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Are concentrations of alkaline earth elements in maternal hair associated with risk of neural tube defects?☆,☆☆

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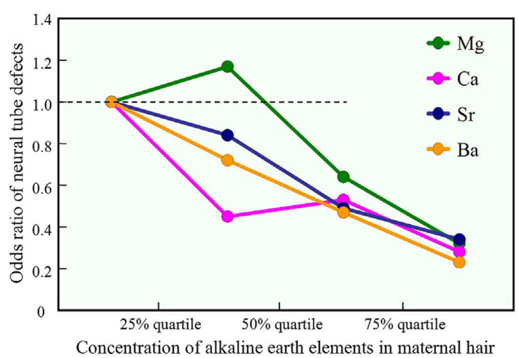
HIGHLIGHTS

- Alkaline earth elements (AEEs) play important roles in fetal neurodevelopment.
- We aimed to investigate an association of AEEs in maternal hair with risk of NTDs.
- We recruited 191 women delivering fetus with NTDs (cases) and 261 healthy controls.
- Higher AEEs in maternal hair were consistently associated with an increase NTD risk.

GRAPHICAL ABSTRACT



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ABSTRACT

The relationship between maternal intake of alkaline earth elements (AEEs) during the period of neural tube closure and the risk of neural tube defects (NTDs) is still unclear. We propose that AEE deficiency during the early period of pregnancy is associated with an elevated risk of NTDs in the offspring. In this study, we recruited 191 women with NTD-affected pregnancies (cases) and 261 women who delivered healthy infants (controls). The concentrations of four AEEs (Ca, Mg, Sr, Ba) in maternal hair sections that grew during early pregnancy were analyzed. Information on the dietary habits of the mothers was also collected by questionnaire. Higher concentrations of the four AEEs in hair had protective effects against the risk of total NTDs, with odds ratios with 95% confidence interval (comparing groups separated by each median level) of 0.44 (0.28–0.68) for Mg, 0.56 (0.36–0.87) for Ca, 0.45 (0.28–0.70) for Sr, and 0.41 (0.26–0.65) for Ba. Significant negative dose-response trends were identified for the relationships between the four AEE concentrations in maternal hair and the risks of anencephaly and spina bifida, but not for encephalocele. The frequencies of maternal consumption of fresh green vegetables, fresh fruit, and meat or fish were positively correlated with the concentrations of AEEs in hair. We concluded that the maternal intake of AEEs may play an important role in preventing NTD formation in offspring, and that this intake is related to maternal dietary habits of consuming fresh green vegetables, fresh fruit, and fish or meat.

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1. Introduction

Neural tube defects (NTDs), resulting from the failure of neural tube closure by the 28th day postconception, are a group of serious birth defects worldwide (Wallingford et al., 2013). Researchers had expended substantial efforts elucidating the etiology of NTD development from genetic and environmental perspectives, as well as their interaction effects (Wang et al., 2014; Li et al., 2011; Wang et al., 2015; Carmichael et al., 2003). Among the influential factors, maternal diet was found to play an important role in preventing NTDs (Carmichael et al., 2003; Yin et al., 2011; Li et al., 2006), in which the minerals or nutrients of various types of food may act as mediating factors (Hostetler et al., 2003; Shaw et al., 1999; Tapola et al., 2004). Animal studies showed that alkaline earth elements (AEEs), especially calcium (Ca) and magnesium (Mg), are essential for embryonic development (Webb and Miller, 2003; Hurley et al., 1976). Epidemiological studies using questionnaires also indicated that maternal deficiency of Ca or Mg was associated with the risk of NTDs (Carmichael et al., 2003; Shaw et al., 1999). Diet is an efficient and convenient way to supplement AEEs with acceptable cost for the general population. Hence, comprehensively investigating the association between the maternal intake of AEEs and NTDs via a reliable epidemiological study is worthwhile.

