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Decreased brain volumes in manganese-exposed welders

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ABSTRACT

Background: A great deal of research has been devoted to identifying subclinical functional brain abnormalities in manganese (Mn)-exposed welders. However, no previous study has investigated morphological brain abnormalities, such as changes in brain volume, in welders. This study evaluates morphological changes in brain volume among welders, and investigates the relationship between structural brain abnormalities and subclinical dysfunction in this population.
Methods: We used voxel-based morphometry (VBM) to assess differences in gray and white matter brain volumes between 40 welders with chronic Mn exposure and 26 age-matched control subjects. Correlation analyses were used to investigate the relationship between brain volume changes and decreased performance on neurobehavioral tests.
Results: Brain volumes in the globus pallidus and cerebellar regions were significantly diminished in welders with chronic Mn exposure compared to controls (FDR-corrected $P < 0.05$). These changes in brain volume were negatively correlated with cognitive performance and grooved pegboard scores.
Conclusion: There are measurable brain volume reductions in the globus pallidus and cerebellum of welders chronically exposed to Mn, and these volume reductions correlate with cognitive and motor neurobehavioral deficits. Our findings therefore indicate that volumetric measurement could be a useful subclinical marker among welders that show no signs of manganism.

1. Introduction

Manganese (Mn) is the fourth most widely used heavy metal in the world. An increased Mn concentration in the brain is a critical step in Mn neurotoxicity. Also known as manganism, this movement disorder is observed in Mn miners, ferromanganese alloy processing workers, and welders (Chia et al., 1993; Myers et al., 2003; Bowler et al., 2006; Park et al., 2007). Neurobehavioral dysfunction due to Mn exposure predominantly affects fine motor functions, with Mn-exposed workers often performing poorly on motor-related tasks such as the grooved pegboard and finger-tapping tests (Shin et al., 2007; Chang et al., 2009a). These workers also exhibit reduced cognitive performance, particularly with regards to memory functions (Iregren, 1990; Lucchini et al., 1995, 1999; Mergler and Baldwin, 1997; Chang et al., 2010a).

With respect to subclinical functional brain abnormalities in Mn-exposed welders, advanced magnetic resonance imaging (MRI) techniques (i.e., functional MRI and diffusion tensor imaging) and magnetic resonance spectroscopy have revealed that there is cerebral involvement in the pathoanatomy of Mn neurotoxicity among Mn-exposed welders (McKinney et al., 2004; Chang et al., 2009b; Guilarte et al., 2006; Chang et al., 2010a,b; Kim et al., 2011). Studies using voxel-based morphometry (VBM) have demonstrated that whole-brain-level voxel-wise comparisons of gray and white matter can help characterize the subtle changes in brain structure seen in a variety of diseases associated with neurological and psychiatric dysfunction (Koo et al., 2006; Kinkingnehun et al., 2008; Bendfeldt et al., 2009; Agosta et al., 2010). However, no previous study has investigated changes in

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brain volume among welders with chronic Mn exposure. Furthermore, it is important to examine whether cognitive or motor-related neurobehavioral deficits often found in Mn-exposed welders are associated with structural brain abnormalities in this population.

The purpose of the present study was to evaluate the relationship between structural brain abnormalities and subclinical neurobehavioral dysfunctions in welders with chronic exposure to Mn. VBM was used to: (i) assess the difference in gray and white matter volume between welders and age-matched control subjects; and (ii) investigate the relationship between brain volume reduction and decreased performance on neurobehavioral tests. We hypothesized that: (i) chronic Mn exposure in welders decreases performance on motor and cognitive neurobehavioral tests; (ii) chronic Mn exposure in welders causes significant volume reductions (a sign of atrophy) in brain regions associated with motor functions; and (iii) the globus pallidus (GP) and cerebellum, which are key brain regions involved in fine motor control, are particularly susceptible to this volume reduction (as Mn exposure predominantly affects fine motor functions).

