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Prenatal Dichlorodiphenyldichloroethylene (DDE) exposure and neurodevelopment: A follow-up from 12 to 30 months of age

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Abstract

In order to evaluate the persistency of the association between DDE and infant neurodevelopment we assessed mental and psychomotor development between 12 and 30 months of age in an ongoing cohort in Mexico.

A total of 270 singleton children without perinatal asphyxia diagnosis, with a birth weight ≥ 2 kg, mothers > 15 years of age with organochlorine maternal serum levels measured at least in one trimester of pregnancy, and who were evaluated at least in two of the four visits at 12, 18, 24 and 30 months of age, were included in this report. The Spanish version of Bayley Scales of Infant Development II (BSID-II) was administered to the children and Psychomotor Development Index (PDI) and Mental Development Index (MDI) were calculated. Information about stimulation at home was measured using the Home Observation of Measurement of the Environment (HOME) at six months, and breastfeeding history was obtained through direct interviews with the mothers.

Maternal serum DDE levels were determined during pregnancy by means of electron capture gas-liquid chromatography. The association between DDE prenatal exposure and neurodevelopment was estimated using separate generalized mixed effects models.

Our results suggest that the association between prenatal DDE and infant neurodevelopment does not persist beyond 12 months of age even after adjusting for known risk factors for neurodevelopment. In addition, we observed an interaction between early home stimulation and mental improvement at 24 and 30 months of age($p<0.001$).

The association of DDE with infant neurodevelopment seems to be reversible. However, we cannot rule out that other DDT metabolites may play a role in neurodevelopment.

Introduction

Dichlorodiphenyltrichloroethane (DDT) is an insecticide used worldwide to combat malaria which was banned in Mexico since 1999. However, it’s primary metabolite,

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Dichlorodiphenyldichloroethylene (DDE), is highly persistent in the environment (Jaga, 2003), and due to its capacity to cross the placental barrier easily (Dorea et al.,2001), many children in the world are exposed to this compound during prenatal and postnatal periods even in countries where this compound is not currently used.

Experimental studies showed that DDE causes neurotoxicity and behavioral alterations. In infants, the relationship between fetal DDE exposure and neurodevelopment has been evaluated in four cohort studies. Three of these studies detected a consistent negative association between prenatal DDE and psychomotor neurodevelopment (as measured by the Psychomotor Development Index (PDI) from the Bayley Scales): In Mexican farmers in California, children six months of age had a significant reduction of ~ 0.4 points on PDI for each doubling dose of prenatal DDE concentration (Eskenazi et al., 2006); which is consistent with the negative association between maternal DDE levels during pregnancy and PDI in Mexican infants living in a malaria-endemic area during the first year of life (0.52 points for each doubling dose of DDE) (Torres-Sanchez et al., 2007). A higher reduction on PDI and Mental Development (as measured by the Mental Development Index (MDI) from the Bayley Scales) due to a doubling dose of DDE (~4 points) was also reported in a cohort exposed to multiple compounds in Spain (Ribas-Fito et al., 2003).

Information about the persistence of this effect beyond 1 year of age is scarce. Rogan and Glade (1991), reported a positive but not significant association between DDE exposure and PDI at 18 and 24 months of age; this is in line with the absence of an association reported at 24 months of age in the cohort study of Mexican farmers (Eskenazi et al., 2006).

The aim of this report was to evaluate the persistence until 30 months of age the association between prenatal DDE exposure and neurodevelopment previously reported in an ongoing cohort of children less than 12 months of age whose mothers were not occupationally exposed to DDT and showed DDE levels during pregnancy similar to those observed among Mexican farmers in the USA (Eskenazi et al., 2006).

Material and Methods

From 2001 to date, we have carried out a cohort study in four municipalities in the state of Morelos, Mexico. A detailed description of this study population is reported elsewhere (Torres-Sánchez, et al. 2007). Briefly, women of reproductive age without antecedents of chronic illness were identified during prenuptial talks. Those who agreed to participate in the study were followed up before, during and after their pregnancy. During each quarterly prenatal visit we administered a questionnaire that collected data about the progress of the pregnancy, anthropometric measurements (maternal weight and height), and dietary information. A blood sample was also collected in order to assess organochlorine levels. A total of 333 women were part of the original cohort.