Possible protective effects of Ca and Mg were first observed in environmental/ecological surveys. For example, Bound et al. proposed that Ca is an antagonist of lead toxicity and thereby associated with reduced NTD prevalence in the UK (Bound et al., 1997). A negative association of anencephalus mortality during 1950–1969 in 36 Canadian cities with a population over 50,000 with Mg concentration of domestic tap water was also observed (Elwood, 1977). In addition, an environmental geochemistry study revealed that strontium (Sr) deficiency in local soil in Shanxi Province, China, may be a distinctive environmental feature associated with the high rate of birth defects (Yu and Zhang, 2011). However, in epidemiological studies, there has been limited investigation using population biological samples to evaluate the association of AEE intake with NTD risk. Maternal serum Ca levels have been found to be lower in pregnancies complicated by NTDs than in healthy pregnant women (Daglar et al., 2016). Moreover, the consumption of mineral water fortified with Ca improved folate status and decreased plasma homocysteine concentration in women (Tapola et al., 2004), which reduce the risk of NTDs (Mills et al., 1996; Berry and Li, 2002). However, the association between Ca concentration in amniotic fluid and the risk of NTDs is unclear. Dawson et al. found that Ca concentration in amniotic fluid of mothers affected by NTDs was higher than that of healthy controls (Dawson et al., 1999), whereas no significant differences were observed between controls and cases of spina bifida (11 subjects) and anencephaly (20 subjects) (Pettit et al., 1979). For Mg, it was reported that the plasma Mg concentration of the mothers of six congenitally malformed children did not differ from that of controls (Stoll et al., 1999), and the same finding was found in another study of amniotic fluid of the mothers of 11 fetuses with spina bifida and 20 fetuses with anencephaly (Pettit et al., 1979). These results still need confirming by well-controlled epidemiological studies with a larger sample size. In addition, to the best of our knowledge, the effects of the maternal intakes of another two typical AEEs (Sr and Ba) have not been reported. Therefore, there is a knowledge gap regarding the associations between the long-term maternal intake of AEEs and the risk of NTDs.

Risk or protective factors should mainly act on NTD development during the early period of pregnancy because NTDs result from the failure of neural tubes to close by the fourth week postconception (Wallingford et al., 2013). AEEs in blood or amniotic fluid may be easily affected by the short-term diet. Because of the practical difficulty of collecting maternal serum or amniotic fluid at early stages of pregnancy, it was challenging to investigate the association between AEE intake during this time window and NTD risk in previous studies. Determining the concentrations of metals in hair has been found to be a useful approach to assess the internal accumulated levels among individuals (Pereira et al., 2004; Wang et al., 2009). More importantly, it can be used to indicate the exposure level during a specific time window by assuming a consistent growth rate of hair (Srinivas et al., 2001). In the current study, we investigated the hypothesis that AEE deficiency in mothers during the early period of pregnancy is associated with an elevated risk of NTDs in their offspring. The aims of our study were as follows: (1) to investigate the associations between the levels of AEEs (i.e., Mg, Ca, Ba, or Sr) in maternal hair that grew from one month before conception to two months after it and the risk of NTDs, and (2) to determine the relationships between maternal dietary habits and concentrations of AEEs in maternal hair.

2. Materials and methods

2.1. Study location and population

Data came from an ongoing case-control study of major external birth defects, which was conducted in four counties (Pingding, Xiyang, Taigu, and Zezhou) in Shanxi Province, and six counties (i.e., Mancheng, Yuanshi, Shijiazhuang, Laoting, Fengrun, and Xianghe) in Hebei Province in northern China, from January 2003 to December 2007. These two provinces have been identified as the Chinese regions with the highest prevalence of NTDs (Xiao et al., 1990). Cases were live-born or stillborn infants with major external birth defects identified by an active surveillance system. All cases were reviewed by three pediatricians at Peking University Health Science Center. When an infant was identified as having any major external malformation, a newborn control with no external structural birth defects was matched to this case infant by county, sex, maternal ethnic group, and date of conception (as closely as possible). Information was collected by trained health workers through face-to-face interviews within 1 week after delivery or pregnancy termination. The structured questionnaire used in these interviews included questions on the women's socio-demographic characteristics, lifestyle behaviors, use of folic acid supplements, and frequency of consumption of selected categories of food from 1 month before through 2 months after conception. Before asking these questions, the interviewers helped the women to confirm the exposure period based on the date of their last menstrual period. Detailed information on the questionnaire is provided in Supplementary Materials. In addition, we also collected women's hair samples, if they consented to this. These hair samples were collected using stainless steel scissors, which were cut from the back of the head, as near as possible to the scalp. The samples were then sealed separately in labeled polyethylene zip-lock bags, which were not opened until analysis in the laboratory. The study was approved by the Institutional Review Board of Peking University Health Science Center.

In the current study, we selected all NTD cases with hair samples investigated between January 2003 and December 2007. To utilize the hair samples effectively, all controls with hair samples, including controls for NTDs as well as for other major external structural malformations, were included in the study. A total of 191 NTD cases (85 anencephaly, 79 spina bifida, 24 encephalocele, and 3 cases whose subtype was not clear) and 261 controls were available.

2.2. Hair AEE analysis

The section of hair that was tested grew from one month before conception to two months after it (~3 cm) was estimated, by assuming that ~1 cm of hair grew per month among this population. The quantitative analysis was conducted in the Central Lab of Biological Elements at Peking University Health Science Center, the protocol of which was approved by China Metrology Accreditation. Each raw human hair sample (~25 mg) was cut into segments with a length of 3–5 mm and transferred into a washed 2-mL glass vial. Hair samples and blank vials were washed once with 1 mL of Triton X-100 (1%, *v*/v) (Sigma-