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A follow-up study of neurobehavioral functions in welders exposed to manganese

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ABSTRACT

Welders may be exposed to high amounts of manganese (Mn). In this study 63 welders and 65 referents were followed up with neurobehavioral tests approximately 6 years after the initial examination at baseline. The welders were exposed to the geometric mean (GM) Mn concentration of 116 $\mu g/m^3$ at baseline and 148 $\mu g/m^3$ at follow-up. Their mean duration of employments as welders was 19.5 years at follow-up. Being exposed as a welder was associated with a decline between baseline and follow-up in the performance on the Static Steadiness Test, Finger Tapping Test and Grooved Pegboard Test. However, the decline was also associated with having high concentrations of carbohydrate deficient transferrin in serum (sCDT), indicating high alcohol consumption. When subjects with sCDT above the upper reference limit of the laboratory ($\geq$1.7%) were excluded from the analyses, no difference in the decline in performance was observed between welders and referents for any of the applied neurobehavioral tests. Three welders had developed bradykinesia at follow-up, as assessed by a substantial decline in their Finger Tapping Test performance. They had also experienced a severe decline in Foot Tapping, Grooved Pegboard and Postural Sway Test scores (while blindfolded), while postural tremor as assessed with the CATSYS Tremor 7.0 was normal. Their neurobehavioral test performance at baseline 6 years previously had been normal.

1. Introduction

The severe central nervous system (CNS) disorder manganism, which is mainly characterized by movement disturbances, is caused by high, long-term occupational exposure to manganese (Mn) (Couper, 1837; McMillan, 1999). There is concern that the occupational exposure to Mn containing welding aerosols also may cause the disease, which traditionally has been diagnosed in workers employed in industries such as Mn alloy production, mining and crushing of Mn ore, and in steel and dry cell battery production (Rodier, 1955; Tanaka and Lieben, 1969; Emara et al., 1971; Cook et al., 1974; Huang et al., 1989).

Welders are by number the largest group of workers exposed to Mn. The predominant sizes of particles generated during welding are below 1 μm in aerodynamic diameter, thus the particles can easily penetrate into the alveolar region of the lung (Antonini et al., 2009a; Berlinger et al., 2011). The particles are typically agglomerated into chainlike structures formed by small primary particles with a complex chemical composition as well as compounds such as $KMnF_3$, $MnFe_2O_4$ or K_2MnO_4 (Voitkevich, 1995). Only a fraction of Mn in welding aerosol particles appears to be soluble in an artificial lung lining fluid and thus available for pulmonary uptake (Ellingsen et al., 2013).

Magnetic resonance imaging (MRI) has shown increased amounts of Mn in globus pallidus, midbrain, nucleus caudatus and putamen of welders (Kim et al., 1999; Criswell et al., 2012). PET-scan imaging suggested decreased striatal D2 receptor of non-human primates and dopamine D2 receptor density in the midbrain of Sprague-Dawley rats after Mn exposure (Guilarte, 2010; Sriram et al., 2010). Reduced striatal post-synaptic D2 receptor density was also reported to occur in chronic manganism (Aschner et al., 2009). However, the study of Sprague-Dawley rats pointed to additional neurotoxic manifestations of Mn exposure such as increased concentrations of cell markers of neuroinflammation (e.g. IL-1β and TNF-α) and astrogliosis (Antonini et al., 2009b).

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Relatively few studies of Mn-exposed welders using neurobehavioral methods have been published. Cross-sectional studies have shown impaired motor functions (Siegl and Bergert, 1982; Sjögren et al., 1996; Bowler et al., 2003, 2006; Ellingsen et al., 2008; Chang et al., 2009; Laohaudomchok et al., 2011; Ellingsen et al., 2013) as well as impaired cognitive functions (Bowler et al., 2003, 2006; Wang et al., 2006; Yuan et al., 2006; Chang et al., 2009; Laohaudomchok et al., 2011). These studies may indicate that functional alterations of the CNS may occur as a result of exposure to welding aerosols containing Mn. However, several of the studies have been small and without appropriate exposure assessment. The results across studies appeared not to be consistent in a recent meta-analysis of neurobehavioral studies of occupationally Mn-exposed populations, and the authors pointed to various potential confounders not appropriately accounted for, e.g. alcohol consumption (Meyer-Baron et al., 2011). A recent review also pointed to lack of appropriate confounder control in several neurobehavioral studies (Santamaria and Sulsky, 2010).

