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Screening for early detection of parkinsonism using a self-administered questionnaire: A cross-sectional epidemiologic study

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ABSTRACT

Background: Manganese (Mn) is a common component of welding fume. Exposure to Mn fume has been associated with parkinsonism. A simple and reliable screening tool to evaluate Mn exposed workers for neurotoxic injury would have broad occupational health application.
Methods: This study investigated 490 occupational welders recruited from a trade union list. Subjects were examined by a movement disorders specialist using the Unified Parkinson Disease Rating Scale motor subsection 3 (UPDRS3). Parkinsonism, intermediate, and normal groups were defined as UPDRS3 score $\geq$15, 6–15, and $<$6, respectively. Workers completed a health status questionnaire (PDQ39) and a Parkinson disease (PD) Symptoms Questionnaire. Areas under receiver operator curve (AUC) were analyzed based on these scores, adjusted for age, smoking, race, gender, and neurologist, using normal as the reference.
Results: The AUC was 0.79 (95% confidence interval [CI] = 0.73–0.84) for PDQ39 and 0.78 (95% CI = 0.72–0.85) for PD Symptoms Questionnaire score. At 70% sensitivity, the specificity for PDQ39 score and PD Symptoms Questionnaire score for the prediction of parkinsonism was 73.1% and 80.1%, respectively.
Conclusions: These results suggest the questionnaires have reasonably good sensitivity and specificity to predict parkinsonism in Mn exposed workers. These questionnaires could be a valuable first step in a tiered screening approach for Mn exposed workers.

1. Introduction

Manganese (Mn) is an essential element involved in several cellular metabolic mechanisms and in protection against lipid peroxidation, but is also an established basal ganglia neurotoxin (Segura Aguilar and Kostrzewa, 2004). The proposed mechanisms of Mn neurotoxicity include impairment of cellular antioxidant defenses, disruption of mitochondrial oxidative energy metabolism, and dopaminergic toxicity (HaMai and Bondy, 2004). Symptoms of Mn poisoning include parkinsonism, dystonia, and neuropsychiatric dysfunction (Guilarte, 2010). The fulminant clinical syndrome associated with Mn exposure is called manganism, but this syndrome has been most commonly associated with levels of occupational exposures not usually seen in modern times (Iregren, 1999). However, exposure to levels of Mn fume at or below the OSHA permissible exposure limit (5 mg/m^3) has been associated with parkinsonian signs (Laohaudomchok et al., 2011; Roels et al., 1985, 1987) and abnormal performance on neuropsychiatric tests (Bouchard et al., 2007; Park et al., 2009). Moreover, a recent study found that Mn exposed welders with no neurologic symptoms demonstrate dopaminergic dysfunction on PET imaging, indicating preclinical neurotoxicity (Criswell et al., 2011).

Although low level exposure to manganese is common through consumption of certain foods (nuts, grains, tea leaves, legumes), Mn-based fungicides, and consumer products such as ceramics, porcelain, paints, and varnishes (Jankovic, 2005), high level

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exposure to Mn is especially common with occupational exposures to welding, smelters, and foundries. Given the importance of occupational welding in the development and maintenance of the infrastructure of developed and developing countries, there is an urgent need to balance the importance of welding trades with potential neurotoxic health effects in exposed workers. It is estimated there are almost a half-million full-time welding, soldering, and brazing workers in the United States alone (BoLS, 2013). Regular clinical examination by specialists is not practical or cost-effective, especially in remote workplaces. A novel, tiered-approach to screening Mn exposed workers using occupational health nurses has been demonstrated to identify workers with neurotoxic injury (Myers et al., 2009). Mass-screening of high-risk occupational groups using a self-administered tool would be an even more cost effective approach for identifying workers with neurotoxic brain injury and could be a useful first step in monitoring workers.

The objective of this study was to investigate the sensitivity and specificity of two self-administered questionnaires for predicting parkinsonism in a group of shipyard and fabrication welders exposed to Mn. The results of this study may be used to develop a screening tool for parkinsonism in occupational Mn exposed groups which may allow intervention to mitigate progressive neurodegeneration.

2. Methods

2.1. Informed consent

This study was approved by Human Subjects committees at Washington University and the University of Washington. Written informed consent was obtained from each subject before participation in the study.

2.2. Study subjects

Subjects for this study were participants in an ongoing worksite-based epidemiological cohort study of the relationship between welding fume and parkinsonism. Workers were recruited from two Midwestern shipyards and one heavy equipment fabrication facility in the US from the active union membership list provided to our research team by the local trade union. To be included in this study, workers needed to be active or former employees at one of these worksites. All subjects were engaged in shipbuilding and repair or heavy equipment fabrication. A research coordinator attempted to contact union members to elicit their participation.

