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Prenatal naled and chlorpyrifos exposure is associated with deficits in infant motor function in a cohort of Chinese infants

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ABSTRACT

Background: Organophosphate insecticides (OPs) are used worldwide, yet despite nearly ubiquitous exposure in the general population, few have been studied outside the laboratory. Fetal brains undergo rapid growth and development, leaving them susceptible to long-term effects of neurotoxic OPs. The objective here was to investigate the extent to which prenatal exposure to OPs affects infant motor development.

Methods: 30 OPs were measured in umbilical cord blood using gas chromatography tandem mass spectrometry in a cohort of Chinese infants. Motor function was assessed at 6-weeks and 9-months using Peabody Developmental Motor Scales 2nd edition (PDMS-2) (n = 199). Outcomes included subtest scores: reflexes, stationary, locomotion, grasping, visual-motor integration (V-M), composite scores: gross (GM), fine (FM), total motor (TM), and standardized motor quotients: gross (GMQ), fine (FMQ), total motor (TMQ).

Results: Naled, methamidophos, trichlorfon, chlorpyrifos, and phorate were detected in ≥10% of samples. Prenatal naled and chlorpyrifos were associated with decreased 9-month motor function. Scores were 0.55, 0.85, and 0.90 points lower per 1 ng/mL increase in log-naled, for V-M ($p = 0.04$), FM ($p = 0.04$), and FMQ ($p = 0.08$), respectively. For chlorpyrifos, scores were 0.50, 1.98, 0.80, 1.91, 3.49, 2.71, 6.29, 2.56, 2.04, and 2.59 points lower for exposed versus unexposed infants, for reflexes ($p = 0.04$), locomotion ($p = 0.02$), grasping ($p = 0.05$), V-M ($p < 0.001$), GM ($p = 0.007$), FM ($p = 0.002$), TM ($p < 0.001$), GMQ ($p = 0.01$), FMQ ($p = 0.07$), and TMQ ($p = 0.008$), respectively. Girls appeared to be more sensitive to the negative effects of OPs on 9-month motor function than boys.

Conclusions: We found deficits in 9-month motor function in infants with prenatal exposure to naled and chlorpyrifos. Naled is being aerially sprayed to combat mosquitoes carrying Zika virus, yet this is the first non-occupational human study of its health effects. Delays in early-motor skill acquisition may be detrimental for downstream development and cognition.

1. Introduction

Synthetic pesticides are used extensively for pest management in a wide range of residential, occupational, and agricultural settings. China reports some of the highest pesticide usage rates in the world (Ding and Bao, 2013; U.S.EPA, 2011; Zhang et al., 2011), at up to 5 times the global average (Huang et al., 2001; Zhang et al., 2014). Organophosphate insecticides (OPs) account for more than a third of all insecticide use in China (Zhang et al., 2014). The primary route of OP exposure in the general population is via the diet, though exposure can also occur from ingestion of contaminated drinking water or dust, residential pest control applications, or topical treatments (Huang et al., 2001; NPIC, 2010; U.S·CDC, 2016). Additionally, warming temperatures have seen a surge in the transmission of mosquito-borne infectious diseases (Bai et al., 2013), likely leading to aerial OP spraying to combat disease spread.

OPs are neurotoxicants, and over the last couple of decades have emerged as a particular concern for developmental neurotoxicity.

Abbreviations: OP, organophosphate; PDMS-2, Peabody Developmental Motor Scales-2nd edition; V-M, visual-motor integration subtest; GM, gross motor score; FM, fine motor score; TM, total motor score; GMQ, gross motor quotient; FMQ, fine motor quotient; TMQ, total motor quotient

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Developing fetal brains undergo rapid growth and maturation, leaving them susceptible to possible long-term effects of exposure (Garcia et al., 2005). Fetal susceptibility is further increased by the fact that OPs can cross the placenta (Bradman et al., 2003; Koutroulakis et al., 2014; Tzatzarakis et al., 2009). Associations have been reported between prenatal exposures to OPs and deficits in IQ (Bouchard et al., 2011; Engel et al., 2011; Rauh et al., 2011), and increases in autism spectrum (Shelton et al., 2014), attention deficit-hyperactivity (Marks et al., 2010; Rauh et al., 2006), and pervasive developmental disorder (Eskenazi et al., 2007; Rauh et al., 2006).

Despite a growing body of evidence regarding prenatal OP exposure and such neurodevelopmental endpoints, less is known about effects on early-life motor function. Motor skill acquisition in infancy provides a foundation for downstream cognitive and socio-emotional development in childhood (Clearfield, 2004, 2011). Motor functions improve rapidly in infancy with increasing central nervous system maturation and serve as an early benchmark of healthy neurological development (Noritz and Murphy, 2013). Delays in meeting early motor milestones may be indicative of a developmental disorder (De Felice et al., 2015; Noritz and Murphy, 2013).

Epidemiological studies provide preliminary evidence that prenatal OP exposure may negatively affect infant or child motor function. Maternal urinary OP metabolites during pregnancy (total dialkyl phosphates [DAPs] (Young et al., 2005; Zhang et al., 2014), dimethylphosphates [DMPs] (Young et al., 2005), diethylphosphates [DEPs] (Engel et al., 2007; Young et al., 2005), and malathion dicarboxylic acid [MDA] (Engel et al., 2007)) have been associated with deficits in infant/newborn reflexes. Chlorpyrifos, measured directly in umbilical cord plasma, has been found to be inversely associated with psychomotor development in 3-year-olds (Rauh et al., 2006). Two studies of maternal occupational exposure to unspecified OPs during pregnancy found deficits in fine, but not gross, motor skills in infants (Handal et al., 2008) and reduced motor speed and coordination in 6- to 8-year-olds (Harari et al., 2010).