2. Subjects and methods

2.1. Subjects

Males aged more than 40 years, who were current full-time welders with more than five years of welding experience in factories making mild steel blocks for shipbuilding in Korea, were recruited to the present study. The welders were contract workers rather than regular factory employees. The main type of welding performed by the workers over the past 10 years was gas metal arc welding (GMAW) using CO_2 as a shielding gas. Exposure in the workplace had been assessed by qualified industrial hygienists, and welding was shown to be the only source of Mn in the workplace. Age- and gender-matched, non-welding production workers from the same workplaces, who were not exposed to other hazardous materials (e.g., paint), were recruited as controls. We selected these workers instead of office workers (who also lacked Mn exposure) because the socioeconomic status and behavioral patterns of office workers differed from those of the welders. Two workers with a university education (more than 12 years of education) were included in control group only, and were excluded from the present study to avoid between-group differences in neurobehavioral performance. Workers with a recent history of head injury, hand injury or other physical impairments (e.g., history of chronic liver disease, iron deficiency anemia, carbon dioxide poisoning, stroke, depression or seizure disorders) were excluded. Workers with specific, non-Mn-related physical conditions that could affect MRI signals, such as trauma, hyperosmolar conditions, hypoxia, stroke, and tumors (Warakaulle and Anslow, 2003), were not included in the study. Of the recruited workers, two welders and two control individuals failed to complete all of the examinations. Thus, a total of 66 workers (40 welders and 26 controls) were included in the final analyses. Workers visited a university hospital during the weekend, and were examined at least 12 h after their most recent work shift. Each participant completed a questionnaire, provided blood samples, and underwent neurobehavioral tests and MRI examination on the day of the visit. Written informed consent was obtained from all subjects before the examination, and the study protocol was approved by the Institutional Review Board of Ulsan University Hospital.

2.2. Exposure

We analyzed airborne Mn measurements that had been taken twice yearly at each workplace since 2006. Airborne Mn released by the welding process was collected on mixed cellulose ester membrane filters (0.8-μm pore size, 37-mm diameter; SKC, USA) in personal air samplers (AirLite; SKC, USA). All pumps were calibrated before and after use. Sampling was performed for at least 6 h, excluding workers' breaks, with flow rates of 1–2.5 L/min. Samples were measured in a laboratory involved in the quality control programs organized by the Korean Occupational Safety and Health Agency (KOSHA). Analysis was performed using inductively coupled plasma atomic emission spectroscopy (ICP-AES; ULTIMA2; Horiba Jobin Yvon, France) according to NIOSH analytical methods 7300 (NIOSH, 1994).

2.3. Blood Mn

Blood was collected by venipuncture of the antecubital vein. Special care was taken to avoid contaminating skin and equipment with workplace dust. Mn levels were measured using a graphite furnace atomic absorption spectrophotometer (Varian AA240Z; Varian Techtron Pty, Victoria, Australia). All analyses were performed in a laboratory that participates in the quality control programs organized by KOSHA.

2.4. Questionnaires and blood measurements

Each individual completed a questionnaire and underwent blood sample collection during a single day. The questionnaire assessed basic demographic information (such as age and educational level), information about smoking, alcohol consumption, medications, recent medical history, subjective symptoms, and job type, including the type and duration of welding. Each participant was asked detailed questions about his work history. Blood samples were obtained by venipuncture of the antecubital vein and analyzed for complete blood counts, hemoglobin and hematocrit levels, and liver functions (aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase levels).

2.5. Neurological examinations

Each subject underwent neurological examinations aimed at detecting clinical signs of manganism. Manganism is a progressive syndrome that typically begins with relatively mild, nonspecific symptoms that can gradually evolve to a severely debilitating disease with some features similar to Parkinson syndrome (Rodier, 1955; Olanow, 2004; Schuler et al., 1957; Yamada et al., 1986; Huang et al., 1989, 1993; Calne et al., 1994; Chu et al., 1995). Neurological examinations were administered by an occupational physician (YK) who has specialized in the assessment of Mn-exposed workers for over 15 years.

2.6. Neurobehavioral examination

The utilized neurobehavioral tests included the digit symbol test, the digit span test, the Korean Auditory Verbal Learning Test (K-AVLT), the Korean Complex Figure Test (K-CFT), the verbal fluency (word fluency) test, the Stroop test, the grooved pegboard test, and the finger-tapping test. A single examiner scored each test item for all participants blinded to exposure status. All neuropsychological test scores were reviewed by an experienced clinical psychologist prior to analysis of the results. Outlying values on the neurobehavioral tests were evaluated to determine possible explanations for poor performance. Full details of the neurobehavioral examination methods were provided in our previous paper (Chang et al., 2009a).

2.7. MRI

The MRI examinations were performed using a 3.0 Tesla whole-body scanner (Signa Exite HD; GE, USA) with an eight-channel