Neurologic manifestations in welders with pallidal MRI T1 hyperintensity

K.A. Josephs, MST, MD; J.E. Ahlskog, PhD, MD; K.J. Klos, MD; N. Kumar, MD; R.D. Fealey, MD; M.R. Trenerry, PhD; and C.T. Cowl, MD, MS

Abstract—*Background:* Neurologic symptoms have been attributed to manganese fumes generated during welding. Increased T1 MRI signal in the basal ganglia is a biologic marker of manganese accumulation. Recent studies have associated welding and parkinsonism, but generally without MRI corroboration. *Objective:* To characterize the clinical and neuropsychological features of patients with MRI basal ganglia T1 hyperintensity, who were ultimately diagnosed with neurotoxicity from welding fumes. *Methods:* The medical records of welders referred to the Department of Neurology with neurologic problems and basal ganglia T1 hyperintensity were reviewed. *Results:* All eight patients were male career welders with increased T1 basal ganglia signal on MRI of the brain. Several different clinical syndromes were recognized: a parkinsonian syndrome (three patients), a syndrome of multifocal myoclonus and limited cognitive impairment (two patients), a mixed syndrome with vestibular–auditory dysfunction (two patients), and minor subjective cognitive impairment, anxiety, and sleep apnea (one patient). Neuropsychometric testing suggested subcortical or frontal involvement. Inadequate ventilation or lack of personal respiratory protection during welding was a common theme. *Conclusions:* Welding without proper protection was associated with syndromes of parkinsonism, multifocal myoclonus, mild cognitive impairment, and vestibular–auditory dysfunction. The MRI T1 hyperintensity in the basal ganglia suggests that these may have been caused by manganese neurotoxicity.

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Welding utilizes an electric arc to melt and bond metals. Fumes with high concentrations of aerosolized metals generated by welding may cause systemic as well as neurologic problems.[1-4] Although many elemental metals are released in welding plumes, the neurotoxicity is presumed to be primarily mediated by manganese.[5-9] Manganese neurotoxicity presents commonly as a parkinsonian syndrome[7,8,10,11] and has been reported to be associated with welding.[5,12]

A biologic marker of manganese accumulation within the CNS is bilaterally increased T1 MRI signal within the basal ganglia, especially the globus pallidus, but also the striatum.[1,13-18] Although T1 signal changes in these nuclei may be seen in several other conditions (e.g., nonketotic hyperglycemic episodes, hypoxia, neurofibromatosis, and other paramagnetic ions), it is an uncommon pattern. When the T1 hyperintensity is confined to the lentiform nuclei, and in the appropriate clinical setting, it has relative specificity for brain manganese. This MRI appearance suggests that the ambient fume intensity has been sufficient to affect the brain. Although an association between welding and parkinsonism has been postulated in two recent clinical series, the MRI scans in these patients were either normal or not reported.[5,12]

We report eight patients referred for neurologic evaluation and diagnosed with neurotoxicity from welding fumes. All had chronic and intense exposure to ambient welding fumes with reported inadequate ventilation or other safety measures and the characteristic MRI T1 basal ganglia abnormalities.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the June 28 issue to find the title link for this article.

Methods. The eight patients were referred to the Mayo Clinic for a variety of neurologic complaints and were evaluated by staff from both the Department of Neurology and the Division of Occupational Medicine (Toxicology). In none of the eight patients was manganese neurotoxicity the referral diagnosis. None of our patients was referred by an attorney, and none of the authors has

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From the Departments of Neurology (Drs. Josephs, Ahlskog, Klos, Kumar, and Fealey) and Psychiatry (Neuropsychology) (Dr. Trenerry) and Division of Preventive and Occupational Medicine (Dr. Cowl), Mayo Clinic, Rochester, MN.