Postnatal follow-up began at one month of age and postnatal evaluations were scheduled at 1, 3, 6 months and every six months thereafter. The information gathered during postnatal visits varied according to the age of the child. During the visit at 1 month of age, information relating to aspects of birth and initiation of breast-feeding was collected. During subsequent visits the information focused on the child's state of health and feeding practices. At the time of the interview, the mother was asked specifically whether the child was being breastfed and, if not, the reasons for suspending breastfeeding and what kind of foods were being introduced into the diet. After 12 months of age we asked about the number of persons living with the child, and whether or not the child attended day care. Additionally, during all visits anthropometric measurements (weight, length, and cephalic circumference) were taken and neurodevelopment was evaluated for each child.

Neurodevelopment evaluation

In order to evaluate the mental and psychomotor development of children from 12 to 30 months of age, we applied the Spanish version of the Bayley Scales of Infant Development II (BSID-II) used during the first year of life. The test was administered in a quiet place in the home with only the mother or caregiver present. Two trained psychologists who administered the test battery were blinded to the prenatal DDE exposure levels. The interobserver agreement rates were 0.96 for MDI and 0.98 for PDI. Both the PDI and the MDI are standardized to have a mean of 100 and a SD of 15.

Maternal intelligence quotient (IQ) was measured using a Spanish version of the Wechsler Adult Intelligence Scale (Wechsler 1981). The quality of the home environment was assessed at 6 months of age through the Home Observation for Measurement of the Environment (HOME;Caldwell and Bradley 1984). In the analyses we used the total score of this test.

Chemical Analysis

During each trimester of pregnancy we obtained a blood sample from each participant. By means of electron capture gas-liquid chromatography, maternal serum levels of DDE and p,p′-DDT were determined. Concentrations of DDE and p,p′-DDT were reported in wet basis as nanograms per milliliter (parts per billion). Information about the procedure and quality control was reported previously (Torres-Sánchez et al.,2007). The detection limit was 0.05 ng/ml and 0.0045 ng/ml for DDE and p,p′-DDT, respectively.

This report presents information from 270 singleton children without perinatal asphyxia diagnosis, with birth weight ≥ 2 kg, whose mothers were > 15 years of age and had serum organochlorine levels at least in one trimester of pregnancy, and who were evaluated at least in two of the four visits at 12,18, 24 and 30 months of age. This study was approved by the Ethics Committee of the National Institute of Public Health.

Statistical analysis

Skewed distribution of DDE levels was log-transformed. To interpret the change of PDI or MDI for each two-fold increase of DDE, natural log coefficients were multiplied by 0.69.

The association between prenatal DDE exposure and PDI and MDI of the child between 12 and 30 months of age was estimated using separate generalized mixed effects models for each trimester of pregnancy. Known risk factors for infant neurodevelopment potentially related to DDE were assessed as potential confounders and further maintained in the final models in those cases where they changed the estimator of interest in more than 10%. In general, the equation of the models was the following:

$$Yij = Xij\,\beta + Zij\,yi + \varepsilon ij$$

Ij: represents the observation *j* in the subject *i; Yij* corresponds to the dependent variables mental or psychomotor development of each subject during the 12, 18, 24 and 30 months of age and *Xi* are the independent variables with fixed effects: logtransformed DDE levels at each trimester of pregnancy, maternal age (years) and education (years), maternal IQ, type of birth (vaginal/cesarean), sex of child (female/male), birth weight (grams), history of breastfeeding (none, ≤3 months and, > 3 months), and HOME score (HOME Scale) at 6 months of age.

Further, *Zij*γ are the variables with random effects (cephalic circumference (cm), height (cm) and weight (kg)). The model assumes that the random effects have a normal distribution, with the average equaling 0 and with constant variation. To determine whether the addition of a

random intercept significantly improved the adjustment of the model, we used the test for maximum likelihood with an $\alpha < 0.05$. A possible modification effect due to the sex of the child and/or the HOME Scale on the DDE-neurodevelopment relationship was assessed by incorporating the corresponding interaction terms in the model. Likewise the influence of breastfeeding and HOME scale on neurodevelopment at 12, 18 and 30 months was assessed. A probability value ≤ 0.05 for the interaction was considered statistically significant.

Diagnosis of the model

Using histograms and normal quantile graphs, we evaluated residual normality. We also evaluated residual homoskedasticity through graphs of model prediction versus standardized residuals. All analyses were made using STATA 9.2.

Results

Selected characteristics of children included and not included in the current analysis were very similar (Table 1). However, a significant higher percentage of cesarean sections and children from nuclear family were observed among those who were not included. The average score for the quality of the home environment of the study population on the HOME scale was 30 points. Only 20.4 percent of children had less than 26 points, which can be considered low. Bayley PDI and MDI scores did not show significant variation during the period from 12 to 30 months (data not shown). The average scores for both indexes were 92.7 ± 8.2 and 89.8 ± 8.8 for PDI and MDI, respectively. Mean serum DDE levels during pregnancy ranged from 6.3 to 7.9 ng/ml at the first and third trimester, respectively (Table 2). All samples had detectable DDE levels and, only 21.2% of them had DDT levels above the detection limit. The DDE/DDT ratios during pregnancy were low.

