Environment International xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Environment International

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

Full length article

Maternal stress modifies the effect of exposure to lead during pregnancy and 24-month old children's neurodevelopment

Marcela Tamayo y Ortiz [a], Martha María Téllez-Rojo [b,*], Belem Trejo-Valdivia [b], Lourdes Schnaas [c], Erika Osorio-Valencia [c], Brent Coull [d], David Bellinger [e], Rosalind J. Wright [f], Robert O. Wright [g]

[a] National Council of Science and Technology, Avenida Insurgentes Sur 1582, Benito Juárez, Crédito Constructor, 03940 Ciudad de México, D.F., México
[b] National Institute of Public Health, Universidad No. 655 Colonia Santa María, Ahuacatitlán, Cerrada Los Pinos y Caminera, C.P. 62100, Cuernavaca, Morelos, México
[c] National Institute of Perinatology, Calle Montes Urales #800, Miguel Hidalgo, Lomas Virreyes, 11000 Ciudad de México, D.F., México
[d] Department of Biostatistics, Harvard T.H. Chan School of Public Health, 677 Huntington Ave, Boston, MA 02115, United States
[e] Department Environmental Health, Harvard T.H. Chan School of Public Health, 677 Huntington Ave, Boston, MA 02115, United States
[f] Department of Pediatrics, Icahn School of Medicine at Mount Sinai, 1428 Madison Ave, New York, NY 10029, United States
[g] Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, 1428 Madison Ave, New York, NY 10029, United States

ARTICLE INFO

Article history:
Received 28 July 2016
Received in revised form 12 October 2016
Accepted 3 November 2016
Available online xxxx

Keywords:
Prenatal
Neurodevelopment
Lead
Stress
Effect modification

ABSTRACT

Background: Lead and psychosocial stress disrupt similar but not completely overlapping mechanisms. Exposure during the prenatal period to each of these insults singularly has been found to alter normal neurodevelopment; however, longitudinal associations with stress modifying the effect of lead have not been sufficiently analyzed in epidemiologic studies.
Objective: To evaluate prenatal stress as an effect modifier of gestational lead neurotoxicity.
Methods: We used a structural equations modeling approach with a trivariate response to evaluate cognitive, language and motor scores of the Bayley Scales of Infant Development-III in 24 month-old children ($n = 360$). Maternal blood lead levels were measured at the 2nd and 3rd trimester and psychosocial stress during pregnancy was assessed using a negative life events (NLE) scale derived from the CRYSIS questionnaire.
Results: 3rd trimester lead (mean 3.9 ± 3.0 SD μg/dL) and stress (median = 3 NLE) were negatively associated with Bayley III scores. Using the model's results we generated profiles for 0, 2, 4 and 6 NLE across lead levels (up to 10 μg/dL) and observed a dose–response for the developmental scores when lead levels were below 2 μg/dL. Each NLE curve had a different shape across increasing lead levels. Higher stress (NLE = 6) resulted in lower cognitive scores for both sexes, in lower language scores in girls but not boys. In the absence of stress we saw a negative association with lead for all scores, however for language and motor scores, higher stress seemed to mask this association.
Conclusions: Our work examined and confirmed prenatal stress exposure as a modifier of the well-known neurotoxic effects of prenatal lead. It adds to the existing evidence pointing at the importance of studying the co-exposure of chemical and non-chemical exposures, specifically of considering the emotional environment of children at early developmental stages of life.

1. Background

Prenatal exposures to lead and to psychosocial stress have been individually associated with infant neurodevelopment (Bellinger, 2013; Bock et al., 2015; Hu et al., 2006; Laplante et al., 2008; O'Donnell et al., 2009; Talge et al., 2007). Both of these exposures are likely to co-occur, higher lead exposures being more common in communities with lower socioeconomic status, which in turn can imply chronic stress exposure (Cory-Slechta et al., 2004). In Mexico, lead exposure remains common at a population level, particularly through the use of lead-glazed pottery (Caravanos et al., 2014; Diaz-Ruiz et al., 2016) and stress exposure has also been documented (Medina-Mora Icaza et al., 2004). Studies combining these exposures have been performed mainly in animals and research in humans remain scarce (Schneider and Cory-Slechta, 2016).