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Address correspondence and reprint requests to Dr. K.A Josephs, Department of Neurology, Divisions of Behavioral Neurology and Movement Disorders, Mayo Clinic, Rochester, MN 55905; e-mail: josephs.keith@mayo.edu

Table 1 *Clinical features*

Case no.	Symptoms at onset	Presenting symptoms	Motor findings
1	Headaches, tinnitus, transient diplopia (44 y old)	Headaches, hand tremor, unsteadiness and falls, memory loss, personality change, 20-lb weight loss, mood change, tinnitus, hearing loss (46 y old)	Right hand postural tremor, mildly ataxic and wide-based gait, mildly reduced right arm swing
2	Cognitive impairment with memory loss and confused behaviors, later jerks (62 y old)	Jerks of limbs and trunk, unsteadiness, cognitive impairment, headache, and confused behaviors (63 y old)	Postural action tremor, multifocal myoclonic jerks affecting walking
3	Headaches, then imbalance and falls (32 y old)	Headaches, unsteadiness, and falls (33 y old)	Slow, unsteady shuffling gait, reduced arm swing, bradykinesia, hypokinetic dysarthria, hypomimia, positive pull test
4	Irritability, then tremor of head and hands (46 y old)	Upper extremity and head tremor, reduced dexterity, slowness and stiffness, micrographia, irritability and mild depression, headaches (48 y old)	Head tremor, mild right hand rest tremor, moderate right > left hand postural action tremor ≫ rest tremor, reduced right arm swing, stooped posture
5	Episodic vertigo, tremor, episodes of loss of consciousness thought to be syncope (21 y old)	Episodic vertigo and marked imbalance, syncope, tremor, mild cognitive complaints (22 y old)	Generalized body tremulousness, markedly unsteady gait
6	Daytime sleepiness due to sleep apnea, right hand dysfunction and slurred speech (40 y old)	Right hand reduced dexterity and slowness, slurred speech, unsteadiness (41 y old)	Moderate bilateral postural tremor, right > left side reduced arm swing, rigidity and bradykinesia, positive pull test, hypokinetic dysarthria, stooped posture
7	Memory loss and slowed cognition, anxiety (22 y old)	Irritability, memory loss anxiety, headaches, insomnia, twitches of muscles and reduced sexual drive (32 y old)	Normal
8	Spells of lightheadedness, impaired cognition, and headaches lasting minutes to hours, may be accompanied by tremulousness (24 y old)	Spells of lightheadedness, headaches, and impaired cognition recurring every few days, persistent mild memory deficits (38 y old)	Multifocal myoclonus, mild postural tremor, mild reduced left arm swing

been involved with depositions or legal disputes. At a minimum, all patients had blood studies (complete blood count, chemistry profile, total serum proteins, iron studies, thyroid, liver, and renal function tests, and heavy metals), urine studies (urinalysis, heavy metal screen), brain MRI, formal psychometrics, plus other tests and consultations as appropriate to the complaints. Where myoclonus was clinically suspected, evaluation was done in the Movement Disorders Neurophysiology Laboratory. In all eight patients, an occupational medicine physician obtained detailed information regarding the patients' working environment.

All patients were studied with a battery of neuropsychological tests,[19] including Wechsler Adult Intelligence Scale-3 or Wechsler Abbreviated Scale of Intelligence, cognitive processing and set maintenance skill (Trail Making Test, Stroop Neuropsychological Screening Test, or Stroop Color-Word Test), naming ability (Boston Naming Test), verbal fluency (Controlled Oral Word Association Test, Category Fluency), and learning and memory (Wechsler Memory Scale-3 and Rey Auditory Verbal Learning Test).

Results. All patients were men and had 1- to 25-year histories of welding prior to their first neurologic symptoms. The initial symptoms varied (table 1). By the time of presentation, multiple symptoms were experienced by all patients, with combinations of cognitive impairment (six of eight), headaches (six of eight), imbalance (five of eight), and tremor (six of eight). Taken with the neurologic examination, several different clinical syndromes were recognized, as follows.

Parkinsonian syndrome. Parkinsonism was the predominant presentation in three patients (Cases 3, 4, and 6), plus two cases had unilaterally reduced arm swing (Cases 1 and 8). Although parkinsonism associated with welding is thought to be symmetric,[12] two of the three cases (Cases 4 and 6) were asymmetric. These cases differed from idiopathic Parkinson disease (PD) in several respects: associated headaches (Cases 3 and 4), head tremor (Case 4), cognitive impairment (Case 6), upper extremity action tremor greater than rest tremor (Cases 4 and 6), and early falling (Case 3). The response to carbidopa/levodopa was partial in all three patients by examination and less than typically occurs in PD. Case 3 received up to 600 mg of levodopa daily with only slight improvement. Cases 4 and 6 were treated with doses up to 1,000 to 1,200 mg daily and reported moderate improvement in their hand tremor, but examination revealed substantial residual parkinsonism. The ages of these three patients were also atypical for PD, ranging from 32 to 46 years at symptom onset.