The negative association between prenatal DDE exposure and PDI observed during the first year of life (previously reported; Torres-Sanchez et al., 2007) was no longer present beyond 12 months of age. Likewise, no association was detected with MDI (Table 3). Sex of child and HOME Scale did not modify the DDE- neurodevelopment relationship (data not included).

Breastfeeding had no influence on neurodevelopment as the children's age increased. Conversely, the HOME score measured at six months of age, showed a greater significant influence at 24 and 30 months of age in our population (Table 4).

Discussion

From an ongoing cohort study, we have previously reported a significant reduction of −0.52 points on PDI for each doubling dose of DDE in the first trimester of pregnancy in children living in a malaria-endemic zone in Mexico –where DDT was banned about 12 years ago – whose mothers were not occupationally exposed to DDT.

The results of this report, in which children were assessed up to the age of 30 months, show no persistency of the DDE-neurodevelopment association after 12 months in this population. This is consistent with the absence of the same association beyond 12 months of age reported by Eskenazi et al., 2006, in a Mexican farmer cohort study in California with similar DDE levels (geometric mean 1166.37 vs. 1436.9 ng/g) but with levels four times lower than those found in other Mexican groups (Koepke et al., 2004). Our negative findings between 12 and 30 months of age do not imply that harmful effects may not emerge at older ages. DDE might be negatively associated with other brain functions as has been suggested by Ribas-Fitó et al. 2006, who found a significant reduction (−1.93) in memory functions at 4 years of age due to doubling of prenatal DDE levels.

Other DDT metabolites, i.e. p,p′-DDT and o,p′-DDT, could also be related to neurodevelopmental damage. In two recent studies a deleterious and stronger long term effect of prenatal p,p′-DDT and o,p′-DDT exposure in children evaluated at 12 and 24 months of age (Eskenazi et al. 2006) and at 4 years old (Ribas-Fitó et al., 2006) was reported. The former found a significant reduction (~-2 points) for each 1-log10 increase of prenatal p,p′-DDT and a marginal negative effect (~-3 points) for each 1-log10 increase of prenatal o,p′-DDT on MDI; the latter reported a mean reduction of 7.86 and 10.86 points in verbal and motor performance respectively (evaluated by McCarthy test) among children exposed to more than 0.20 ng/ml compared to those exposed to 0.05 ng/ml of p,p′-DDT in cord serum. In our study population, the levels of p,p′-DDT and o,p′-DDT were very low, as were the corresponding ratios with DDE, which is consistent with the absence of current use of DDT in the study area. Thus, we were not able to evaluate their potential association with neurodevelopment.

Some methodological considerations must be taken into account when interpreting our results. A significantly high proportion of children born by cesarean section and belonging to a nuclear family, were lost during the follow-up. However, we consider that possibility of selection bias is low, because none of those characteristics were related to maternal DDE levels. Likewise, we reject a possible differential measurement error, because the psychologists who administered the BSID-II were blinded to the levels of prenatal DDE exposure.

In order to evaluate the hypothesis of a different window of exposure for brain functions developed after the first year of life, we evaluated separately the effect of DDE levels at each trimester of pregnancy, and the results did not change. Also we evaluated the DDE values on a lipid basis, and our results remained the same. Finally, we rule out potential confounders as an alternative explanation for our results, because the analysis included those variables which were significantly associated to maternal DDE levels and which represented an independent risk factor for neurodevelopment.

Because of the finding we believe that it is necessary to address the role of the quality of the early home environment on MDI at later ages (24 and 30 months of age) as a potential tool for balancing deleterious damage in children.

In short, our results indicate that DDE is not persistently related to neurodevelopment. However, the possibility that DDT is causing impairment cannot be ruled out; thus, its reintroduction should not be considered appealing to the precautionary principle.

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Table 1

Selected characteristics of the study population.