Lead can interfere with normal brain development by disrupting several critical processes such as neuron migration, synaptogenesis, myelination and selective synaptic pruning (Faustman et al., 2000). It can also affect the release of neurotransmitters and stimulation of neurotransmission (Bressler et al., 1999; Bressler and Goldstein, 1991).

* Corresponding author.
E-mail addresses: mtamayo@hsph.harvard.edu (M. Tamayo y Ortiz), mmtellez@insp.mx (M.M. Téllez-Rojo), bvaldivia@insp.mx (B. Trejo-Valdivia), lschnaas@hotmail.com (L. Schnaas), erikaosorio4@hotmail.com (E. Osorio-Valencia), bcoull@hsph.harvard.edu (B. Coull), david.bellinger@childrens.harvard.edu (D. Bellinger), rosalind.wright@mssm.edu (R.J. Wright), robert.wright@mssm.edu (R.O. Wright).

http://dx.doi.org/10.1016/j.envint.2016.11.005
0160-4120/

Even at low levels, lead can induce neuronal cell death (Dribben et al., 2011). All of these processes are inter-related and their regulation by environmental signaling mold the underlying architecture of the brain. The hippocampus and nucleus accumbens are particularly susceptible to the toxic effects of lead, consequently memory and behavior/executive functions are affected (Nihei et al., 2001; Verina et al., 2007). Studies have found a detrimental effect of prenatal lead exposure with neurodevelopment (Boucher et al., 2014; Hu et al., 2006; Lin et al., 2013) that can persist in adulthood (Mazumdar et al., 2012).

Maternal psychosocial stress during pregnancy has been associated with different types of adverse neurodevelopmental outcomes in the child, like reduced cognitive abilities and language development (Bock et al., 2015; Laplante et al., 2008; Tarabulsy et al., 2014). Animal studies using the same spatial memory tests showed similar results when rats were exposed to lead as when they were exposed to stress; lead has been found to disrupt cognition through its effects on the mesocorticolimbic dopamine pathway and stress hormones act on this same pathway via the hypothalamic–pituitary–adrenal (HPA) axis (Cory-Slechta et al., 2008). The HPA axis responds to stress by producing cortisol, which is necessary for normal brain development in infants (Ng, 2000). However, chronic stress can result in an altered production of cortisol (McEwen, 2004), which can cross the blood–brain-barrier and bind to the highly abundant glucocorticoid receptors in the hippocampus, known to be involved in learning, memory, and emotional processing (Preston and Eichenbaum, 2013). A study examining cortisol in amniotic fluid and prenatal maternal psychosocial stress found that higher cortisol levels predicted lower cognitive Bayley scale scores, this was independent of the stress measures and these were also negatively associated child's cognition (Bergman et al., 2010).

Epidemiological studies have looked at maternal self-esteem and its simultaneous exposure with lead in humans (Surkan et al., 2008; Xu et al., 2015), however to our knowledge none have studied prenatal exposure to lead and the potential modifying effect of stress on neurodevelopment, particularly in a prospective design.

In this study we examine if the exposure to stress in the prenatal period modifies the effect of lead on cognitive, language and motor development in 24 month-old infants.

2. Methods

2.1. Study population

Study participants are part of the ongoing PROGRESS (Programming Research in Obesity, GRowth, Environment and Social Stressors) birth cohort in Mexico City. Women attending a prenatal consult were approached in 4 clinics belonging to the Mexican Social Security System (IMSS) between July 2007 and February 2011; if in their first trimester, they were invited to participate in the study, and answered a screening questionnaire. Inclusion criteria considered: being <20 weeks pregnant, ≥18 years old (Mexican legal voting age), being heart or kidney disease free, having access to a telephone, planning to reside in Mexico City for the next 3 years, no use of steroids (including glucocorticoids) or *anti*-epilepsy drugs, and not consuming alcohol on a daily basis (Braun et al., 2014). PROGRESS study protocols were approved by the institutional review boards of the Icahn School of Medicine at Mount Sinai, Harvard T. H. Chan School of Public Health, the National Institute of Public Health Mexico, the Mexican Social Security System, and the National Institute of Perinatology, Mexico. At each visit the study protocol was explained to women, who provided informed consent before any procedure was carried out.