Syndrome of multifocal myoclonus and limited cognitive impairment. Multifocal myoclonus was prominent in two patients (Cases 2 and 8), both of whom also had cognitive impairment and headaches. The myoclonus impaired gait

and balance in one (Case 2) but was less severe in the other patient (Case 8). Evaluation in the Movement Disorders Neurophysiology Laboratory confirmed myoclonus in both cases (muscle burst durations of 75 milliseconds in Case 2 and <50 milliseconds in Case 8). Both patients had a history of confused behavior, which the wife of Case 2 described as putting dishes in the wrong cupboard or forgetting the sequence of simple household tasks. In Case 8, this confusion occurred episodically (every few days, lasting hours) and was associated with lightheadedness, headache, and a general sense of weakness; lesser cognitive impairment was present between these episodes. Prolonged EEG monitoring captured these spells, revealing no associated epileptiform activity. Psychometric testing confirmed mild cognitive impairment in both cases with reduced auditory verbal learning efficiency, measured by the total number of words acquired across the five Auditory Verbal Learning Test learning. Both had episodic headaches, beginning early in their welding careers.

Mixed syndrome with vestibular–auditory symptoms. A mixed syndrome with prominent vestibular–auditory symptoms was documented in two patients (Cases 1 and 5), plus Case 8 (described above) had asymmetric hearing loss, tinnitus, and episodic lightheadedness that could have been vestibular in origin. The initial symptoms experienced by Case 1 were tinnitus, diplopia, and headaches. Although the diplopia resolved spontaneously, he subsequently developed imbalance, hearing loss, and positional vertigo. On exam, he walked with a mildly wide-based, ataxic gait and had a mild postural tremor of the right hand, but without other evidence of ataxia. Vestibular laboratory testing revealed mildly abnormal vestibular function with a nonspecific pattern and abnormal posturography. Audiometry revealed bilateral high-tone sensorineural hearing loss. Because of complaints of cognitive dysfunction, psychometric testing was performed, revealing mild but definite deficits, especially on tasks that required complex visual–spatial discriminations, working memory, psychomotor speed, and sustained concentration.

Case 5 presented to the hospital after developing increasingly severe episodes of vertigo. The hospital admission examination was remarkable for his severe truncal instability with generalized tremulousness, being barely able to stand. He was the only patient in this series who underwent chelation therapy; he received 1 mg of ethylenediaminetetra-acetic acid (EDTA) infused IV over 12 hours on 3 consecutive days as treatment for manganese neurotoxicity. He also received intensive physical therapy; 1 month after completing chelation therapy, his neurologic examination had markedly improved, although still with the MRI T1 hyperintense signal in the basal ganglia, plus elevated blood manganese. This prompted one additional course of EDTA chelation treatment. One year later, he still had mild residual complaints of cognitive impairment, variable tremulousness, anxiety, and vertigo, despite discontinuing welding. His psychometric testing at that time was marginally abnormal, revealing low-average cognitive speed and reduced learning efficiency, though the proportion of information retained on delayed recall was grossly normal.

Minor syndrome with subjective cognitive impairment, anxiety, and sleep apnea. Case 7 presented with nonspecific complaints of cognitive dysfunction, anxiety and irritability, "shakiness," and a sleep disorder. He had no symptoms or signs to suggest parkinsonism, myoclonus, imbalance, or vestibular or auditory dysfunction; tremor was not apparent on examination. He did have chronic episodic headaches, but these predated welding. Sleep apnea had been diagnosed elsewhere and was treated with continuous positive airway pressure, which failed to reverse his other symptoms. Although his problems were nonspecific, they overlapped with others in this series, suggesting that they might have a common origin. Neuropsychological testing revealed essentially a normal profile.

General clinical observations. Most patients in this series experienced sleep disorders, vestibular or auditory symptoms, and mild cognitive dysfunction. Sleep disorders included sleep apnea in two (Cases 6 and 7) and possible sleep apnea in two others (based on history and abnormal overnight oximetry in Cases 2 and 4). Case 1 experienced both daytime sleepiness and nocturnal insomnia. Besides the vestibular and auditory syndromes described above in Cases 1, 5, and 8, Case 6 experienced several episodes of vertigo with nausea, and Case 2 had isolated right-sided hearing loss. Occupationally related noise exposure may have been a factor in the auditory deficiency, however.

