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Review

The neurobehavioral impact of manganese: Results and challenges obtained by a meta-analysis of individual participant data

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ABSTRACT

Results from a meta-analysis of aggregated data provoked a new analysis using individual data on the neuropsychological performance of occupationally exposed workers.

Data from eight studies examining 579 exposed and 433 reference participants were included, 28 performance variables analyzed. The performance scores were adjusted for well-known individual-level covariates; the influence of possible, but unknown study-level covariates was attenuated by means of a *z*-normalization. Associations between performance and exposure were estimated by ANOVAs and ANCOVAs, the latter representing multi-level models.

Four cognitive and motor performance variables each indicated significantly lower performances of exposed individuals when confounding was considered; slowed motor performances and deficits in attention and short-term memory were found. Performance on a single test was significantly related to the biomarker manganese in blood. The outcomes on susceptibility were weak.

The slowing of responses was the most distinct feature of performances of exposed workers. It remains unclear, whether this result is related to the employed tests or provides important information about early stages of the neurotoxic impairment. More specific cognitive tests need to be employed to answer this question. The lack of dose–response relationships was related to features of the biomarker: it does not reflect the Mn in brain responsible for changes in performances.

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Contents

1. Introduction

The serious neurological sequelae following massive exposure to manganese (Mn) have been described as early as 1837 (Couper, 1837). The efforts to decipher the neurotoxic effects and mechanisms of Mn, however, increased distinctly during the last decades. The number of publications ascertained in PubMed for the search-terms Mn AND neurotox* increased from 77 between 1981 and 1990 to 452 between 2001 and 2010. The research devoted to the topic is related to the fact that our contemporary life-style is accompanied by several sources of Mn exposure that add to the natural exposure; the use of MMT (methylcyclopentadienyl manganese tricarbonyl) as an anti-knock agent and the welding of Mn-containing steel may be mentioned. Mining of Mn ore and production of the Mn-containing materials are other sources that put workforce and members of the general public at risk of neurotoxic effects of a trace element that is essential at lower concentrations. In terms of environmental exposures some studies examined the neurobehavioral impact of Mn on adults, adolescents and children living in the vicinity of mining and manufacturing facilities (among others Lucchini et al., 2012; Mergler et al., 1999; Riojas-Rodriguez et al., 2010; Rodriguez-Agudelo et al., 2006).

In the 1980s epidemiological studies started investigating the neurobehavioral impact of Mn in the occupational field (Siegl and Bergert, 1982); this was followed by studies in many parts of the world; among them were South Africa (Myers et al., 2003), Norway (Bast-Pettersen et al., 2004), South Korea (Kim et al., 2007), and China (Cowan et al., 2009b). In 2009 we tried to quantify the existing evidence for neurotoxic effects by means of a meta-analysis of aggregated data (AD) (Meyer-Baron et al., 2009). Reduced motor and cognitive processing speed was substantiated when exposed and unexposed workers were compared. But, questions on exposure–effect relationships and the heterogeneity of study outcomes remained unresolved. Inconsistent relationships between performance scores and the biomarker Mn in blood (MnB) might have resulted from the use of aggregated data. Heterogeneity among neurobehavioral outcomes from different studies could not be addressed satisfactorily, because the influence of covariates could not be diminished.

For the above mentioned reasons we opted for a meta-analysis of individual participant data (IPD). This approach provides distinct advantages not only in terms of the consideration of confounders and the estimate of dose–response relationships, but also in terms of the investigation of individual-specific risk factors (Lambert et al., 2002; McElvenny et al., 2004; Stewart and Tierney, 2002); these are of special importance when susceptible subpopulations have to be protected from sequelae of neurotoxic substances.

It is an obstacle for an IPD analysis in neurobehavioral toxicology that behavior is determined by the social and cultural background; the behavior may therefore not be comparable among studies from diverse cultures. This may be one of the reasons for the observation by Curran and Hussong (2009) that the use of individual data in meta-analyses is relatively novel in behavioral science. We attempted to take account of the cultural differences and opted for an approach to attenuate their influence on outcomes by considering the performance level of reference samples. The methodology was described in a previous paper (Meyer-Baron et al., 2011).

Our current analysis sought to answer the following questions: (1) Can the neurobehavioral effects of Mn exposure be confirmed when confounding is considered? (2) Is there evidence for an exposure–effect relationship when performance scores are related to individual concentrations of the biomarker Mn in blood (MnB)? (3) Can individual-specific risk factors for Mn effects be identified?

2. Materials

The recruitment of the studies and the preparation of the data set will be briefly summarized; for details see Meyer-Baron et al. (2011).

Studies analogous to the AD meta-analysis on Mn (Meyer-Baron et al., 2009) were considered eligible for the present study, since the same criteria for the inclusion were employed: (1) occupational Mn exposure examined by an epidemiological study, (2) outcomes published, (3) exposed and control groups consisted of random samples, (4) standardized neuropsychological tests employed, (5) tests employed in different studies, (6) concentrations of MnB reported. The samples were random in the sense that the studies recruited samples from cohorts of active workers without (suspected) occupational diseases. Studies ascertained by February 2009 were considered.

When agreement about the supply of the data was obtained from the principal investigators, a contract about the confidential use of the anonymous data was signed. The raw data were renamed in a common way and checked for congruence and plausibility before a master data set was created.

Neuropsychological test variables were considered when at least two results from different studies were available. We included also those performance variables that were not reported in the original papers due to insignificant results.

3. Methods

Details on the methodology and reasons for each step of our analysis were explained previously (Meyer-Baron et al., 2011) and will only be briefly summarized.