International Journal of Hygiene and Environmental Health 217 (2014) 678–686

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

Arsenic methylation capacity and developmental delay in preschool children in Taiwan

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ARTICLE INFO

Article history:
Received 12 November 2013
Received in revised form 4 February 2014
Accepted 21 February 2014

Keywords:
Arsenic methylation capacity
Developmental delay
Arsenic
Lead
Mercury

ABSTRACT

Environmental exposure to lead or mercury can cause neurodevelopmental damage. Arsenic is another neurotoxicant that can affect intellectual function in children. This study was designed to explore the difference of arsenic methylation capacity indices between with and without developmental delay in preschool children. We also aimed to identify whether blood levels of lead or mercury modify the effect of arsenic methylation capacity indices. A cross sectional study was conducted from August 2010 to March 2012. All participants recruited from the Shin Kong Wu Ho-Su Memorial Teaching Hospital. In all, 63 children with developmental delay and 35 children without developmental delay were recruited. Urinary arsenic species, including arsenite (As^{III}), arsenate (As^{V}), monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}) were measured with a high-performance liquid chromatography-linked hydride generator and atomic absorption spectrometry. Lead and mercury levels of red blood cells were measured by inductively coupled mass spectrometry. All participants underwent developmental assessments to confirm developmental delays, including evaluations of gross motor, fine motor, speech-language, cognition, social, and emotional domains. Urinary total arsenic and MMA^{V} percentage were significantly positively associated and DMA^{V} percentage was negatively associated with the risk of developmental delay in a dose-dependent manner after adjustment for blood lead or mercury levels and other risk factors. A multivariate regression analysis indicated that blood lead level and arsenic methylation capacity each independently contributed to the risk of developmental delay. This is the first study to show that arsenic methylation capacity is associated with developmental delay, even without obvious environmental arsenic exposure.

Introduction

Neurodevelopmental disorders include learning disabilities, sensory deficits, developmental delays, and cerebral palsy (Boyle et al., 1994). Data from the public information collected by the Department of Statistics of the Ministry of the Interiors of Taiwan, and accessible via the Department's website, found that the prevalence of developmental delays in 3–5 year-old children increased from 1.05 to 1.47% between 2007 and 2010 (Department of Statistics, 2010). The developmental delays occurred more often in males than in females. Since children with developmental delays require more healthcare services than the general population, the increased prevalence of delays raises an important public health issue.

Evidence has shown that industrial chemicals can cause neurodevelopmental damage. An early study reported that low-level lead exposure was associated with neuropsychological dysfunction in children (Landrigan et al., 1975), and another study showed that

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http://dx.doi.org/10.1016/j.ijheh.2014.02.004
1438-4639/

dentin lead levels were associated with neuropsychologic deficits that may interfere with classroom performance and increased the frequency of non-adaptive classroom behavior in a dose-dependent manner (Needleman et al., 1979). Organic mercury caused developmental toxicity in infants born to mothers who consumed fish from contaminated waters in Minamata Bay, Japan in the 1960s (Harada, 1995). A cohort study provided evidence of dose-related impairments in memory, attention, language, and visuospatial perception in children with prenatal exposure to methylmercury (Grandjean et al., 1997). Arsenic is another known neurotoxicant that affects intellectual function in children. A 50-year follow-up study found that infants who survived poisoning by arsenic-contaminated milk showed effects such as mental retardation and neurological disease (Dakeishi et al., 2006). Tsai et al. (2003) found that cognitive deficits in adolescents in Taiwan were associated with arsenic contamination of drinking water. Wasserman et al. (2004) also reported that arsenic-contaminated water reduced intellectual function of 10 year-old children in Bangladesh in a dose-dependent manner. These findings suggest that environmental exposure to arsenic may induce neurodevelopmental damage.

Inorganic arsenic enters the human body and is biotransformed to monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V). Previously, methylation of inorganic arsenic was considered a detoxification mechanism, since MMA^V and DMA^V have relatively low toxicity (Yamauchi and Fowler, 1994) and are rapidly excreted in the urine (Vahter, 2002). However, in vitro toxicity studies have shown that monomethylarsonous acid (MMA^{III}) and dimethylarsinous acid (DMA^{III}) are more toxic than inorganic arsenite (Styblo et al., 2000, 2002; Tokar et al., 2014). The extent of arsenic metabolism in humans is remarkably variable and may influence human toxicity. Previous studies of arsenic metabolism have suggested that children are poor methylators compared to adults (Chowdhury et al., 2003; Concha et al., 1998). Therefore, arsenic methylation capacity in children may be related to developmental disorders. However, evidence for developmental neurotoxicity of arsenic or arsenic metabolites is less well established than lead and methylmercury. Thus, the aims of this study were to assess the relationship between arsenic methylation capacity and developmental delay in preschool children and to evaluate whether lead or mercury modify the effect of arsenic methylation capacity on developmental delay.

