Environmental Pollution 226 (2017) 89–93

Contents lists available at ScienceDirect

Environmental Pollution

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

A pilot study on the association between rare earth elements in maternal hair and the risk of neural tube defects in north China☆

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ARTICLE INFO

Article history:
Received 22 December 2016
Received in revised form
18 February 2017
Accepted 20 March 2017

Keywords:
Neural tube defects
Risk
Rare earth elements
Hair

ABSTRACT

Rare earth elements (REEs) have many applications in industry, agriculture, and medicine, resulting in occupational and environmental exposure and concerns regarding REE-associated health effects. However, few epidemiological studies have examined the adverse effects of REEs on pregnancy outcomes. Therefore, this study examined the relationship between the REE concentrations in maternal hair growing during early pregnancy and the risk of neural tube defects (NTDs) in offspring. We included 191 women with NTD-affected pregnancies (cases) and 261 women delivering healthy infants (controls). The cases were divided into three subtypes: anencephaly, spina bifida, and encephalocele. Four REEs in maternal hair were analyzed by inductively coupled plasma-mass spectrometry: lanthanum (La), cerium (Ce), praseodymium (Pr), and neodymium (Nd). A questionnaire was used to collect information about maternal sociodemographic characteristics and dietary habits. The median concentrations of Ce and Pr in the NTD group were higher than those in the control group, whereas there were no significant differences for La and Nd. The adjusted odds ratios (ORs) for the four REE concentrations above the median in the case groups were not significantly > 1. An increasing frequency of the consumption of beans or bean products and fresh fruit was negatively correlated with the four REE concentrations. Our results did not suggest that the concentrations of REEs in maternal hair were associated with the risk of NTDs or any subtype of NTDs in the general population.

1. Introduction

Neural tube defects (NTDs), which are a group of birth defects resulting from the failure of normal neural tube closure between the third and fourth weeks of embryonic development, have a worldwide incidence ranging from 1 to 10 per 1000 births (Au et al., 2010; Chen, 2008). Anencephaly, spina bifida, and encephalocele are three common types of NTDs (Chen, 2008). Anencephaly and spina bifida occur in an estimated 300,000 newborns throughout the world each year (Christianson et al., 2006), which places great physical, emotional, and financial burdens on the affected children and families (Wallingford et al., 2013). The etiology of NTDs is a complex combination of genetic and environmental factors (Botto et al., 1999). Environmental factors, such as maternal age, parity, social class, metabolic diseases, and exposure to specific anticonvulsants, pesticides, and heavy metals, are confirmed risk factors for NTDs (Sever, 1995; Wallingford et al., 2013; Wang et al., 2015; Wang et al., 2014). Oxidative stress has been accepted as an important gene pathway in the pathogenesis of NTDs (Han et al., 2011; Wallingford et al., 2013). Unregulated cell apoptosis during neural tube closure due to oxidative stress may lead to NTDs (Au et al., 2010). Several studies have reported that oxidative stress may be involved in diabetes- and arsenic-induced NTDs (Han et al., 2011; Yu et al., 2016). Therefore, it is worthwhile to screen for risk factors that can cause strong oxidative stress damage to the human body.

Rare earth elements (REEs) is a general term for the lanthanide series of elements, which comprises lanthanum through lutetium

☆ This paper has been recommended for acceptance by David Carpenter.

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http://dx.doi.org/10.1016/j.envpol.2017.03.046

and yttrium, and these elements have similar physicochemical properties (Li et al., 2013; Liu et al., 2015). REEs are widely used in industry, agriculture, and medicine. Lanthanide compounds can stimulate the growth of crops and have been used widely in farms as an important trace fertilizer, especially in China (Chen et al., 2001). China has the world's largest reserve of rare earth resources (Hirano and Suzuki, 1996), and Shanxi is a major coal-producing province in China. Exploitation of coal may lead to the contamination of soil or water with REEs (Zhao et al., 2007). Indeed, the increasing applications of REEs and the increased mining of rare earth minerals may release more REEs into the environment, which would increase environmental exposure to REEs in the general population (Wei et al., 2013). Animal studies have revealed that REEs can cross the placental barrier and also enter breast milk (Naharin et al., 1974; Naharin et al., 1969). It was reported that there were positive correlations between maternal blood and cord blood levels of REEs, which suggests that maternal REEs can enter the infant's body via the placental barrier in humans (Zhang et al., 2005).

REEs can alter the balance between the formation and the elimination of free radicals and induce oxidative stress (Pagano et al., 2015; Valcheva-Traykova et al., 2014), which might play an important role in the etiology of NTDs (Au et al., 2010; Han et al., 2011; Yu et al., 2016). REEs have ionic radii that are similar to that of calcium, which enables them to compete with calcium ions (Pałasz and Czekaj, 2000). Consequently, REEs can replace calcium ions on certain cell membrane loci and alter enzymatic activities (Das et al., 1988). A deficiency in calcium is associated with an increased risk of NTDs (Shaw et al., 1999). Hence, a high intake of REEs might interfere with the protective effects of calcium against NTDs.