There are few follow-up studies available of occupationally Mn-exposed populations. Such studies have methodological advantages compared to cross-sectional studies that are vulnerable to the effect of healthy workers staying in work while subjects with work-related disease may have left work. A prospective study of battery workers exposed to MnO_2 did not reveal a substantial decline in neurobehavioral performance during a 10 years follow-up period, while performance improved when exposure ceased (Roels, 1999). In a small 3.5 years follow-up of 26 subjects of whom 13 were welders and 13 were ex-welders, no significant differences in any of the neuropsychological or motor functions variables were shown between the two groups (Bowler et al., 2011). Only cognitive functions improved, while olfactory, extrapyramidal and mood disturbances remained constant or exacerbated.

In the present study, welders and referents who were examined with neurobehavioral methods at baseline in 2002/2003, were re-examined in 2008/2010 in order to assess a possible decline in performance over a 6 years period. The results from the examinations at baseline have been published (Ellingsen et al., 2008). This work is part of a larger study of welders' exposure and health in Russia, where manganism among welders for decades has been regarded as a serious occupational health issue.

2. Material and methods

2.1. Study design and subjects

During 2002/2003, 96 welders exposed to welding aerosols and 96 referents were examined with neurobehavioral methods (baseline). Details on the selection of participants and design of that study have been reported (Ellingsen et al., 2008). Briefly, at least 1 year of employment as a welder and currently employed were required for inclusion in that study. Referents were turners/fitters employed in the same plants as the welders, one plant is producing heavy machinery and one plant is a shipyard.

The purpose of the present follow-up study was to re-examine these subjects during 2008/2010 (follow-up). Out of the originally 96 examined welders, two had died and 18 had moved out of the region and were thus not available for the study. Five welders were on sick-leave and eight refused to participate. Fifteen referents had moved out of the region and were thus not available for participation at follow-up. Sixteen referents refused to participate. Thus, 63 welders and 65 referents were re-examined at follow-up.

Exclusion criteria were identical at baseline and at follow-up. Among the health-related exclusion criteria were known current or past diseases of the CNS that is probably unrelated to Mn exposure such as brain tumours or transitory ischaemic attacks. Known drug or alcohol abuse, diabetes mellitus, severe kidney or liver diseases and larger damage of the dominant hand also lead to exclusion. Subjects that had been on sick leave for more than 14 days at the examination day, were not considered for inclusion. Subjects occupationally exposed to organic solvents (>3 years) in jobs such as painters or spray-painters or occupationally exposed to neurotoxic metals (e.g. lead (Pb) or mercury (Hg)) for more than 1 year were also excluded. Subjects ever employed at plants producing solvents were not included.

Air samples were collected by personal sampling ideally on the 2 days preceding the neurobehavioral examinations. These examinations and a structured interview were carried out at the occupational health clinics of the respective facilities. A whole blood sample (from the cubital vein) was collected in the morning of the examination day. A first voided morning urine sample from the same day was also collected. The same sampling procedures were followed for the examinations at baseline (Ellingsen et al., 2008). Background characteristics for the studied subjects at follow-up are shown in Table 1.

Participation in the study was voluntary, and an informed written consent was obtained from each participant. The study was approved by the Norwegian Regional Ethical Committee for Medical Research (REK2), by the Ethics Committee of the Northwest Public Health Research Centre (NWPHRC) (St. Petersburg, Russia) and the Office of Research Protection, US Army Medical Research and Material Command (Fort Detrick, MD, USA).

2.2. Neurobehavioral examinations

The subjects were examined for around 1½ to 2 h. The same test sequence was used for all participants. Before being tested, the subjects were interviewed focusing on background variables,

Table 1
Background variables of welders and referents recorded at follow-up.

	Welders (*N* = 63) AM[a] (range)	Referents (*N* = 65) AM (range)	*p*-value
Age (years)	42.7 (26–70)	45.8 (22–70)	0.13
Weight (kg)	82.9 (53.7–120.1)	82.8 (55.7–117.8)	0.99
Education (years)	11.7 (7–17)	12.2 (8–19)	0.12
Alcohol consumption (g/year)	5260 (0–23920)	4610 (0–35360)	0.56
sCDT (%)[b]	0.8 (<DL-9.1)	0.7 (<DL-6.6)	0.23
Coffee consumption (cups/day)	1.0 (0–5)	1.2 (0–6)	0.51
Current smokers (in %)[c]	49.2	55.4	0.48
Shift workers (in %)[c]	31.7	29.2	0.76
Head injury (in %)[c]	11.1	10.8	0.95
Months of follow-up	70.8 (59–90)	70.7 (61–80)	0.92

[a] Arithmetic mean.
[b] Geometric mean.
[c] Prevalence.