Of the eight cases, six had prominent cognitive complaints (all but Cases 3 and 4) (for neuropsychological data, see table E-1 on the *Neurology* Web site at www.neurology.org). Psychometric testing results were somewhat variable across patients but suggested a pattern of mild cognitive dysfunction demonstrated by reduced learning efficiency along with reduction in cognitive speed and flexibility. In general, the pattern is suggestive of a subcortical or frontal pattern of involvement.

No patient had clear cerebellar signs on examination apart from gait instability (Cases 1 and 5), which could have had other neuroanatomic origins.

Welding and exposure history. All eight patients were career welders with reasonable cause for manganese toxicity. All performed metal inert gas or tungsten inert gas (Case 2 only) welding, usually welding stainless steel or galvanized steel. In all cases, there was either lack of an exhaust ventilation system or welding in confined spaces with inadequate ventilation. In some patients, additional exposure occurred as a result of cutting steel hardened with manganese. Personal respirators were not used by any of the eight patients. In one patient who wore a mask during welding, it was reported that part of the job requirement involved crawling in confined spaces in welding areas where no exhaust system was available.

Metal studies. Serum manganese levels were elevated in all but one patient (Case 3); in that patient, the value was near the upper end of normal. In only one of seven cases (Case 7) was the 24-hour urine manganese level elevated. With discontinuation of exposure, repeat serum manganese levels normalized within a few months in three patients in whom this was assessed (Cases 1, 2, and 6; table 2). A single patient continued to weld in the same occupational setting against medical recommendations (Case 7), and the serum manganese level remained high 1 year later.

Serum copper levels were measured in seven patients (all except Case 4) and were normal. Serum chromium levels were measured in three patients (Cases 1, 7, and 8), with elevations in two (Cases 1 and 8). In all eight cases,

Table 2 *Serum manganese levels during first year after diagnosis*

Case no.	Initial presentation, ng/mL	Month 1, ng/mL	Month 2, ng/mL	Month 5, ng/mL	Month 6, ng/mL	Month 9, ng/mL	Month 12, ng/mL
1	0.9	0.8					
2	1.3	0.8					
3	0.8		0.8				
4	1.2	1.2					
5*	1.3	1.2					0.9
6	1.0	0.8	1.0	0.8	0.7		
7†	1.1					0.9	
8	1.0						

Normal serum Mn level: 0.4–0.85 ng/mL. Month 1 = 1 month after presentation; Month 2 = 2 months after presentation, etc.

* Received chelation treatment.
† Patient continues to weld.

24-hour urine screen for lead, arsenic, cadmium, and mercury was normal. In two cases (Cases 1 and 8), additional metals were tested in the serum, including vanadium, nickel, gold, silver, cobalt, aluminum, and selenium; these were normal.

General laboratory studies. Routine laboratory studies in all eight patients were normal. Testing included complete blood count (including hemoglobin and erythrocyte mean cell volume), chemistry profile, total serum protein, thyroid, liver, and renal function studies, erythrocyte sedimentation rate, urine analysis, serum iron, and ceruloplasmin. Other testing was variably performed, appropriate to the clinical picture, and was normal or unremarkable. This included CSF studies that were performed in two patients (Cases 2 and 5).

Imaging. In all eight cases, there was a bilateral hyperintense signal on T1-weighted MRI sequences in the globus pallidus. This was most easily recognized on sagittal sequences (figure) but could also be seen on axial imaging. In patients in whom follow-up MRI head scans were performed after stopping welding, there was a trend for the hyperintense T1 signal to fade with increasing time from exposure; however, subtle increased signal was still present in two cases up to 4 months after welding was discontinued. Therefore, of the six patients with multiple head MRI scans (table 3), two had continued exposure (Cases 7 and 8), with the T1 signal intensity either increased (Case 8) or unchanged (Case 7). In the other four patients in which the exposure was removed, two showed decreased T1 signal intensity (Cases 1 and 3), and one remained unchanged (Case 5); in the fourth (Case 6), the second MRI head scan performed 6 years after stopping welding revealed resolution of the abnormal pallidal T1 signal. Six of the eight patients (all except Cases 2 and 7) had brain CT, and this was normal in all. No patient underwent functional brain imaging.

Treatment. Seven of the eight patients were treated with a low-manganese diet, whereas the eighth patient (Case 5) received chelation therapy with EDTA. The impact of the dietary therapy is unclear. The chelated patient was unique in that he had a subacute presentation; most of his symptoms resolved with chelation.

