NeuroToxicology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

NeuroToxicology

Full Length Article

A screening tool to detect clinical manganese neurotoxicity

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ARTICLE INFO

Article history:
Received 27 January 2017
Accepted 20 February 2017
Available online xxx

Keywords:
Manganese
Welding
Predictive model
Parkinsonism

ABSTRACT

Manganese (Mn) over-exposure in occupational settings is associated with basal ganglia toxicity and a movement disorder characterized by parkinsonism (i.e., the signs and symptoms of Parkinson disease). A simple test to help non-neurologists identify workers with clinical Mn neurotoxicity represents an unmet need. In a cohort of Mn-exposed workers from welding worksites, with extensive clinical data, we developed a linear regression model to predict the Unified Parkinson Disease Rating Scale motor subsection part 3 (UPDRS3) score. We primarily considered factors easily obtained in a primary care or occupational medicine clinic, specifically easily assessed signs of parkinsonism and factors likely to be associated with UPDRS3 such as age, timed motor task results, and selected symptoms/conditions. Secondarily we considered other demographic variables and welding exposure. We based the model on 596 examined workers age $\leq$ 65 years and with timed motor task data. We selected the model based on simplicity for clinical application, biologic plausibility, and statistical significance and magnitude of regression coefficients. The model contained age, timed motor task scores for each hand, and indicators of action tremor, speech difficulty, anxiety, depression, loneliness, pain and current cigarette smoking. When we examined how well the model identified workers with clinically significant parkinsonism (UPDRS3 $\geq$ 15) the receiver operating characteristic area under the curve (AUC) was 0.72 (95% confidence interval [CI] 0.67, 0.77). With a cut point that provided 80% sensitivity, specificity was 52%, the positive predictive value in our cohort was 29%, and the negative predictive value was 92%. Using the same cut point for predicted UPDRS3, the AUC was nearly identical for UPDRS3 $\geq$ 10, and was 0.83 (95% CI 0.76, 0.90) for UPDRS3 $\geq$ 20. Since welding exposure data was not required after including its putative effects, this model may help identify workers with clinically significant Mn neurotoxicity in a variety of settings, as a first step in a tiered occupational screening program.

1. Introduction

Chronic occupational exposure to manganese (Mn) has been associated historically with a severe, atypical neurologic disorder characterized by parkinsonism, dystonia, cognitive dysfunction, and behavioral dysfunction (Rodier, 1955; Wang et al., 1989). The exposures causing this phenotype were as high as 1,000,000 μg Mn/m^3 (Rodier, 1955; Wang et al., 1989). In workers with lower occupational exposures, typical of the modern workplace, the phenotype of occupational Mn exposure is substantially different from the phenotype associated with historical, high exposures. In fact, exposures at or below the current Occupational Safety and Health Administration (OSHA) exposure limit of 5000 μg Mn/m^3 have also been associated with clinical neurotoxicity (Roels et al., 1987, 1985). In particular, we have previously described that Mn-exposed welders have a phenotype that is predominantly characterized by symmetric parkinsonism that includes rigidity and bradykinesia, and cognitive control dysfunction (Racette et al., 2012). These neurologic abnormalities are associated with reductions in Parkinson-specific quality of life and appear to be progressive (Harris et al., 2011; Racette et al., 2017).

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http://dx.doi.org/10.1016/j.neuro.2017.02.009
0161-813X/

There have been several attempts to develop an operational definition of manganism to inform clinical criteria to identify those with clinical Mn neurotoxicity (Calne et al., 1994; Jankovic, 2005). These criteria are based on the classic phenotype associated with very high Mn exposures and were focused on distinguishing manganism from Parkinson disease (PD). However, these criteria have never been updated to reflect the distinct phenotypic differences between historic and modern Mn exposures. Given our previous findings, suggesting that more than 15% of Mn-exposed welders have clinically relevant parkinsonism (Racette et al., 2012), we sought to fill this knowledge gap by developing clinical criteria that could serve as an initial screening tool for Mn-exposed workers to identify those experiencing clinically relevant Mn neurotoxicity.

2. Materials and methods

Study design and clinical assessment- We identified participants from a union membership list and recruited from one indoor fabrication shop and two shipyards in the Midwestern U.S. between the years 2006 and 2016, as detailed previously (Racette et al., 2017). Workers on the list had to have been employed at one of these welding worksites for at least 90 days. No workers or retirees from these worksites were excluded from participation, except as noted below. Two movement disorders trained neurologists (B.A.R, S.R.C.) performed neurologic exams that included the Unified Parkinson Disease Rating Scale motor subsection part 3 (UPDRS3) (Fahn et al., 1987), blinded to workers' exposure history and validated with timed motor testing data (Racette et al., 2017). Examinations were conducted in local union halls near each worksite. The study neurologists completed 1537 exams, and after excluding 45 exams in workers with a history of stroke, brain tumor, or other medical conditions that would compromise the UPDRS3 score, 1492 exams in 886 individuals were available (Racette et al., 2017).

