Published in final edited form as:

Neurotoxicology. 2014 December ; 0: 232–237. doi:10.1016/j.neuro.2013.08.010.

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 15, 6–15, and <6, respectively. Workers completed a health status questionnaire (PDQ39) and a Parkinson's disease (PD) Symptoms Questionnaire. Areas under

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interests.

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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.

Keywords

Parkinson disease; parkinsonism; neurodegenerative disease; manganese; occupational exposure; epidemiology

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 (5mg/m³) has been associated with parkinsonian signs (Laohaudomchok et al., 2011, Roels et al., 1987, Roels et al., 1985) 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 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's 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 minutes 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., 1997, Jenkinson et al., 1995), and sensitivity to changes in health status (Harrison et al., 2000). The PDQ39 takes approximately fifteen minutes 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 respondent to endorse how often, due to Parkinson's 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 0.90 or greater are considered excellent predictive values. An AUC of 0.50 demonstrates the probability the association is based on chance alone. Sensitivity, specificity, and AUC calculations for this study were

adjusted for age at examination (continuous), gender, race (non-Hispanic Caucasian, yes/no), smoking (ever/never smoke more than 100 cigarettes), and examining neurologist (Racette or Criswell). The best model fit was determined using a log-likelihood chi-square test. An AUC value was also calculated using age as the only predictor to estimate the model's sensitivity and specificity for predicting parkinsonism by age alone. All ROC curves were compared to the age only model using a contrast matrix that compared estimated prediction values between the two curves. Threshold values for PDQ39 total scaled score and PD Symptoms Questionnaire total symptoms score for prediction of parkinsonism were calculated using the optimal sensitivity and specificity prediction value. All statistical analyses were calculated using SAS v9.3 (SAS Institute Inc, Cary, NC).

3. RESULTS

This study evaluated a total of 490 subjects. The demographics of this subset of workers were similar to the full occupational cohort (n=836; data not shown). The mean age overall was 45.7 years. Race was similar between the parkinsonism, normal, and intermediate groups. The parkinsonism group had a higher percent of workers that were male, and a lower percent of ever smokers, than workers in the intermediate or normal groups. The mean age of each group increased as the UPDRS3 group increased. In all, 66 subjects met the definition of parkinsonism for this study, 238 subjects had an intermediate UPDRS3 score, and there were 186 normal subjects (Table 1). The PDQ39 total scaled score (and eight individual health dimension subscores) and the PD Symptoms Questionnaire total symptoms score increased as the UPDRS3 group increased, as previously demonstrated (Harris et al., 2011). Cigarette use and race did not improve the model fit for any model and were therefore not included in the final prediction models.

3.1 PDQ39 Prediction Model

The AUC for the final PDQ39 prediction model was 0.79 (95% CI = 0.73–0.84) (Table 2; Figure 1). The adjusted AUC for the eight individual dimensions of health subscores were similar to the total scaled score (range: 0.76–0.79). Cognition had the lowest AUC values (AUC = 0.76), and the largest AUC subscores were ADL and mobility (AUC = 0.79). The AUC value for the model using age as the only predictor of parkinsonism was 0.68 (95% CI = 0.60–0.76). Including both age and PDQ39 score in the predictive model demonstrated a significantly better model fit than when either age or PDQ39 were modeled alone (log-likelihood chi-square, p-values = 5.61, <0.05 and 19.2, <0.001, respectively). Furthermore, a comparison of the ROC curves between the final PDQ39 prediction model and the model with age as the only predictor demonstrated a greater AUC value in the final PDQ39 prediction model (p<0.01). The resulting AUC for PDQ39 total score comparing the intermediate group to the normal group, adjusted for age at examination, gender, and examining neurologist, was 0.67 (95% CI = 0.62–0.72). This value was similar to the probability based on age alone (AUC = 0.65; 95% CI = 0.60–0.70) (Table 2; Figure 1).