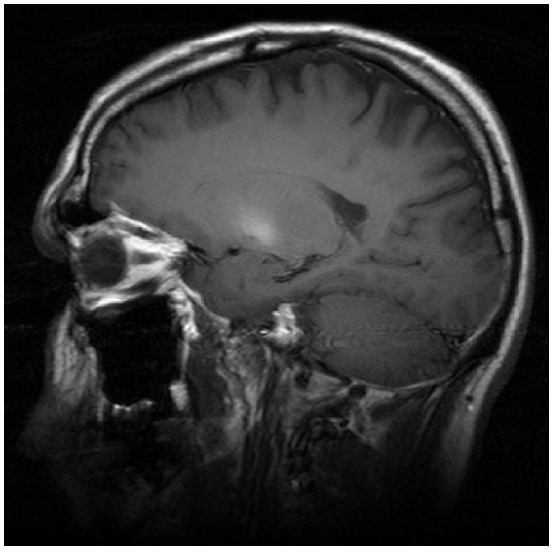

Figure. Case 3. High T1 signal change on sagittal MRI in the globus pallidus in a case of manganese toxicity secondary to occupational exposure from welding.

Discussion. Welding is a common occupation, and the association of welding with a medical condition does not necessarily imply that toxins from welding are the cause. However, circumstantial evidence suggests that welding-related manganese neurotoxicity may have been causative in these cases for several reasons: 1) the MRI T1 basal ganglia hyperintensity, which is a relatively specific biomarker of brain manganese accumulation; 2) the overlap of symptoms and signs among these patients; 3) shared clinical features with previously described cases of manganese neurotoxicity, for example, tremor and parkinsonism; 4) inadequate ventilation or protection during welding, which may predispose to manganese toxicity. On the other hand, some of the symptoms experienced by these patients are less specific, such as headache or irritability, and could have been coincidental in some cases. The precise clinical spectrum

Table 3 *Changes in T1 signal intensity in globus pallidus in welders with multiple MRI head scans*

	1st MRI scan		2nd MRI scan		3rd MRI scan		4th MRI scan	
Case no.	Welding status	MRI outcome	Welding status	MRI outcome	Welding status	MRI outcome	Welding status	MRI outcome
1	Welding	High T1 signal in globus pallidus	Stopped welding at time of scanning	No change in signal intensity	Stopped welding 4 mo ago*	Signal intensity reduced*		
3	Stopped welding 1 mo ago	High T1 signal in globus pallidus	Stopped welding 3 mo ago*	Signal intensity reduced*	Stopped welding 5 mo ago	No change in signal intensity		
5	Welding	High T1 signal in globus pallidus	Stopped welding 1 mo ago	No change in signal intensity				
6	Welding	High T1 signal in globus pallidus	Stopped welding 6 y ago*	Absent signal*				
7	Welding	High T1 signal in globus pallidus	Welding, 2 y from 1st scan	No change in signal intensity	Welding, 3 y from 1st scan	No change in signal intensity	Welding 4 y from 1st scan	No change in signal intensity
8	Welding	High T1 signal in globus pallidus	Welding, 7 mo from first scan*	Signal intensity increased*				

* Changes from one MRI scan to the next.

of welding-related manganese neurotoxicity requires further study and confirmation.

Although there was overlap among these cases, there was also heterogeneity. Thus, several clinical syndromes emerged: predominant parkinsonism, multifocal myoclonus and cognitive impairment, a vestibular–auditory syndrome with mild cognitive dysfunction, plus only minor symptoms of mild cognitive dysfunction, anxiety and irritability, "shakiness," and a sleep disorder (experienced by only one patient). Whereas the syndrome of predominant parkinsonism has been reported,[7,8,10,11,20-25] the second syndrome of cognitive dysfunction and multifocal myoclonus has not been previously described; however, myoclonus has been documented in a single case report,[13] and cognitive impairment is commonly reported.[7,8,10,11,14,20] Myoclonus is uncommon and unlikely to be coincidental; it was confirmed electrophysiologically. A vestibular–auditory syndrome has not been previously emphasized as a syndrome of manganese toxicity; however, two of our patients had prominent vestibular–auditory complaints, and a third patient had less prominent symptoms. Auditory and vestibular symptoms have been reported in manganese toxicity,[10,23,26] and welders exposed to manganese have longer latencies in an event-related auditory evoked potential measurement.[27] However, hearing loss and tinnitus are common complaints and may have been coincidental or due to occupational noise exposure in these cases or both. In the single patient with symptoms of mild cognitive dysfunction, anxiety, irritability, and sleep disorder, these may be nonspecific, but such symptoms are also commonly reported in the literature, as are irritability, sleep disturbances, and anxiety.[1,7,8,10,11,21]

