Environmental Research 110 (2010) 476–483

Contents lists available at ScienceDirect

Environmental Research

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

Environmental exposure to lead, but not other neurotoxic metals, relates to core elements of ADHD in Romanian children: Performance and questionnaire data☆, ☆☆

Rodica Nicolescu [a], Cristian Petcu [b], Aurelia Cordeanu [a], Klaus Fabritius [a], Margret Schlumpf [c], Rolf Krebs [d], Ursula Krämer [e], Gerhard Winneke [f,*]

[a] Institutul de Sanatate Publica, Str. Dr. Leonte 1-3, 050463 Bucuresti, Romania
[b] Resident Physician, Str. Vladimirescu 20, 077145 Pantelimon, Romania
[c] GREENTOX GmbH, Universität Zürich, CH-8057 Zürich, Switzerland
[d] Zurich University of Applied Sciences, CH-8820 Wädenswil, Switzerland
[e] Epidemiology Group. Institut für Umweltmedizinische Forschung an der Heinrich-Heine-Universität Düsseldorf, D-40225 Düsseldorf, Germany
[f] D-41516 Grevenbroich, Pfannenstraße 31 (former affiliation: Medical Institute of Environmental Hygiene, Heinrich-Heine-Universität Düsseldorf), Germany

ARTICLE INFO

Article history:
Received 28 January 2009
Received in revised form
26 March 2010
Accepted 14 April 2010

Keywords:
Neurotoxic metals
Lead
ADHD
Attention performance
Questionnaire
Parents
Teachers
Children
Romania

ABSTRACT

Neurobehavioral measures of attention, and clinical features of the attention-deficit hyperactivity disorder (ADHD) have been studied in pediatric environmental lead research. However rarely, if ever, have performance measures of attention or executive functions and questionnaire-based quantitative ADHD-observations been studied in the same subjects. We examined associations between pediatric blood lead concentrations (PbB), as well as those of mercury (Hg), and aluminum (Al), and performance in four different attention tasks, as well as behavioral ratings from an ICD-10 (hyperactivity) and DSM-IV-coded (attention deficit) German questionnaire (FBB-ADHS). Asymptomatic, 8–12 year old children from two Romanian cities were studied, namely Bucharest and Pantelimon, a city near a metal-processing plant. Blood was analyzed for Pb, Al, and Hg. Data from 83 children were available for final analysis. We assessed attention performance by means of four tasks of the computer-based ADHD-taylored German KITAP-battery. We also received questionnaire ratings from parents and teachers covering three ADHD-dimensions. Multiple linear regression analysis was used to estimate associations between the three neurotoxic trace metals in blood and the different ADHD features. After adjusting for eleven potentially confounding variables we found consistent borderline to significant associations between Pb, but not other metals, in blood and various performance- and questionnaire data. False alarm responses (FAR) in the KITAP subtests rather than response latencies exhibited positive associations with PbB. Questionnaire ratings for ADHD dimensions also revealed PbB-related adversity. With any two-fold increase of PbB outcome changed markedly, namely up to 35%. Restriction to children with PbBs < 10 μg/dl had only a marginal influence on outcome.The converging evidence from performance- and questionnaire data confirms that core elements of ADHD are adversely affected by low environmental PbB even below 10 μg/dl, but not by other neurotoxic trace metals. Observed effect-sizes are considerably larger than those typically found for lead-related IQ-deficit, thus suggesting that attention deficit could be the more basic adverse effect of lead in children. This is the first study from Central and Eastern Europe dealing with links between environmental exposure of children to neurotoxic metals and ADHD.

☆ *Funding sources*: This work was financed by the Swiss National Science Foundation, the Swiss Agency for Development and Cooperation, and the Romanian Ministry for Education and Research within the Swiss-Romanian cooperation program "Environmental Science and Technology in Romania - ESTROM". This study was performed in the subproject NEPOLL estimating the degree of water/soil-pollution and body burden of children adjacent to an industrial area near Bucharest, Romania.

☆☆ *Study approval*: This study has been reviewed and approved by the Ethics Committee of the "Romanian College of Physicians".

* Correspondence to: Institut für umweltmedizinische Forschung, Heinrich-Heine-Universität Düsseldorf, Auf'm Hennekamp 50, D-40225 Düsseldorf, Germany. Fax: +49 2182 3019.
E-mail addresses: gerhard.winneke@gmx.de, gerhard.winneke@uni-duesseldorf.de (G. Winneke).

0013-9351/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.envres.2010.04.002

1. Introduction

The study of behavior and its alteration by chemicals or therapeutic agents in toxic doses is an established approach within neurotoxicology. General neurotoxicology draws upon a broad spectrum of neuroscience methods to study adverse effects of chemicals on the structure and/or function of the mature or developing nervous system, and behavior is part of this spectrum.

A systematic internet search of several data banks covering animal and human data revealed some degree of established developmental neurotoxicity for 201 industrial chemicals (Grandjean and Landrigan, 2006). Within this group of chemicals only three metals were marked as having shown to be neurotoxic in man, namely inorganic lead, organic mercury and arsenic. The general claim made is that due to the lack of systematic studies several of the listed chemicals may have detrimental effects on the developing nervous system, possibly causing neurodevelopmental disorders like autism, attention-deficit disorder, mental retardation or cerebral palsy, the true causes of which are mostly unknown.