Subjects also completed a timed motor task using a counter with two levers spaced 20 cm apart, as previously described (Criswell et al., 2010). Scores were reported for each of three trials for each hand, and we calculated the mean of the trials for the dominant hand and non-dominant hand. Lower values indicate poorer performance, and are strongly associated with UPDRS3 scores in this cohort ($p < 0.0005$) (Racette et al., 2017). For the present study, we focused on workers who had both a complete UPDRS3 exam and at least one trial of the timed motor task per hand. We also restricted this analysis to workers exposed to welding fume (Mn) and of working age ($\leq$65 years) to ensure the model could be applied to current Mn-exposed workers. If subjects had more than one exam with a timed motor task, we only included the earliest exam. In total, we included 596 (67%) workers in the present analysis. The most common reason for exclusion was a lack of the timed motor task, which was only administered from 2006 to 2013.

In addition to the clinical motor assessments, workers completed a PD specific quality of life questionnaire (PDQ39, Jenkinson et al., 1997) and a PD symptom questionnaire (Duarte et al., 1995; Tanner et al., 1990). We also obtained detailed demographic and lifestyle information from a questionnaire (Hobson et al., 2009), including medical conditions, the use of medications, and common PD risk factors such as cigarette smoking, and consumption of other types of tobacco, caffeine and alcohol. (Checkoway et al., 2002) Finally, all subjects completed a comprehensive welding exposure questionnaire (Hobson et al., 2009), which we used to determine duration and intensity of welding fume exposure and hence cumulative Mn exposure (Racette et al., 2012, 2017). We validated these measures in a subset of 38 workers with pallidal index data from T1-weighted magnetic resonance imaging (Racette et al., 2017).

Statistical analysis- We performed statistical analyses in R (version 3.3.2, R Core Team, Vienna, Austria) and Stata (version 11.0, College Station, Texas). We built a predictive model of parkinsonism, with simple linear regression, using the UPDRS3 score as a continuous measure as our outcome variable. Given that UPDRS3 scores were rated by two examiners over several years, we first adjusted UPDRS3 subscores for examiner and examiner by time differences, and then summed these subscores to obtain the total (adjusted) UPDRS3 score as previously (Racette et al., 2017). We included age and timed motor task data *a priori* as predictors because of their strong associations with UPDRS3 (Racette et al., 2017), while using locally weighted scatterplot smoothing (LOWESS) to inform how to model these continuous measures. We then individually introduced additional potential predictors into the model to identify those with a biologically plausible direction of association at $p \leq 0.1$ (one-sided alpha of 0.05) and/or with a clinically meaningful difference (approximately ≥ 1 point difference in UPDRS3 score) and sufficiently narrow 95% confidence intervals (CIs). The primary potential predictors of interest were factors that could be determined by a non-neurologist to further (i.e. beyond the objective timed motor test results) capture the motor and associated non-motor effects of Mn overexposure. We also examined some of the UPDRS3 subscores that directly contribute to the UPDRS3 score, specifically, those that reasonably might be assessed by a non-neurologist clinician: action tremor, arising from chair, gait, posture, and speech. For this we dichotomized the respective subscores to indicate presence ($\geq$1) of the sign rather than retaining them on the 1–4 scale, which would likely require neurologist expertise. We also examined whether the model would be improved by inclusion of factors from the PD symptom questionnaire, the PDQ39, and selected self-reported medical conditions and medications, namely depression and anxiety, which have been associated with Mn overexposure (Bowler et al., 2006, 1999; Mergler et al., 1994).

Secondary predictors we considered included other selected medical conditions: asthma, diabetes, heart disease, high blood pressure, pain, rheumatoid arthritis, and history of head injury which required hospitalization. We also examined sex, race/ethnicity, education, handedness, body mass index (BMI), family history of PD in a first degree relative, and consumption of tobacco, caffeine and alcohol as potential predictors. Finally, we assessed the potential contribution of several welding exposure variables including percent of time spent working in confined spaces, job category (welder, welder helper, around welding) and/or flux core arc welding, whether the subject had worked at the site within the last year (retiree status), total duration of welding work, and weighted welding years (Hobson et al., 2011; Racette et al., 2012).

In selecting the final model, we assessed the consistency of results for primary predictors that were similar (e.g. self-reported depression and use of medications used for depression), and when their coefficients were sufficiently similar, we combined these variables to improve precision and to simplify the model before selecting the final model. Finally, we entered age, timed motor task data, and the additional identified predictors simultaneously into a multivariable linear regression model to identify the strongest independent predictors. For those variables that remained, we tested for interactions on the multiplicative scale, while initially including all main effects terms when obtaining the interaction *p*-value. We then verified model fit and checked for multicollinearity and influential data points.

Please cite this article in press as: B.A. Racette, et al., A screening tool to detect clinical manganese neurotoxicity, Neurotoxicology (2017), http://dx.doi.org/10.1016/j.neuro.2017.02.009