Consistent with multiple prior reports of manganese neurotoxicity,[1,21,28-31] many of our patients' symptoms persisted after removal from exposure. Thus, manganese exposure may produce irreversible symptoms.

The serum manganese level was mildly elevated in seven of our eight patients and was at the upper limits of normal in the other. The absence of striking blood manganese elevations in the setting of clinical manganese neurotoxicity is not unexpected.[1,10] Although the behavior of manganese in the bloodstream of humans has not been well characterized, available evidence suggests that measured serum manganese primarily reflects that which is protein bound. When circulating proteins are saturated, free manganese rapidly binds to other tissues or is rapidly excreted from the body.[32,33] Thus, free manganese does not accumulate in the circulation.[34] Consequently, serum manganese levels do not correlate with the intensity of exposure.

The primary route of manganese excretion is via the biliary system,[35] with the kidneys only a secondary route. Hence, urinary manganese is also a poor index of chronic manganese exposure. In our eight cases, only one had elevated urinary manganese levels. In normal humans, nearly all manganese comes from diet, where about 3 to 6% is absorbed from the gastrointestinal tract,[8,33] Ninety percent is excreted from the body as feces.[34] This hepatobiliary circulation of manganese is similar to that of copper; with both elements, only trace amounts appear in the urine,[34] except in acute or subacute massive exposure or chelation.[30]

The patients in this series were unlikely to have coincidental PD for several reasons. The tremor in these cases was predominantly postural and kinetic, rather than a prominent rest tremor, as described in other series.[8,14] Second, the response to carbidopa/

levodopa was minimal,[36] or partial at best, unlike PD. Finally, the pallidal MRI hyperintensity is not seen in PD.

MRI T1 hyperintensity in the lentiform nuclei is an uncommon brain imaging pattern, especially with normal head CT scanning (n = 6). In the setting of prominent ambient manganese exposure, as occurred in these otherwise healthy welders, there are no other explanations for the imaging findings.

In three cases in which serial scans were performed after terminating welding, the high T1 signal intensity faded and eventually disappeared. This finding is similar to a report on a single case of manganese toxicity from occupational exposure,[1] plus reports of manganese toxicity from other sources.[37,38]

The severity or the character of the neurologic syndrome did not appear to relate to the intensity or anatomic distribution of the MRI basal ganglia T1 hyperintensity. In fact, abnormal T1 imaging has been reported in asymptomatic individuals with manganese exposure.[39]

Neuropsychological testing revealed only mild cognitive deficits and inefficiencies but was consistent with patient complaints. On the whole, the degree of impairment was sufficient to be noticeable to the patient and produce inefficiencies and frustration during some activities of daily living. The pattern of reduced learning efficiency with reduced cognitive speed and flexibility was reminiscent of that seen in patients with parkinsonian syndromes, although this pattern was also found in our patients who did not have parkinsonism.

Only one of our patients underwent chelation therapy with EDTA, and he had an almost immediate improvement of his symptoms. This patient's symptoms, however, were somewhat atypical, with a subacute temporal course. The literature is unclear in regard to the efficacy of chelation therapy in manganese toxicity, with reports varying from no improvement to complete resolution of symptoms.[7,10,40]

Welding with inadequate ventilation or without adequate personal respiratory protection may result in neurotoxicity. We identified combinations of mild cognitive impairment, multifocal myoclonus, vestibuloauditory symptoms, as well as parkinsonism in welders with inadequate safeguards that had MRI evidence of brain manganese accumulation. These were seen in association with lesser or nonspecific symptoms, including headache, irritability, personality change, and sleep disorders. Manganese neurotoxicity may have been causative, although this requires further investigation. The reason for the heterogeneity of the clinical phenotypes was unclear but may relate to the varied chronicity and intensity of exposure plus other metabolic factors such as the body burden of other metals that share transport and metabolism with manganese.[9,41,42]

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