International Journal of Hygiene and Environmental Health 218 (2015) 139–146

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Neurobehavioral function and low-level metal exposure in adolescents

Michal Kicinski[a], Jan Vrijens[b], Griet Vermier[c], Elly Den Hond[d], Greet Schoeters[d,e], Vera Nelen[f], Liesbeth Bruckers[g], Isabelle Sioen[h], Willy Baeyens[b], Nicolas Van Larebeke[b,i], Mineke K. Viaene[j], Tim S. Nawrot[a,k,*]

[a] Centre for Environmental Sciences, Hasselt University, Diepenbeek, Belgium
[b] Department of Analytical and Environmental Chemistry, Vrije Universiteit Brussel (VUB), Brussel, Belgium
[c] Integrated Psychiatric Centre OPZ Geel, Geel, Belgium
[d] Flemish Institute for Technological Research, Environmental Risk and Health, Mol, Belgium
[e] Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium
[f] Department of Health, Provincial Institute for Hygiene, Antwerp, Belgium
[g] Interuniversity Institute for Biostatistics and Statistical Bioinformatics, Hasselt University, Diepenbeek, Belgium
[h] Department of Public Health, Ghent University, Ghent, Belgium
[i] Department of Radiotherapy and Nuclear Medicine, Ghent University, Ghent, Belgium
[j] Department of Neurology, Sint Dimphna Hospital, Geel, Belgium
[k] School of Public Health and Primary Care, KU Leuven, Leuven, Belgium

ARTICLE INFO

Article history:
Received 11 March 2014
Received in revised form
15 September 2014
Accepted 16 September 2014

Keywords:
Adolescents
Cognition
Copper
Lead
Metals
Neurotoxicity

ABSTRACT

An excessive metal exposure is harmful to the brain. However, many aspects of metal neurotoxicity remain unclear including the magnitude of the low-level exposure effects and the level of exposure that can be assumed safe. The aim of our study was to investigate the association between a low-level metal exposure and three neurobehavioral domains (sustained attention, short-term memory, and manual motor speed). We measured Cd, Cu, Mn, Pb, and Tl in blood, Cd, Ni, and toxicologically relevant As in urine and methyl Hg in hair in 606 adolescents between 13.6 and 17 years of age. A two-fold increase in blood Cu was associated with a 0.37 standard deviations decrease in sustained attention (95% CI: −0.67 to −0.07, $p = 0.02$) and 0.39 standard deviations decrease in short-term memory (95% CI: −0.70 to −0.07, $p = 0.02$), accounting for gender, age, smoking, passive smoking, household income per capita, occupation of the parents, and education level of the mother. None of the other metals was significantly associated with the neurobehavioral domains that were measured. The observed associations between blood Cu and neurobehavioral performance are in line with recent studies in elderly. However, the relevance of our results for public health remains to be elucidated.

Introduction

Excessive exposure to metals has a strong neurotoxic potential. Transition metals copper, manganese, and mercury catalyze redox reactions. Heavy metals lead and cadmium and a metalloid arsenic bind to proteins and interfere with metal transport and protein function and are also capable of inducing oxidative toxicity (Wright and Baccarelli, 2007). Exposure to toxic metals may have serious public health consequences because contaminants such as lead, mercury, and arsenic are widespread. Forty years of epidemiological research has demonstrated that a lead exposure is associated with impaired cognitive function in children (Landrigan et al., 1975; Lidsky and Schneider, 2003; Pocock et al., 1994). There is a growing amount of evidence that lead exposure resulting in blood lead levels lower than 10 μg/dL may affect cognitive performance (Gilbert and Weiss, 2006; Jusko et al., 2007; Lanphear et al., 2005). This raises the issue of changing the current safety threshold (Gilbert and Weiss, 2006). However, it is currently unclear what levels of lead exposure can be assumed safe (ATSDR, 2007; CDC, 2005).

A high methylmercury exposure has disastrous consequences for the brain, as evidenced by cases of methylmercury poisoning (Amin-zaki et al., 1978; Harada et al., 2001; Karada, 1978;

* Corresponding author at: Hasselt University, Centre for Environmental Sciences, Agoralaan gebouw D, Diepenbeek, 3590 Hasselt, Belgium.
Tel.: +32 11 268382; fax: +32 11 268299.
E-mail address: tim.nawrot@uhasselt.be (T.S. Nawrot).

http://dx.doi.org/10.1016/j.ijheh.2014.09.002
1438-4639/

Marsh et al., 1980). Cohorts from the Faroe Islands and the Seychelles provide information about the neurobehavioral effects of methylmercury exposure resulting from extensive consumption of fish and other seafood from the ocean. In seven-year-old children from the Faroe Islands, a prenatal methylmercury exposure was associated with a decline in sustained attention (measured using the Continuous Performance Test), short-term memory (the Digit Span Test), manual motor speed (the Finger Tapping Test), verbal learning (the California Verbal Learning Test), and language skills (the Boston Naming Test) (Grandjean et al., 1997). At the age of 14, a prenatal methylmercury exposure was still associated with neurobehavioral performance in this population (Debes et al., 2006). However, methylmercury exposure was not associated with neurobehavioral outcomes in children from the Seychelles exposed to methylmercury to a similar extent as those from the Faroe Islands (Davidson et al., 2006). Results of studies with lower exposure levels were inconsistent (Boucher et al., 2012; Freire et al., 2010; Gao et al., 2007; Jedrychowski et al., 2007). Because fish is an important source of essential fatty acids, detailed data on the neurological effects associated with different methylmercury exposure levels is needed in order to decide when a restriction of fish consumption due to methylmercury contamination is advisable.

