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Prenatal exposure to arsenic and neurobehavioral development of newborns in China

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ABSTRACT

The link between arsenic exposure and deficits in children's neurodevelopment has been suggested, but it remains unclear regarding the arsenic-related effects on the developing brain in early life. To investigate the associations of in utero arsenic exposure with neonatal neurobehavioral development, we conducted a cross-sectional study of 892 mother-infant pairs from 10 hospitals of different levels in Shanghai, China. The concentrations of arsenic were determined in cord blood samples. Neurobehavioral measures were administered at 3 days postpartum in full-term newborns using the neonatal behavioral neurological assessment (NBNA). Logistic regression models were used to estimate odds ratios for dichotomous NBNA outcomes. After adjusting for potential confounders, a natural log unit (ln-unit) increase in cord blood arsenic was associated with 90% increased odds of low NBNA score (95% confidence interval [CI]: 1.62, 2.23). As for clusters, each ln-unit arsenic increase was associated with 47% increased odds of low score for behavior (95% CI: 1.31, 1.66) and 36% increased odds of low score for passive muscle tone (95% CI: 1.23, 1.51). Odds ratios comparing extreme tertiles were 8.62 (95% CI: 4.19, 17.8) for total scale, 3.69 (95% CI: 2.35, 5.82) for behavior, and 3.32 (95% CI: 2.21, 4.97) for passive tone (all p-trend < 0.001). Stratified analyses showed that these associations were strengthened in newborns of mothers over 29 years of age. Our results provide evidence for an inverse association between low-level prenatal arsenic exposure and neurobehavioral performance of newborns, particularly among those born to older mothers. Further studies are warranted to confirm these findings and to determine whether such decrements in early neurodevelopment persist in later childhood.

1. Introduction

Arsenic is a well-known environmental toxicant that is prevalent in drinking water in many areas of the world (WHO, 2001). Millions of people worldwide are exposed to arsenic in drinking water at concentrations exceeding the World Health Organization guideline value of 10 μg/L (Bloom et al., 2014; George et al., 2014). Arsenic is highly toxic to the central nervous system (WHO, 2001; Hall, 2002). Studies in school-age children have indicated that increasing arsenic exposure may cause deficits in children's intellectual performance, cognitive function and behavior (Calderon et al., 2001; Rosado et al., 2007; Tsai et al., 2003; Wasserman et al., 2007, 2011).

The developing brain of the fetus is particularly vulnerable to toxic insult (Rodier, 1995; Grandjean and Landrigan, 2006). Arsenic easily crosses the placenta during pregnancy and can potentially affect subsequent neurodevelopment in childhood (Vahter, 2009; Hall et al., 2007). Several previous studies reported that in utero arsenic exposure was associated with cognitive and motor impairment in preschool children at 4–5 years of age (Hamadani et al., 2011; Freire et al., 2018). However, other studies found no association of arsenic exposure during pregnancy with offspring development at 7 or 18 months (Tofail et al., 2009; Hamadani et al., 2010). We are unaware of any prior studies that focused on the effect of prenatal exposure on neurodevelopment in early infancy, with the exception of one reporting an inverse association between arsenic levels in cord blood and neurodevelopment of newborns at birth using the Brazelton neonatal behavioral assessment scale

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(NBAS) (Parajuli et al., 2013). Due to the small sample size (n = 100), the ability to generalize its findings may be limited.

It has been demonstrated that neonatal behaviors, as measured by the NBAS, were excellent predictors of infant mental and psychomotor development and child intelligence (Canals et al., 2011). Moreover, neurobehavioral testing with the NBAS could be a sensitive and valid method for detecting early dysfunction of nervous system resulting from exposure to environmental agents (Tronick, 1987). For example, decrements in neonatal behavioral performance associated with cord blood levels of polychlorinated biphenyls have been found (Sagiv et al., 2008; Stewart et al., 2000). To establish a testing method that adapts to the characteristics of Chinese, Bao et al. (1991) formulated the neonatal behavioral neurological assessment (NBNA) based on the Brazelton and Amiel-Tison scale for neonatal behavioral neurological measurement as well as their own experience. The NBNA had distinct stability and reliability, which is appropriate for large-scale investigations (Bao et al., 1993).