Materials and methods

Study participants

All study subjects were recruited from the Shin Kong Wu Ho-Su Memorial Teaching Hospital, a 921-bed medical center located in northern Taiwan, between August 2010 and March 2012. Preschool children with suspected developmental delays were referred to the medical center from communities near the hospital by local kindergartens, hospitals, and community centers. All subjects in this study underwent developmental assessments to confirm developmental delays, including evaluations of gross motor, fine motor, speech-language, cognition, social, and emotional domains. The evaluations were performed by members of the early development intervention team at the study hospital using the Peabody Developmental Motor Scales, Gross Motor Function Measure, Preschool Language Evaluation Tool, Child Expression Evaluation Tool, Chinese Wechsler Intelligence Scale for Children (3rd edition), and Bayley III Scales of Infant and Toddler Development. A developmental delay was defined as performance two standard deviations or greater below the mean on age-appropriate, standardized, norm-referenced tests. The evaluation team consisted of a physiatrist, a pediatrician, a psychiatrist, an otolaryngologist, an ophthalmologist, physical therapists, occupational therapists, speech therapists, a psychologist, and a social worker. A total of 63 preschool children who were diagnosed with developmental delays were included in the study. In addition, 35 children without developmental delays were recruited from the Department of Pediatrics of Shin Kong Wu Ho-Su Memorial Teaching Hospital to serve as controls. The Research Ethics Committee of the Shin Kong Wu Ho-Su Memorial Teaching Hospital approved the study, and the study was performed in accordance with the World Medical Association Declaration of Helsinki. Parents or primary caregivers of all the children provided informed consent before a questionnaire interview and biological specimen collection.

Questionnaire interview

Structured questionnaires were administered through interviews in the clinics. The information obtained by the questionnaire included demographics of children and their parents, socioeconomic characteristics and lifestyle factors of parents such as cigarette smoking and environmental smoke exposure, and personal and family medical histories.

Biological specimen collection

Spot urine samples of children and their mothers were collected at the time of recruitment and immediately transferred to a −20 °C freezer and stored until the analysis of arsenic species. Blood samples of children and their mothers were collected and centrifuged; the red blood cells were collected and immediately transferred to a −80 °C freezer and stored until analysis of the lead and mercury concentrations.

Urinary arsenic species assessment

Urinary arsenic profiles of As^{III}, DMA^V, MMA^V and As^V were measured by high-performance liquid chromatography on line with a hydride generator and atomic absorption spectrometer (HPLC-HG-AAS). The protocol for the determination of the arsenic species was described in a previous study (Hsueh et al., 1998). Recovery rates of the four arsenic species were calculated using the following formula: ([(sample spiked standard solution concentration) − sample concentration]/standard solution concentration) × 100. The recovery rates of As^{III}, DMA^V, MMA^V, and As^V ranged from 93.8 to 102.2%, with detection limits of 0.02, 0.08, 0.05 and 0.07 μg/L, respectively. Freeze-dried SRM 2670 urine, which contained 480 ± 100 μg/L arsenic, was purchased from the National Institute of Standards and Technology (NIST, Gaithersburg, MD, USA). This standard was used to assess the validity of measurement and analyzed along with the urine specimens of the study subjects. The detected concentration of arsenic in the SRM 2670 standard was 507 ± 17 μg/L (n = 4). To ensure the stability of urinary arsenic profiles, we performed the detection of arsenic species within 6 months after sample collection (Chen et al., 2002).

Red blood cell lead and mercury measurements

Red blood cells were thawed at room temperature and then digested with nitric acid by microwave (Perkin Multiwave 3000). Lead and mercury levels of red blood cells were measured by inductively coupled mass spectrometry (ICP-MS, Thermo X-series II). SeronormTM Trace Elements Whole Blood, which contained certified levels of lead and mercury (310 (range 186–434) μg/L and 16.0 (range 9.6–22.4) μg/L, respectively), was used to assess the validity of measurement and analyzed along with the blood specimens of the study subjects. Lead and mercury concentrations of SeronormTM Trace Elements Whole Blood were measured