Arsenic, a potent toxicant, can also cause injury to the central nervous system (Jomova and Valko, 2011). In children highly exposed through contaminated groundwater, the urine levels of this metal were negatively associated with cognitive performance (Hamadani et al., 2011; Rosado et al., 2007; Wasserman et al., 2006). The neurobehavioral effects of a low-level exposure to arsenic remain largely unexplored.

Some (Gao et al., 2008; Vermeir et al., 2005; Viaene et al., 2000) but not all (Emsley et al., 2000; Nordberg et al., 2000) studies on cadmium exposure and cognition revealed negative associations. Human cases of poisoning and animal studies have showed that nickel (He et al., 2013; Sunderman et al., 1988) and thallium (EPA, 2009; Kuo et al., 2005) are neurotoxic at high exposure levels. However, little is known about the neurobehavioral effects of these heavy metals at a low level of exposure.

Essential nutrients manganese (Roels et al., 2012; Santamaria and Sulsky, 2010) and copper (Chambers et al., 2010; Desai and Kaler, 2008) are neurotoxic at high doses. As both deficiency and excess of these elements can be harmful, the optimal levels need to be carefully determined. This is difficult at this moment due to the scarcity of data.

Here, we investigated the association of metal exposure with sustained attention, short-term memory, and manual motor speed in 606 adolescents.

Materials and methods

Study population and data collection

The study population is described in detail elsewhere (Kicinski et al., 2012). Briefly, the study was a part of a biomonitoring program for environmental health surveillance in Flanders, Belgium. Between 2008 and 2011, we recruited third year secondary school students in two industrial areas, Genk ($n = 197$) and Menen ($n = 199$), and from the general population of Flemish adolescents ($n = 210$). In the industrial areas, all pupils living within the selected study area were eligible. A multistage sampling was performed to select participants from the general Flemish population.

Two weeks before the study, participants received two questionnaires to fill in, one for themselves and one for their parents. The questionnaire for adolescents included questions about their smoking behavior. Questions about education level, income, and occupation were included in the questionnaire for parents. Each participant received a plastic bottle and was asked to collect a first morning urine sample at the day of the neurobehavioral examination. During the study session, the neurological tests were administered and blood and hair samples were collected. The samples were transported to the laboratory in a cool box and subsequently stored at −20 °C until analysis. A team of nurses and other health-care personnel with years of experience at biomonitoring programs involving neurobehavioral testing and collecting of biological samples performed the examinations. An experienced psychologist Griet Vermier trained that team on how to administer the NES tests. Both parents and teenagers provided informed consent for participation. The study was approved by the Ethical Committee of the University of Antwerp.

Exposure indicators

100 μL distilled nitric acid was added to 500 μL urine to eliminate the organic matrix. Afterwards, the samples were diluted with Milli *Q* water. Urine Cd and Ni levels were determined using inductively coupled plasma–mass spectrometry (ICP–MS) (Heitland and Koster, 2004). The method was validated using certified control materials (Seronorm Trace Elements Urine and Lyphochek Controls for Trace Metals Testing). As external quality control, we participated in ring tests of the German External Quality Assessment Scheme. Toxicologically relevant arsenic concentrations in the urine were defined as the sum of inorganic arsenic, monomethylarsonic acid, and dimethylarsinic acid and measured using Flow-Injection Hydride Generation Atomic Absorption Spectrometry (Hanna et al., 1993). The method was validated using certified reference materials (Seronorm Trace Elements Urine and ClinChek® Urine Controls). As external quality control, we participated in ring tests of the German External Quality Assessment Scheme. The metals measured in the urine were expressed per gram creatinine.

Cd, Cu, Pb, Mn, and Tl concentrations in the whole blood were measured using inductively coupled plasma–mass spectrometry (ICP–MS) (Schroijen et al., 2008). The method was validated using certified reference samples (Sero A.S.). As external quality control, we participated in ring tests of the German External Quality Assessment Scheme. Headspace–gas chromatography–atomic fluorescence spectrometry was applied to measure the hair methyl Hg levels (Gao et al., 2010). We validated this method using blanks, samples spiked at difference levels, and certified reference materials (IAEA-086).

The level of Ni in the urine was lower than the limit of detection (LOD) for five participants. All participants had detectable levels of the remaining metals.

Neurobehavioral outcomes

The Neurobehavioral Evaluation System (NES) is a computer-administered battery of tests that was developed to study the neurological effects of exposure to environmental agents (Baker et al., 1985) and has been commonly utilized for this purpose (Grandjean et al., 1997; Starks et al., 2012; Van Kempen et al., 2012; Wang et al., 2009). In this study, we administered the Continuous Performance, Digit Span, and Finger Tapping tests from the NES3 version of the battery (Letz, 2000) (Fig. 1). We chose these tests because they measure important neurobehavioral domains. Moreover, studies observing a negative association between neurotoxicants and results in these tests (Debes et al., 2006; Grandjean et al., 1997; Lanphear et al., 2000; Needleman et al., 1990) suggested that the tests were sensitive to the effects of environmental pollution.

In the Continuous Performance Test, a series of letters was displayed on the screen. The task was to immediately respond to the