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Manganese and selenium concentrations in umbilical cord serum and attention deficit hyperactivity disorder in childhood

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ABSTRACT

Existing evidence on the effects of manganese and selenium during fetal life on neurodevelopmental disorders is inadequate. This study aims to investigate the hypothesized relationship between fetal exposure to manganese and selenium and attention deficit hyperactivity disorder (ADHD) diagnosis in childhood. Children born between 1978 and 2000 with ADHD ($n=166$) were identified at the Department of Child and Adolescent Psychiatry in Malmö, Sweden. Controls from the same region ($n=166$) were selected from the Medical Birth Register and were matched for year of birth and maternal country of birth. Manganese and selenium were measured in umbilical cord serum. The median cord serum concentrations of manganese were 4.3 μg/L in the cases and 4.1 μg/L in the controls. The corresponding concentrations of selenium were 47 and 48 μg/L. When the exposures were analyzed as continuous variables no associations between cord manganese or selenium concentration and ADHD were observed. However, children with selenium concentrations above the 90th percentile had 2.5 times higher odds (95% confidence interval 1.3–5.1) of having ADHD compared to those with concentrations between the 10th and 90th percentiles. There was no significant interaction between manganese and selenium exposure ($p=0.08$). This study showed no association between manganese concentrations in umbilical cord serum and ADHD. The association between ADHD diagnoses in children with relatively high cord selenium was unexpected and should be interpreted with caution.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder with inattention, impaired impulse control, and hyperactivity as core symptoms (Faraone et al., 2006; Gustafsson et al., 2000). About five percent of children are diagnosed with ADHD and the problems often persist into adulthood (Faraone et al., 2006; Lara et al., 2009). The etiology of ADHD is not yet fully known, but both genetic and environmental factors are involved Swanson et al. (2007). Disturbance of the dopaminergic system is the main characteristic of ADHD (Faraone et al., 2005; Gizer et al., 2009). Exposure to environmental toxins, such as lead, mercury, and persistent chlorinated biphenyls (PCBs), has been linked to ADHD (Banerjee et al., 2007; Braun et al., 2006; Eubig et al., 2010).

Manganese is an essential trace element involved in many metabolic functions in the body (Santamaria and Sulsky, 2010). Exposures to high levels of manganese have been linked to hyperactivity and ADHD in children (Bouchard et al., 2006; Farias et al., 2010). Manganese has been suggested to mediate its toxic effect on the nervous system mainly by causing selective destruction of dopaminergic neurons, and by altering brain expression of dopamine, dopamine receptors and dopamine transporter proteins (Dorman et al., 2000; Kern et al., 2010; Storch et al., 2004; Tran et al., 2002). Manganese may trigger autoxidation or turnover of dopamine, resulting in increased production of free radicals and other cytotoxic metabolites, along with a depletion of cellular antioxidant defense mechanisms (Garner and Nachtman, 1989; Liccione and Maines, 1988; Parenti et al., 1988; Verity, 1999).

Abbreviations: ; ADHD, attention deficit hyperactivity disorder; BMI, body mass index; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; LOD, limit of detection; MMUSB, Malmö Maternity Unit Serum Biobank; OR, odds ratio; SD, standard deviation; SMBR, Swedish Medical Birth Register

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Selenium is an essential trace element with potent antioxidant properties (Battin et al., 2006) and has recently been found to protect from prenatal manganese neurotoxicity (Yang et al., 2014). In mice, manganese-induced impairment in dopaminergic neurotransmission is reversed by selenium treatment (Khan, 2010). The increased permeability of the blood–brain-barrier induced by free radicals is inhibited by selenium (Oztas et al., 2001).

Manganese and selenium both cross the placenta and the fetal blood–brain barrier (Michalke et al., 2009; Wilson et al., 1991; Yokel, 2009). The potential associations between manganese and selenium exposures during fetal life and later development of nervous system symptoms are relatively unexplored. The primary aim of the present case–control study was to investigate the possible associations between manganese and selenium concentrations in neonatal blood at birth and ADHD diagnosis in childhood. We then hypothesized that a high neonatal manganese concentration is associated with ADHD, and that a high selenium concentration imparts protection against ADHD. The secondary aim of the study was to explore the associations between manganese and selenium concentrations in maternal and fetal blood, where we hypothesized positive correlations.