Previous studies assessing arsenic exposure and child neurodevelopment mostly targeted the arsenic-contaminated spot in rural areas of developing countries (Tofail et al., 2009; Hamadani et al., 2010, 2011; Parajuli et al., 2013; von Ehrenstein et al., 2007). Results of these studies could be influenced by concurrent exposure to other neurotoxic elements or several confounding factors relevant to poverty such as poor nutritional status. The effect of arsenic on child neurodevelopment in relatively developed urban areas remains unknown. As the largest and most economically developed city of China, Shanghai is facing rapid industrialization and urbanization. The fast growth has also led to increasingly serious environmental problems including the emission of heavy metals. Arsenic exposure at a relatively low level was shown to associate with reduced birth weight and gestational age among the newborns in Shanghai (Xu et al., 2011). Therefore, there is a concern that the neonatal neurodevelopment in this region may be affected, which serves as the motivation of this study. Our aim is to examine the relationship between cord blood arsenic and neurobehavioral development of newborns at 3 days postpartum in Shanghai, China.

2. Methods

2.1. Study population

The present study was conducted in 10 hospitals using a stratified multi-stage cluster sampling methodology in Shanghai between 2008 and 2009 as described previously (Yu et al., 2014). Overall, hospitals with maternity units across the urban and suburban areas were divided into five categories: tertiary hospital (general and specialized), regional hospital (general and specialized), and community hospital. According to the proportion of live births reported in individual hospital and each category, 10 hospitals of different levels were randomly selected and pregnant women who went to these units for delivery were recruited. Mother–infant pairs were eligible to participate if the mother was ≥18 years of age, had lived in the area for at least 2 years, delivered a live-born singleton infant at term (37–42 weeks of gestation), and reported no mental diseases for herself and her spouse. Infants with disorders potentially affecting neurodevelopment such as asphyxia, traumatic brain injury, meningitis, severe neonatal illness or those with 5-min Apgar score lower than 8 were excluded. Of the 1377 enrolled mother-infant pairs, 933 underwent the NBNA measures on the third day of life. After further exclusion of participants who did not have information on cord blood arsenic concentrations (n = 17) or questionnaires (n = 24), 892 newborns were finally included for analysis. This study protocol was approved by the medical ethics committee of Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, and all study participants provided written informed consent.

2.2. Sample collection and arsenic measurements

Umbilical cord blood was collected in trace metal-free polypropylene tube using a sterilized syringe at parturition. After clotting and centrifugation, the serum fraction was separated and stored at −80 °C until analysis. All samples were measured by the Ministry of Education-Shanghai Key Laboratory of Children's Environmental Health in Xinhua Hospital. Serum arsenic concentrations were determined using inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7500ce, Agilent Technologies, Santa Clara, CA, USA). Quantitation of arsenic was based on the response factor relative to an internal standard. The accuracy of analytical method was ensured by the use of "Seronorm" Trace Element Serum L-1, LOT 1309438 (Sero AS, Billingstad, Norway) as the certified reference material in each batch. The values measured for arsenic were within the certified range. Repeated measurements from randomly selected samples (10%) in each batch were performed and there was no significant difference. The limit of detection (LOD) was 0.06 μg/L for arsenic.

2.3. Covariates

Upon enrollment, all participants were interviewed by trained staff at the study hospitals. Information on demographic characteristics, socio-economic status (SES) and lifestyle habits such as maternal age, residence, parents' education, occupation, household income, number of children, alcohol use, active and passive smoking were collected through questionnaires during the interviews. Data of maternal height, body weight at delivery, pregnancy complications, and gestational age were abstracted from medical records. Birth outcomes including birth weight, birth length, and head circumference were determined by obstetric nurses using standard anthropometric procedures.

2.4. Neonatal neurobehavioral outcomes

The NBNA was administered at 3 days postpartum in newborns as a predictor of neonatal neurobehavioral development (Gao et al., 2007). Specifically, the NBNA assesses infant's behavioral capacities (i.e., the ability to respond to the environment such as habituation and orientation to visual and auditory stimuli); the quality of motor tone and reflexes; state regulation and activity during examination (Bao et al., 1991). It consists of five clusters: behavioral ability (six items), passive muscle tone (four items), active muscle tone (four items), primary reflexes (three items), and general reaction (three items). Table 1 lists all the items analyzed. Each of the items is scored on a three-point scale (0,

Table 1
NBNA outcome measures.

Cluster	NBNA item
Behavioral capacity	Habituation to light, rattle Orientation response to visual inanimate (red ball), auditory inanimate (rattle), visual and auditory animate (face and voice) Consolability
Passive muscle tone	Range of extension (shoulder) Rapidity of retraction (upper, lower limbs) Popliteal angle
Active muscle tone	Neck flexion and extension Grip strength Pull-to-sit Up-right
Primary reflexes	Stepping reflex Moro reflex Sucking reflex
General reaction	Arousal Crying state Activity

NBNA, neonatal behavioral neurological assessment.