Human scalp hair has been used widely to reflect the internal accumulation of metals, as its sampling is considered less invasive and more convenient for storage compared with other biological materials, such as blood and urine (Pereira et al., 2004; Wang et al., 2009). REE concentrations in the hair of individuals can be used as biomarkers of their exposure level (Peng et al., 2003; Tong et al., 2004; Wei et al., 2013). We can use specific hair sections to reflect population exposure characteristics during specified time windows by assuming a consistent growth rate of hair (Srinivas et al., 2001).

Therefore, we hypothesized that maternal exposure to REEs during early pregnancy was associated with an elevated NTD risk in their offspring. Consequently, this study (1) determined the hair concentrations of REEs among pregnant women in Shanxi and Hebei Provinces, and (2) examined the association between REE concentrations in maternal hair and the risk of NTDs.

2. Materials and methods

2.1. Study population

The original study has been described previously (Li et al., 2016a). Briefly, the study was conducted in nine counties and two cities in Shanxi and Hebei Provinces between January 2003 and December 2007. The two provinces in northern China have the highest reported prevalence of NTDs worldwide (Xiao et al., 1990). The locations of these sampling sites and the major mining sites around this population were shown in Supplementary Fig. S1. The population-based birth defect surveillance system was established in study areas to monitor major external structural birth defects through active case ascertainment. Cases in the study included liveborn infants, stillborn infants, and prenatally diagnosed, electively aborted fetuses of mothers residing in the study areas. County health workers verified the diagnoses by physical examination of the fetal body or prenatal ultrasound for all pregnancy outcomes and filled out a reporting form for each case. We requested photographs of every infant born with a suspected birth defect, if available. Pediatricians at Peking University reviewed all case report forms, photographs or ultrasound materials before assigning final diagnostic codes. Based on this surveillance system, an ongoing case-control study was conducted to explore risk factors for NTDs. When a woman with an NTD-affected pregnancy (including a live birth, still birth, or pregnancy termination) was confirmed as a case, trained health-care workers conducted face-to-face interviews with the woman within 1 week of delivery to collect exposure information and hair samples if she consented. Then one or two control women with a full-term healthy infant were matched to the case with regard to birthing hospital, county or city of residence, and last menstrual period. Interviewers used a structured questionnaire to collect information about the women's sociodemographic characteristics, gravidity, periconception folate supplementation, fever or flu during early pregnancy, alcohol consumption, active or secondhand smoking during the periconception period, and frequency of consumption of selected categories of foods. The study was approved by the Institutional Review Board of Peking University, and all subjects provided informed consent.

For the current study, we selected 452 valid subjects who provided the hair samples from the originally recruited individuals, including 191 cases and 261 corresponding controls. The cases included 85 subjects affected by anencephaly, 79 by spina bifida, 24 by encephalocele, and three without subtype information. Hair samples from all subjects were cut from the back of the head as near as possible to the scalp and stored at room temperature until analysis.

2.2. Metal analysis

We calculated that the length of the hair section growing from 1 month before conception to 2 months after conception was about 3 cm by assuming a growth rate of ~1 cm/month for this population. The REE analysis method has been described elsewhere (Li et al., 2016b). Briefly, hair samples and blank vials were washed once with 1 mL Triton X-100 (Sigma-Aldrich, St. Louis, USA) (vortexed for 5 min), three times with 1 mL deionized water (vortexed for 5 min), and two times with 1 mL mixture of n-hexane (Ultra Resi-Analyzed®, Merck KGaA) and dichloromethane (J.T. Baker®, USA) (3/2, v/v) (vortexed for 5 min). The REE concentrations were measured using inductively coupled plasma-mass spectrometry (ICP-MS; ELAN DRC II, PerkinElmer, USA). The four REEs examined in this study were lanthanum (La), cerium (Ce), praseodymium (Pr), and neodymium (Nd). The limits of detection were 0.24 (La), 0.016 (Ce), 0.004 (Pr), and 0.12 (Nd) ng/g hair. The measured and reference concentrations of the four REEs for standard hair references (GBW09101a, purchased from the National Standard Material Center in China) were used for quality control. The measured concentrations of La, Ce, Pr, and Nd were 11.96 ± 0.33, 20.93 ± 1.15, 2.47 ± 0.17, and 8.65 ± 0.18 ng/g, respectively, which were close to the reference concentrations in the product description (*i.e.*, 13.4 ± 1.8, 19.7 ± 2.6, ~2.4, and 8.4 ± 1.5 ng/g, respectively). Three procedural blanks and one reagent blank were included with each batch of hair samples. For quality assurance, the quantitative analysis was conducted in the Central Laboratory of Biological Elements in the Peking University Health Science Center, and the protocol was qualified by the China Metrology Accreditation (CMA) system.