Of the 760 mother–infant pairs ensued, 541 children had a Bayley III assessment at 24 months of age. For this analysis, we excluded 2 children who were very premature (≤32 weeks of gestation) and 2 that where both premature and had extremely low birth weight (≤1500 g).

2.2. Lead measurements

Prenatal lead exposure was assessed using maternal venous blood samples drawn during the second (2 T BPb, between the 16th and 20th pregnancy week) and third (3 T BPb, between the 30th and 34th pregnancy week) trimesters. We used royal blue trace metal Vacutainer (Becton-Dickinson and Company, Franklin Lakes, New Jersey) tubes containing EDTA to collect the samples that were kept at 4 °C until they were shipped to the Trace Metals Laboratory at the Harvard T. H Chan School of Public Health (HSPH), where they were stored at −20 °C until analyzed. Lead concentrations were measured using a dynamic reaction cell inductively-coupled plasma mass spectrometer (Elan 6100; PerkinElmer, Norwalk, CT). Five replicate measurements of each sample were taken and averaged. The recovery of the analysis quality control standards and spike samples was 90%–110%, and the limit of detection for the procedure was 0.02 μg/dL.

2.3. Psychosocial stress assessment

We measured maternal stress in the third trimester using the Crisis in Family Systems—Revised (CRISYS-R). The Spanish version of the survey had a test-retest reliability of 0.86 over 2 weeks among Spanish speaking subjects (Berry et al., 2006). Berry and collaborators also verified the construct validity of the survey finding strong associations between reported life stressors and covariates in their study population (greater depressive symptomatology, poorer physical and mental health function and lower household income). This questionnaire has been previously used in studies examining stress (Peters et al., 2012; Suglia et al., 2010; Tse et al., 2012). The 64-item questionnaire assesses the occurrence of a series of life events during the previous 6 months. Women answer if an event occurred during the past semester and if so, whether the experience was positive, negative, or neutral. Life events experienced are assessed across 11 domains: financial, legal, career, relationships, community and home violence, medical problems, other home issues, discrimination/prejudice, and difficulty with authority. We generated an additive score that ranged from 0 to 11 which summarized the number of domains with at least one negative life events (NLE). Higher scores indicate greater psychosocial stress: a larger number of domains with negative life events reported indicates a greater diversity of stress experienced by a woman, which is more likely to overwhelm her coping resources (Schreier et al., 2015).

2.4. Infant cognitive, language and motor development

Cognitive and language development scales were assessed when children were 24 months old using the Bayley Scales of Infant Development III (BSID-III). The scales are based on US norms (with a range from 40 to 160 points) and could be different for our study population (Cromwell et al., 2014), therefore we used the raw scores obtained by children and standardized them to the expected mean of 100 and SD of 15. Study personnel blinded to the infant's lead or maternal stress level administered the tests using a standard protocol.

Information on covariates included: infant sex, birth weight, gestational age (based on last menstrual period and by a standardized physical examination (Capurro test) to determine gestational age at birth) and maternal age, which were collected at time of delivery, maternal IQ (using the Wechsler Adult Intelligence Scale, Spanish version) and Home Observation for Measurement of the Environment (HOME) score (assessed at 24 months postpartum). All psychometric tests, including the Bayley and Crysis were applied by psychologists with training specifically for these questionnaires.

2.5. Statistical analyses

We began by performing an exploratory data analysis of exposure and outcome variables as well as covariates. BPb levels showed a right