Characteristics	Included (n=270)	Non-Included (n=63)	p value*
Maternal			
Age (y)			
Mean ± SD	22.1 ± 4.1	22.6 ± 5.2	0.38
Education (y)			
Mean ± SD	10.8 ± 3.2	11.3 ± 3.6	0.28
Intellectual coefficient			
Mean ± SD	87.6 ± 12.0	90.4 ± 14.0	0.11
Paid Occupation (%)	47.4	50.8	0.63
Parity >1 (%)	20.0	14.3	0.30
Cesarean birth (%)	56.7	76.2	0.004
Infant			
Birth weight (kg)			
Mean ± SD	3.2 ± 0.4	3.2 ± 0.5	0.72
Sex male (%)	58.9	50.8	0.24
Breastfeeding (%)			
Never	7.0	7.9	
≤ 12 weeks	20.4	22.2	0.91
> 12 weeks	72.6	69.8	
HOME Scale			
Mean ± SD	30.4 ± 4.6	29.8 ± 4.8	0.46
% <26 points.	20.4	30.0	0.17
Nuclear Family (%)	43.3	59.7	0.02
Bayley test**			
Psychomotor Development Index (PDI)		--	--
Mean ± SD	92.7 ± 8.2	--	--
Mental Development Index (MDI)		--	--
Mean ± SD	89.8 ± 8.8	--	--

* χ^2 or *t*-test for categorical or continuous variables, respectively.

** From 12 to 30 months of age. Both indexes mental and psychomotor are standardized to have a mean=100 and SD=15.

Table 2

p,p′-DDE and p,p′-DDT maternal serum levels at each trimester of pregnancy.

Compounds*	Mean ± SD**	% above LOD
p,p′-DDE maternal serum levels (ng/ml)		
1st trimester (n=244)	6.3 ± 3.1	
2nd trimester (n=153)	6.5 ± 3.0	100%
3rd trimester (n=160)	7.9 ± 2.8	
p,p′-DDT maternal serum levels (ng/ml)		
1st trimester (n=244)	0.008 ± 2.7	
2nd trimester (n=153)	0.006 ± 2.0	21.2%
3rd trimester (n=160)	0.006 ± 2.3	
DDT/DDE ratios		
1st trimester (n=244)	0.003 ± 0.007	
2nd trimester (n=153)	0.002 ± 0.007	
3rd trimester (n= 160)	0.002 ± 0.003	

* From 270 women: 91 had DDE results only in one trimester, 71 in two trimester and 108 in three trimester.

** Geometric mean and SD.

Table 3

Crude and adjusted coefficients for prenatal DDE exposure and neurodevelopment.

DDE Prenatal exposure (ng/ml)	Psychomotor Index (PDI)**					
	Crude Analysis			Adjusted Analysis		
	β*	95% CI	p value	β*	95% CI	p value
1st trimester	−0.08	−0.51; 0.35	0.70	0.08	−0.34; 0.50	0.72
2nd trimester	0.37	−0.14; 0.90	0.15	0.39	−0.09; 0.88	0.11
3rd trimester	0.19	−0.36; 0.74	0.50	0.37	−0.15; 0.89	0.16
	Mental Index (MDI)***					
1st trimester	−0.11	−0.60; 0.38	0.67	0.05	−0.40; 0.51	0.82
2nd trimester	−0.02	−0.57; 0.54	0.95	0.02	−0.50; 0.53	0.95
3rd trimester	0.41	−0.19; 1.00	0.18	0.56	−0.001; 1.12	0.06

* Change for each double increase of maternal DDE serum levels

** Adjusted by: Maternal age, Home scale, birth weight, breastfeeding, age at evaluation, cephalic circumference and sex of the child

*** Adjusted by: Sex, Home scale, birth weight, breastfeeding, Maternal IQ, age at evaluation, cephalic circumference and height at evaluation time.

Table 4

Interaction between breastfeeding and early HOME stimulation with later infant neurodevelopment

Interactions	Psychomotor Index			Mental Index		
	β*	95%CI	p value	β*	95%CI	p value
Breastfeeding and 18 months of age	1.45	−0.73; 3.63	0.192	0.43	−1.62; 2.49	0.68
Breastfeeding and 24 months of age	−0.05	−2.43; 2.33	0.969	0.04	−2.17; 2.26	0.97
Breastfeeding and 30 months of age	1.55	−1.06; 4.17	0.245	0.74	−1.64; 3.13	0.54
HOME SCALE** and 18 months of age	−0.02	−0.30; 0.26	0.904	0.14	−0.12; 0.40	0.299
HOME SCALE** and 24 months of age	−0.02	−0.32; 0.29	0.916	0.66	0.38; 0.94	0.000
HOME SCALE** and 30 months of age	−0.05	−0.39; 0.29	0.787	0.46	0.15; 0.76	0.003
					p for interaction< 0.001	

*These coeffcients were obtained from model with prenatal DDE exposure at first trimester of pregnancy. Models were adjusted by the same variables that the previous table.

**HOME Scale at six months of age.