Threshold PDQ39 total scaled score values for predicting parkinsonism were calculated using the optimal sensitivity and specificity prediction value. Using a sensitivity of >70% as an acceptable cut-off value for predicting parkinsonism by total scaled score, the specificity value was 73.7%. More specifically, 46 of the 66 defined cases of parkinsonism were

correctly predicted by the model; the positive predictive value was 69.7%. Likewise, 137 of the 186 subjects defined as normal were correctly predicted; the negative predictive value was 73.7%. The predictive probability using these values of sensitivity and specificity resulted in a PDQ39 total scaled score of 45.0 or greater being predictive of parkinsonism for a male worker at the age of 45. Similarly, a score of 30.2 or greater was demonstrated to be predictive of parkinsonism in a male worker at the age of 55, and a score of 15.4 for a male worker at the age of 65.

3.2 PD Symptoms Questionnaire Prediction Model

The AUC for the final PD Symptoms Questionnaire prediction model (total symptoms) was 0.78 (95% CI = 0.72–0.85) (Table 2; Figure 1). Including both age and total symptoms in the predictive model demonstrated a significantly better model fit than when either age or total symptoms were modeled alone (log-likelihood chi-square, p-values = 5.95, <0.05 and 13.88, <0.01, respectively). A comparison of the ROC curves between the final total symptoms prediction model and the model with age as the only predictor demonstrated a greater AUC value in the final total symptoms prediction model ($p < 0.01$). The resulting AUC for PD Symptoms Questionnaire total symptoms score comparing the intermediate group to the normal group, adjusted for age at examination, gender, and examining neurologist was 0.67 (95% CI = 0.62–0.72) (Table 2; Figure 1). This value was similar to the probability based on age alone.

Threshold PD Symptoms Questionnaire total symptoms score values for predicting parkinsonism were calculated using the optimal sensitivity and specificity prediction value. Using a sensitivity of >70% as an acceptable cut-off value for predicting parkinsonism by total symptoms score, the specificity value was 80.1%. More specifically, 46 of the 66 defined cases of parkinsonism were correctly predicted by the model; the positive predictive value was 69.7%. Likewise, 149 of the 186 subjects defined as normal were correctly predicted; the negative predictive value was 80.1%. The predictive probability using these values of sensitivity and specificity resulted in having four symptoms being predictive of parkinsonism for a male worker at the age of 47, and three symptoms for a 55 year old male worker. Similarly, having at least two symptoms was predictive of parkinsonism in a male worker at the age of 61, and at least one symptom was predictive for a male worker at the age of 69.

4. DISCUSSION

This study evaluated findings from a clinically rigorous cross-sectional epidemiologic study of the relationship between welding exposure and parkinsonism. In this study, 66 (13.5%) subjects met the definition of parkinsonism and 238 (48.6%) subjects had an intermediate UPDRS3 score. These prevalence values for parkinsonism are consistent with our previous study of welders in Alabama (Racette et al., 2005), and the intermediate values are consistent with a previous study demonstrating motor slowing in Mn exposed workers (Wennberg et al., 1992). Our results suggest that the PDQ39 and PD Symptoms Questionnaire have reasonably good sensitivity and specificity to predict parkinsonism as demonstrated in this cohort of shipyard and fabrication welders. Most importantly, these questionnaires were validated against the gold standard of an expert neurologist examination

of all subjects in this study. Administration of a predictive questionnaire in occupational health settings could be a cost effective screening approach for Mn associated neurotoxicity in an at-risk occupational cohorts.

The area under the ROC curve for both predictive questionnaire scores, PDQ39 total scaled score and PD Symptoms Questionnaire total symptoms score, adjusted for age at examination, demonstrated an increased probability that a randomly selected subject with a UPDRS3 score ≥ 15 would have a higher predictive questionnaire score than a randomly selected control (UPDRS3 <6) when compared to the probability predicted by age alone. Further, including age and either PDQ39 total scaled score and PD Symptoms Questionnaire total symptoms score in the predictive model demonstrated a significantly better model fit than when either age or the predictive questionnaire score were modeled alone. This predictive effect was further increased when gender was included as a covariate in the models. The probability that a randomly selected subject with an intermediate UPDRS3 score (between 6 and 15) would have a higher predictive questionnaire score than a randomly selected normal worker was similar to the probability predicted by age alone. This could be interpreted to reflect that these scores are no more predictive of an intermediate UPDRS3 score than age. The clinical importance of these “intermediate” findings are less clear since scores in this range are less specific for parkinsonism.