With the exception of the Rauh et al. (2006) study, which only looked at chlorpyrifos, the existing body of work is largely limited by the use of imprecise exposure assessments, such as maternal non-specific urinary metabolites or self-reported occupational exposure during pregnancy. These limited exposure assessments make it difficult to accurately define exposure and attribute observed effects to specific OPs, thus restricting the utility of the findings for regulatory considerations. Additionally, with the exception of a few well-studied OPs, such as chlorpyrifos, many of the OPs in use today have not been studied for neurodevelopmental effects in non-occupationally exposed populations. Therefore, the current study sought to investigate associations between prenatal exposure to multiple OP insecticides, measured directly in umbilical cord blood, and many of which have been understudied in humans, and gross and fine motor function in infancy.

2. Methods

2.1. Population

Pregnant women with healthy, uncomplicated, singleton pregnancies (n = 359) were recruited at 37–42 weeks gestation from Fuyang Maternal and Children's hospital between 2008 and 2011 and enrolled into a longitudinal study of iron deficiency and infant neurodevelopment. Of the 359 participants, 237 had a sufficient volume of cord blood for pesticide analysis. Written informed consent was obtained, and the institutional review boards of the University of Michigan and Zhejiang University Children's Hospital approved this study.

2.2. Cord blood pesticides

The protocol for the determination of pesticides in cord blood has been described elsewhere (Silver et al., 2016). Briefly, cord blood plasma samples were at analyzed the Institute of Toxicology at Nanjing Medical University using gas chromatography tandem mass spectrometry (GC–MS/MS). Methods were modified from previously published protocols (Perez et al., 2010; ThermoScientific, 2010). We analyzed for 24 organophosphate (OP) insecticides and 6 OP metabolites. Limits of detection (LODs) were determined by analyzing fortified serum on a signal-to-noise (S/N) ratio of three. Quality control samples were generated using serum samples with 0.675 and 1.35 ng/mL pesticide standards. Quality control samples and blanks were analyzed in parallel with study samples in each batch.

Individual OPs were treated as continuous when detection rates were ≥ 80% (values below the limit of detection [< LOD] were replaced with LOD/√2), three-level ordinal (< LOD/medium/high [median split for those above LOD]) when detection rates were 40–79%, and dichotomous (< LOD/detect) when detection rates were 10–39%. Naled (99.6% detected) was log-transformed prior to statistical analysis to account for a right-skewed distribution. Methamidophos and trichlorfon (64.6% and 51.0% detected) were converted to 3-level ordinal variables, while chlorpyrifos and phorate (36.7% and 16.9% detected) were treated as dichotomous. A “number of OP detects” variable was created by assigning OP measurements < LOD a value of 0, while detects were assigned a value of 1; these were summed to create an index of OP exposure for each infant (Wickerham et al., 2012).

2.3. Peabody Developmental Motor Scales 2nd edition (PDMS-2)

The Peabody Developmental Motor Scales (PDMS-2) (Folio and Fewell, 1983, 2000) is a standardized test that assesses gross and fine motor abilities in children from birth through 5 years. PDMS-2 was administered here around 6 weeks and 9 months of age. The PDMS-2 has been proven to have excellent internal consistency (r = 0.89–0.97), test-retest reliability (r = 0.89–0.96), and inter-rater reliability (r = 0.96–0.99) (Folio and Fewell, 2000). For this study, PDMS-2 testing was performed by four examiners, with one serving as reference. After training, agreement between the reference and the other three examiners was 95% or higher. Inter- and intra-tester reliability measures were also monitored over the course of the study.

The gross motor function assessment is comprised of 4 multi-item subtests (reflexes, stationary, and locomotion) that measure interrelated motor abilities of large muscle systems (Folio and Fewell, 1983, 2000). Gross motor subtest scores were summed to create a composite gross motor raw score (GM). The fine motor function assessment is comprised of two multi-item subtests (grasping and visual-motor integration [V-M]) that measure the development of fine muscle systems. Fine motor subtest scores were summed to create a composite fine motor raw score (FM). GM and FM were summed to create a composite total motor raw score (TM) to measure overall motor abilities. Additionally, raw subtest scores were converted to standard scores using PDMS-2 guidelines. Standard scores were then summed and converted to gross (GMQ), fine (FMQ), and total motor quotients (TMQ) according to PDMS-2 guidelines (Folio and Fewell, 1983). PDMS-2 data was available for 199 infants.

2.4. Statistical analysis

Statistical analyses were conducted using SAS 9.3 (Cary, North Carolina). Percentile tables were created to determine the individual OP distributions within the sample. Descriptive statistics and frequencies were examined for all covariates of interest, including sex, age at PDMS-2 testing, cord ferritin, gestational age, birth weight, maternal education and occupation, family income, and season of PDMS-2 testing.

Linear mixed models (LMM) were used to evaluate associations between cord OP exposures and PDMS raw scores (subtest [reflexes, stationary, locomotion, grasping, V-M] and composite [GM, FM, TM]),