motor function in elderly subjects and whether an increased echogenicity of the SN is associated with an impaired motor function. *Method:* In a population-based, cross-sectional study, 93 subjects older then 60 years without history of extrapyramidal disorder underwent sonographic and neurologic examinations, with a quantitative motor assessment. *Results:* Elderly healthy subjects without prediagnosed extrapyramidal disorder but with SN hyperechogenicity had more frequent and more severe parkinsonian symptoms and a slower finger tapping than those with a regular echogenicity of the SN ($p < 0.05$, U test). *Conclusion:* With increasing age, subjects with SN hyperechogenicity develop a more substantial slowing of movements than subjects without this echo pattern, stressing the functional relevance of this sonographic finding. The authors speculate that hyperechogenicity of the SN may be detected by transcranial sonography early in life and may serve as a risk marker for nigral injury, although only a minority of these subjects will develop the full clinical picture of PD.

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The majority of patients with Parkinson's disease (PD) exhibit an increased echogenicity of the substantia nigra (SN) on transcranial sonography (TCS).[1] The mechanisms resulting in an increased echogenicity of the SN are still unclear. The same echo pattern of the SN has been identified in approximately 9% of healthy adults, with only a slight increase of the prevalence rate with age.[2] Recent ^{18}fluorodopa ([^{18}F]-dopa) PET studies disclosed a marked decrease in the accumulation of [^{18}F]-dopa in the striatum in some healthy subjects, with this increased SN echogenicity indicating a functional impairment of the nigrostriatal system.[2] According to these findings, we speculate that ultrasound may identify an important susceptibility marker for PD, and that the mechanisms causing this increase in SN echogenicity make nigral neurons more vulnerable to other noxious factors such as endo- or exotoxines.[3,4]

This study was designed to test the hypothesis that the subclinical alteration of nigral neurons detected by TCS might become symptomatic during life, and whether subjects with SN hyperechogenicity tend to develop clinical symptoms of the nigrostriatal system and, eventually, PD. The prevalence rate of PD is far below the rate of SN hyperechogenicity.[5] Therefore, at most, 5% of subjects with SN hyperechogenicity will develop typical PD. Nevertheless, one may ask whether subjects with SN hyperechogenicity more often exhibit motor slowing and stiffness with increasing age compared with subjects without this ultrasound finding. These subjects

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