Both questionnaires demonstrated reasonably good sensitivity and specificity to predict parkinsonism, but neither stood out as a better predictive questionnaire. There is some overlap between the PD Symptoms Questionnaire and the PDQ39, but the PD Symptoms Questionnaire has fewer items to complete (9 vs 39) and may be the optimal screening tool to identify parkinsonism in Mn exposed workers in clinical practice where time may be limited. However, the fewer number of questions may actually limit the predictive ability of the questionnaire to identify workers with early signs of neurotoxic health effects. The difference between having one and two symptoms was predictive for a male worker age 69 and 61, respectively, with no scoring option between one or two symptoms. Since the PDQ39 score covers a broader range of scores, it may be more useful as a predictive questionnaire and for research purposes.

There are several important strengths of our study. This study analyzed a subset of participants from a large well-defined cohort of professional welders being evaluated for an association of welding exposure, specifically exposure to Mn (and other metals), and parkinsonism. An additional strength is the definition of parkinsonism used in this study was based on a neurologic assessment of parkinsonism by a movement disorders specialist. The mean age of this study cohort was 46 years, an age demographic in which Parkinson's disease or other incidental degenerative disease is not likely, and this study restricted analysis to welders with no previous neurologic diagnosis or a record of treatment for neurologic symptoms. Identification of early signs of neurotoxic health effects may allow intervention to mitigate progressive neurodegeneration and is an important advantage to studying younger, active workers. Finally, our evaluation using ROC curves has the advantage of using predictor data, PDQ39 total scaled score and PD Symptoms Questionnaire total symptoms score, over the entire range of values without categorizing data which can lead to misclassification of the clinical outcome.

We acknowledge some limitations to our study and recommend caution in the interpretation of our findings. The UPDRS3 examination score and PDQ39 score were originally designed to assess PD severity and progression in clinical settings and therapeutic trials (Fahn and Elton, 1987). Nonetheless, the UPDRS3 examination contains all of the elements included in a thorough neurologic assessment of patients with parkinsonism with the added benefit of quantification; thus, application of this measure is useful for epidemiologic studies. Workers with co-existent neurologic disease or confounding neurologic findings were excluded from the analysis but non-diagnosed neurologic disease resulting in non-specific motor slowing or tone could explain some of the parkinsonian findings. The relatively young age of our workers makes this unlikely to be a significant confounder. Moreover, the PDQ39 is a measure of health status and quality of life that has been extensively validated for PD and abnormalities that appear to be specific to the parkinsonian spectrum. To our knowledge, the use of the PDQ39 in the context of monitoring for the neurotoxic effects of Mn is novel, and will require further study and refinement to be clinically applicable. Lastly, the predictive values for parkinsonism generated from this and similar analyses will not be available for broad application to communities, rather will only be relevant to similar occupational cohorts.

5. CONCLUSIONS

We have demonstrated the PDQ39 and PD Symptoms Questionnaire have reasonably good sensitivity and specificity to predict parkinsonism in an occupational cohort of welders with no previous neurologic diagnosis or a record of treatment for neurologic symptoms. This cost-effective screening tool has the potential to identify workers with early signs of neurotoxic health effects who could then be evaluated in a tiered occupational health program to mitigate risk of workers developing irreversible neurotoxicity.

Acknowledgments

ROLE OF THE FUNDING SOURCES

This study was supported by the National Institute for Environmental Health Sciences (R01 ES013743, K24 ES017765, and P42ES004696), the Michael J. Fox Foundation, National Institute of Neurological Disorders and Stroke (NINDS) Grant Number 5T32NS007205-27, National Center for Research Resources (NCRR0) and National Institutes of Health (NIH) Roadmap for Medical Research Grant Number UL1 RR024992, the American Parkinson Disease Association, the St. Louis Chapter of the American Parkinson Disease Association and the Barnes Jewish Hospital Foundation (Elliot Stein Family Fund and Parkinson Research Fund). The study sponsors had no involvement in study design; collection, analysis and interpretation of data; the writing of the manuscript; or the decision to submit the manuscript for publication.