2. Material and methods

2.1. Participants

The selection of and diagnostic procedures for ADHD children have previously been described (Ode et al., 2014). Briefly, 419 children born in the city of Malmö between 1978 and 2000 were diagnosed with ADHD and were followed until 2005 at the Department of Child and Adolescent Psychiatry in Malmö. Age at the time of diagnosis varied between 5 and 17 years, with most children being diagnosed between the ages of 8 and 12 years. The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria DSM-III-R_{11} were used before 1994, and from 1994 onwards the DSM-IV_{12} criteria. Intelligence and ability to concentrate were tested with the Wechsler Intelligence Scale (WISC), TEA-Ch, and QB-Tech or IVA+. A pediatric examination with assessment of neurological soft signs was also performed. The school teacher and/or the parents were asked to fill in questionnaires such as the SNAP-IV, Conner's questionnaire or the 5–15 questionnaire, and the BRIEF-questionnaire. Behavior in school and at the visits to the clinic was observed and registered. A team of a psychiatrist, a psychologist and sometimes also a social worker met to achieve a consensus ADHD diagnosis using the DSM criteria.

Using the unique personal identification numbers, maternal and umbilical cord serum samples for children with ADHD were collected from the Malmö Maternity Unit Serum Biobank (MMUSB). The MMUSB has previously been described (Ode et al., 2014). A pool of 10 controls per ADHD child matched for year of birth ± 12 months and country of birth of the mother was retrieved from the Swedish Medical Birth Register (SMBR). The first newborn in the pool of controls with an umbilical cord blood sample found in the MMSUB was chosen as control. If no cord serum was found among the 10 matched controls in the pool, the sample of the next-baby-born was used. Demographic and obstetric data were obtained from the SMBR. The selection procedure for cases and controls is presented in Fig. 1. Manganese and selenium could be analyzed in 180 ADHD and 191 control (166 matched) umbilical cord samples.

The study protocol followed the requirements of the Declaration of Helsinki and was approved by the Research Ethics Committee at Lund University, Sweden.

2.2. Analyses of manganese, selenium, and cotinine

The concentrations of manganese and selenium were determined by inductively coupled plasma-mass spectrometry (ICP-MS; Thermo X7; Thermo Elemental, Winsford, UK). Aliquots of 100 μL serum were diluted 10 times with an alkaline solution according to Barany et al. (1997). The detection limit, calculated as 3 times the standard deviation (SD) of the blank was 0.01 μg/L for manganese and 1.3 μg/L for selenium. The analytical accuracy was checked against two different reference materials. For Seronorm Trace Elements Serum L-1 (lot 0903106; SERO AS, Billingstad, Norway) the results obtained for manganese and selenium were 16 ± 1.0 and 107 ± 6.3 μg/L (mean ± SD, $n=28$) vs. recommended 15 ± 0.9 and 107 ± 7 μg/L, respectively and for human serum reference samples from the Centre de Toxicologie du Québec, Canada (lot QMEQAS06S-06) the obtained values were 3.9 ± 0.26 and 286 ± 15 μg/L ($n=28$) vs. recommended 4.0 ± 1.05 and 287 ± 63 μg/L, respectively. All analyzed samples were prepared in duplicate and the method imprecisions (calculated as the coefficients of variation in measurements of duplicate preparations) were 9.4% and 6.6% for manganese and selenium, respectively.

The smoking status of the cases and controls was determined with analyses of the cotinine concentrations in umbilical cord serum as part of another study (Ode et al., 2013).

2.3. Statistical analyses

Spearman's rank correlation coefficient was used to investigate the correlations of the trace elements between maternal and umbilical cord serum samples and the Wilcoxon matched-pairs signed-ranks test to investigate differences in manganese and selenium concentrations between maternal and cord serum, and between ADHD cases and controls, respectively.

Conditional logistic regression was performed for calculating the odds ratio for every 1 ng/mL increase in the umbilical cord serum manganese or selenium concentrations and for the manganese/selenium ratio and ADHD diagnosis. Based on the distribution of the trace elements among the controls, we defined manganese concentrations above the 90th percentile (6.68 μg/L) and selenium concentrations below the 10th (36.3 μg/L) or above the 90th percentile (59 μg/L) as deviating. These cut-offs were arbitrary selected and the reason for the relatively high and low cut-offs were that both manganese and selenium are essential nutrients and we believe that the waste majority have concentrations within the normal range. For evaluation of potential interaction between the categorized manganese and selenium we included an interaction term in the model (i.e. manganese∗selenium). We calculated crude as well as adjusted odds ratios (ORs). If the crude and the adjusted ORs did not differ by more than 10%, we only present the crude OR. As potential confounders we considered smoking during pregnancy, parity, and gestational age at birth. Women with a cotinine concentration below the detection limit (0.2 μg/L) were classified as non-smokers, women with a concentration above 15 μg/L as active smokers, and women with levels between 0.2 and 15 μg/L as second hand smokers (George et al., 2006). Parity was entered in the analysis as a class variable divided into two groups according to number of previously born children (0 [i.e. primiparous], or ≥ 1 children). Gestational age was divided into three groups: <37, 37–42, and >42 weeks of pregnancy.

The conditional regressions were performed with LogXact statistical software (Cytel Studio 10), while the rest of the analyses were performed with SPSS version 21 (SPSS Inc., Chicago, IL, USA).