The present report deals with core elements of the attention-deficit hyperactivity disorder (ADHD) in children as a neurodevelopmental disorder and its potential association with environmental exposure to neurotoxic metals in asymptomatic children. From the above-mentioned list of neurotoxic chemicals inorganic lead was chosen and, additionally, metallic mercury and aluminum, because evidence for their neurotoxic potential is given, as well. Initially Arsenic (As) in blood was also included as an independent exposure variable. However, As in blood rather than As in urine is an inadequate marker of longterm environmental exposure for both metabolic and kinetic reasons, its use as an exposure marker was discarded for this study.

Organic mercury as methyl mercury has been identified as a developmental neurotoxicant in children from fish-eating populations (National Research Council, 2000), whereas exposure to metallic mercury vapors with signs of neurotoxicity is largely limited to occupational settings and to that due to amalgam fillings in the general population. Its neurotoxicity is well-documented as tremor and psychomotor impairment resulting from excessive workplace exposure. The neurotoxic potential of aluminum was first identified by its causative role in well-documented cases of dialysis dementia and subsequent neurobehavioral observations in laboratory animals; a more controversial issue is the role of Al in the pathogenesis of Alzheimer's disease.

In studying neurodevelopmental consequences of early environmental childhood lead exposure the emphasis of most studies has been on impaired mental development, and the main endpoint in such studies has been the intelligence quotient or IQ (WHO, 1995). Lead-IQ associations are typically small (Pocock et al., 1994; Koller et al., 2004), and pediatric blood lead levels have decreased substantially during the past three decades in most countries, e.g. in Germany from 9.1 μg/dl in 1983 to 3.3 μg/dl in 2000 (Ranft et al., 2008). Yet, there still is concern regarding lead as an environmental health risk for children, because of the apparent lack of an effect threshold for the lead-IQ association, and because of the reported non-linearities of the dose-response function for this endpoint (Canfield et al., 2003; Lanphear et al., 2005; Jusko et al., 2008), but also because of studies reporting links between environmental lead exposure and juvenile delinquency (Needleman et al., 1996).

In addition to intellectual impairment the possible contribution of environmental lead-exposure to aspects of Attention-Deficit-Hyperactivity-Disorder (ADHD) in children as an ICD-10 (hyperactivity disorder) and DSM-IV-(attention deficit disorder) defined disorder has also received considerable attention in the past and, starting with the pioneering contribution of David et al. (1972), several studies in asymptomatic children (e.g. Bellinger et al., 1994; Burns et al., 1999; Chiodo et al., 2007; Gittleman and Eskenasi, 1983; Minder et al., 1994; Walkowiak et al., 1998; Wasserman et al., 1998; Winneke et al., 1989) emphasized the role of childhood lead-exposure as possibly contributing to aspects of ADHD. Also, recent case-control studies or categorical observations in larger populations support links between ADHD and blood lead-levels in clinical cases (Braun et al., 2006; Ha et al., 2009; Nigg et al., 2008, 2010; Wang et al., 2008), although some controversy exists as to the causative role of lead in part of this work (Brondum, 2009).

However, only few studies have elaborated the role of low levels of environmental exposure to inorganic lead relative to the possible contribution of other neurotoxic agents with regard to their ADHD-association and, to the best of our knowledge, no study exists in which data from questionnaire-based observations and information from a spectrum of tests covering executive and attentional functions were collected for pediatric environmental lead-exposure. Also, in contrast to IQ-studies, efforts to come up with effect-size estimates for any increase of exposure do not seem to be available in previous ADHD-studies in the context of low-level exposure to environmental chemicals. Furthermore, it must be stressed that, to the best of our knowledge, there is a lack of pertinent information from Central or Eastern Europe, so far. This is a shortcoming, because neuropediatric awareness and diagnostic ADHD-criteria as well as relevant social background variables are likely to exhibit variability across countries and cultures.

The aim of this study was to close these gaps in a systematic and comprehensive manner in asymptomatic children from Romania, using both performance-based measures of executive and attentional functions and observational data from a standardized ADHD-questionnaire completed by parents and teachers. The other neurotoxic metals were included in order to check for the specificity of lead-related neurotoxicity. The study was approved by the Ethics' Committee of the Romanian College of Physicians, Bucharest, Romania. We requested and received informed written consent from the parents of the participating children, and informed the parents of all individual results of their child later.

2. Materials and methods

2.1. Study areas and timing

Recruitment of the children and blood sampling in the cities of Bucharest and Pantelimon was completed between January and May 2006, analytical results were available until November 2006, performance testing took place between May and June 2007, and questionnaire data were collected until November 2007.

Bucharest, the capital and cultural as well as economic center of Romania, has about 2 million inhabitants. The downtown area is characterized by heavy traffic and business administration. Pantelimon is a medium-sized community of about 18,000 inhabitants approximately 2 km south-east of Bucharest. A waste metal-processing plant, located about 2 km east of Pantelimon, had been processing metal containing technical equipment, mainly batteries, over many years, but these activities ended in 2006, with the exception of one installation which has been modernized. Soil lead levels were measured in several locations around the processing plant, and revealed substantial environmental contamination with up to 5000 mg Pb/kg soil in 200 m distance to the industry. A spatial gradient well into Pantelimon was observed, with maximum lead values of 1300 mg Pb/kg soil.

2.2. Recruitment and description of the sample

We recruited children between 8 and 12 years of age (median: 9,9 years) in Bucharest ($N=54$) and Pantelimon ($N=46$). 17 blood samples from Bucharest were unavailable for trace metal analysis for technical reasons, thus leaving 83 children for the complete data set. Recruitment in Bucharest was organized via four elementary schools in four different low-traffic areas, whereas the children