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Highlights

- We report a cost effective screening option for manganese associated neurotoxicity
- Questionnaires validated against examination by a movement disorder specialist
- A screening questionnaire could be valuable in an occupational health program
- This could benefit remote workplaces unable to offer regular clinical examinations
- Identifying early signs is valuable to mitigate risk of irreversible neurotoxicity

Figure 1.

Receiver operator characteristic (ROC) curve of PDQ39 total scaled score and PD Symptoms Questionnaire total symptoms score, adjusted for age at examination, gender, and examining neurologist, for predicting parkinsonism in a cohort of shipyard and fabrication welders exposed to manganese

Table 1

Demographics of occupational shipyard and fabrication welders

	parkinsonism	intermediate	normal	all
Number in group, n (%)	66 (13.5%)	238 (48.6%)	186 (38.0%)	490
Age at examination, mean (sd)^a	49.5 (12.8)	48.2 (11.6)	41.3 (12.4)	45.7 (12.6)
Non-Hispanic Caucasian, n (%)	65 (98%)	231 (97%)	182 (98%)	478 (98%)
Male, n (%)	64 (97%)	224 (94%)	172 (92%)	460 (94%)
12 years education, n (%)	58 (95%)	222 (97%)	163 (93%)	443 (95%)
Cigarettes use (ever), n (%)	43 (65%)	167 (70%)	127 (68%)	337 (69%)
Examiner (Racette), n (%)	36 (55%)	96 (40%)	55 (30%)	187 (38%)
Site 1	25 (19%)	65 (49%)	44 (33%)	134
Site 2	27 (11%)	115 (46%)	110 (44%)	252
Site 3	14 (13%)	58 (56%)	32 (31%)	104
Total PDQ39 score, mean (sd)	11.1 (12.0)	7.5 (9.3)	7.6 (7.9)	8.0 (9.3)
Total Symptoms, mean (sd)	0.9 (1.4)	0.5 (1.0)	0.4 (0.8)	0.5 (1.0)
0 symptoms, n (%)	36 (55%)	182 (76%)	142 (76%)	360 (73%)
1 symptom, n (%)	17 (26%)	43 (11%)	29 (16%)	71 (15%)
2 symptoms, n (%)	3 (4%)	18 (8%)	11 (6%)	32 (7%)
3 symptoms, n (%)	6 (8%)	6 (2%)	2 (1%)	14 (3%)
4 symptoms, n (%)	1 (2%)	5 (2%)	0 (0%)	6 (1%)
5 symptoms, n (%)	2 (3%)	1 (0.5%)	1 (0.5%)	4 (0.5%)
6 symptoms, n (%)	1 (2%)	1 (0.5%)	1 (0.5%)	3 (0.5%)

^a sd = standard deviation

Area under the receiver operator characteristic curve (AUC) values for predicting parkinsonism in a cohort of shipyard and fabrication welders exposed to manganese

Table 2

Predictor	parkinsonism vs normal				intermediate vs normal			
	AUC (adj ^b)	95% CI	AUC (crude)	95% CI	AUC (adj ^b)	95% CI	AUC (crude)	95% CI
PDQ39 total scaled score	0.79 ^a	0.73–0.84	0.57	0.48–0.65	0.67	0.62–0.72	0.53	0.47–0.58
PD Symptoms Questionnaire total symptoms score	0.78 ^a	0.72–0.85	0.62	0.55–0.69	0.67	0.62–0.72	0.51	0.47–0.55
Age at exam	--	--	0.68	0.60–0.76	--	--	0.65	0.60–0.70

^a p<0.01 compared to the AUC for age only

^b adjusted for age at exam, gender, and examining neurologist