A total of 836 welders were recruited at the time of this study from an available workforce of 1637 welding exposed workers; recruitment is ongoing. Reasons for non-participation included declined participation ($n = 41$), could not be contacted due to disconnected phone numbers or address change ($n = 110$), and were invited to participate but did not present for evaluation or decline participation ($n = 650$). This report describes data from a group of workers who completed the Parkinson Disease Questionnaire (PDQ39), described below, as part of a sub-study which began after the start of the larger study (Harris et al., 2011), and also completed the PD Symptoms Questionnaire ($n = 496$). We excluded subjects from the analysis if they were on a dopamine receptor blocking medication or had a history of co-morbid neurologic disease that confound interpretation of the UPDRS3 ($n = 6$).

2.3. Data collection

All subjects completed three questionnaires. The first requested information on occupational history, medical history, and personal habits. The questionnaire included questions about exposures to tobacco, caffeine, pesticides and herbicides, medications, previous welding exposure, other occupational history, and medical background. Workers also completed the PD Symptoms Questionnaire, a nine item questionnaire developed by Tanner and colleagues in 1990 documented to have excellent sensitivity and specificity for predicting PD (Duarte et al., 1995; Tanner et al., 1990). The PD Symptoms Questionnaire takes 5 min to complete. The nine symptoms are: trouble rising from a chair, micrographia, hypophonia, poor balance, freezing of gait, masked facies, limb tremor, difficulty buttoning buttons, and shuffling steps. The nine symptoms are categorized as yes or no responses, and summed to create a total symptoms variable. This final variable is scored from 0 to 9 total symptoms with a higher score relating to advanced parkinsonism. The third questionnaire, the PDQ39, assesses health status and quality of life in PD patients (Jenkinson et al., 1997) and has demonstrated good internal consistency (Peto et al., 1995), test–retest reliability (Peto et al., 1995), construct validity (Jenkinson et al., 1995, 1997), and sensitivity to changes in health status (Harrison et al., 2000). The PDQ39 takes approximately 15 min to complete, and contains 39 questions assessing eight dimensions of health: mobility, activities of daily living (ADL), emotional well-being, stigma, social support, cognition, communication, and body discomfort. The PDQ39 asks a respondent to endorse how often, due to Parkinson disease, they experience a particular problem and is scored on a 0–100 scale with higher scores corresponding with advancing stage of disease (Harrison et al., 2000; Peto et al., 1995). The workers were instructed to respond to the questions as they relate to their health status. The scores are reported by the eight dimensions of health subscore as well as by a total scaled score, which will be used for the analysis.

Each subject was examined by a board certified neurologist (BAR, SRC), with fellowship training in movement disorders and extensive clinical experience, using the UPDRS3 (Fahn and Elton, 1987). Examiners are validated annually by rating ten PD patient videos for UPDRS3 score; intraclass correlation coefficients are consistently >0.90. Examiners were blinded to exposure history, medical history, PDQ39 score, and PD Symptoms Questionnaire score. The UPDRS3 contains ratings of cardinal features necessary for diagnosing PD and is the most widely used motor examination for patients with PD (Racette et al., 2006). Possible scores on the UPDRS3 range from 0 to 108 with higher scores corresponding to the presence of more severe parkinsonian signs. For the purpose of this study three groups, determined a priori, were used to evaluate parkinsonism in the welders. Parkinsonism was defined as having a UPDRS3 score greater than or equal to 15. This threshold corresponds to the degree of motor impairment found in early, symptomatic PD (Group, 1996). Normal was defined as UPDRS3 <6. Workers with an intermediate UPDRS3 score, ranging from 6 to 15, were also evaluated. These three groups will henceforth be referred to as parkinsonism, normal, and intermediate, respectively.

2.4. Statistical analysis

Descriptive data calculations were performed for the total study sample as well as stratified by the three groups. Receiver operator characteristic (ROC) curve analyses were performed comparing the PDQ39 total scaled score, eight individual subscores, and PD Symptoms Questionnaire total symptoms score in the parkinsonism and normal groups, and the intermediate and normal groups. The ROC curve analyses relate true positive and false positive values to determine optimal sensitivity and specificity prediction values. The area under the receiver curve (AUC) calculates the probability that a randomly selected case would have a higher outcome than a randomly selected control. Generally, AUCs of 0.70–0.80 are considered fair, 0.80–0.90 are considered good, and

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