DAT 9-repeat allele, prenatal lead, and child development.

Katarzyna Kordas[1], Adrienne Ettinger[1], Joel Schwartz[1], David Bellinger[2], Mara Tellez Rojo[3], Mauricio Hernandez Avila[3], Hector Lamadrid[3], Howard Hu[4], Lourdes Schnaas[5], and Robert Wright[1].

[1]Harvard School of Public Health, Boston, MA, USA; [2]Children's Hospital, Boston, MA, USA; [3]National Institute of Public Health, Cuernavaca, Mexico; [4]University of Michigan School of Public Health, Ann Arbor, MI, USA; [5]National Institute of Perinatology, Mexico City, Mexico.

Abstract

Dopamine transporter gene (*DAT*) contains variable number of tandem repeats (VNTRs). The 9-repeat allele is associated with improved attention and executive function. We investigated the effects of prenatal lead exposure and *DAT* polymorphisms on cognitive development in Mexican children. Maternal blood lead (BPb) at delivery was measured. Bayley Scales of Infant Development (BSID) were administered every 6 mo up to 36 mo. McCarthy Scales of Children's Abilities were administered at 42 and 48 mo. For present analysis, 294 and 233 children had complete data at 24 and 48 mo. BSID index (24 mo) and McCarthy scales (48 mo) were modeled as function of BPb and *DAT* VNTR (including interactions). Children with at least one long-repeat (7 or 9) allele (20%) were compared to children with short-repeat allele (1 or 3). Mean PbB was 8.8±4.3 µg/dL. Mean 24-mo MDI and PDI was 92±14 and 93±12 points; 48-mo McCarthy General Scale was 93±13 points. In covariate-adjusted models, *DAT* did not predict BSID. BPb was associated with MDI (β=-0.2, p<.05). This relationship differed by VNTR, in that scores were worse with increasing lead in long vs. short allele strata: (β=-1.0, p<.05 vs. β=-0.2, ns). PbB was not associated with Bayley PDI or McCarthy Scales scores. Long-repeat allele was positively associated with McCarthy Quantitative Scale (2.8±1.1, p=.02). BPb-McCarthy Scale relationship did not differ by VNTR. Prenatal lead was negatively associated with early cognitive development, particularly in children with higher VNTRs in the *DAT* gene.

Introduction

- Postnatal lead exposure in children has been associated with deficits in measures of cognitive development; the effects of prenatal exposure are less well understood.
- Postnatal lead exposure is also linked with diminished performance on tests of executive function, implicating the frontal cortex, and possibly the dopaminergic system.
- At least two genes in the dopaminergic system (*DAT* & *DRD4*) have been studied in relation to cognition and behavior in children.
- The *DAT* gene codes for the dopamine transporter, which is the primary mechanism for clearing dopamine from the synapse.
- Polymorphisms in the *DAT* gene have been identified, including a 40 base pair variable number tandem repeat (VNTR) in the 3' untranslated region.
  - Number of repeats is variable, ranging from 0 to 11, and varies by geographic region.
  - Ten and nine-repeat alleles are most commonly reported in population studies.
- Presence of long-repeat alleles was shown to increase dopamine transporter availability.
- In some studies, long-repeat alleles (9x) were associated with improved attention and executive functions in school children, but also higher risk of ADHD and poor response to methylphenidate therapy (10x).
- There are no studies on interactions between *DAT* genotype and exposure to toxicants on cognitive development of young children.

Objective

- To investigate the role of DAT and lead exposure (prenatal and postnatal) on cognitive development of Mexican children.

Methods

Study Population

- Study conducted in Mexico City, between January 1994 and June 1999.
- Women approached for participation when presenting to the hospital for delivery; 3 hospitals used serving low-to-middle income populations.
- 2944 potential participants screened on the following exclusion criteria:
  - living outside the metropolitan area, no intention to breastfeed, premature delivery, multiple fetuses, pre-eclampsia, psychiatric, renal or cardiac disease, gestational diabetes, history of urinary tract infections, history (family or self) of kidney stones, seizure disorders, ingestion of coritcoids, high blood pressure (>140 systolic, >90 diastolic).
- 617 women enrolled into a study of supplementation with calcium and placebo
- Their infants followed to assess cognitive development

Measures

- Demographic information, reproductive history, collected prenatally with a questionnaire.
- Umbilical and maternal blood collection within 12 hrs of delivery.
- Child blood lead concentrations (BPb) measured every 12 mo between 12 and 48 mo.
- *DAT* genotyping on archived blood samples; Channing Laboratory (Boston, MA).
- Bayley Scales of Infant Development (BSID) administered every 6 mo (12 - 36 mo).
- McCarthy Scales of Children's Abilities administered at 42 and 48 mo.

Analytical Approach

- BSID index (24 mo) and McCarthy Scales scores (48 mo) were modeled as function of BPb and *DAT* genotype to test for main effects.
- The BPb—developmental score associations were modeled in *DAT* genotype strata.
- Mother's BPb at delivery was a proxy for prenatal exposure; child's BPb concurrent to cognitive testing was also modeled (24 and 48 mo).
- Children with short-repeat alleles (1 or 3x) were compared to children with any long-repeat alleles (7 or 9x) for the *DAT* gene.
- Models adjusted for maternal age and schooling, marital status, cognitive score on previous test, sex, and height, and assignment to calcium or placebo in supplementation.

Results

Table 1. Characteristics of children with and without cognitive assessments at 24 mo.

Characteristic	N	In the study	N	Not in the study
Maternal age at screening	335	24.8 ± 5.3*	282	24.1 ± 4.9
Mother's schooling (y)	335	9.4 ± 3.2*		9.0 ± 3.2
Marital status (select)	335		281	
Married		67.8%		63.0%
Single, Separated, Divorced		7.8%		7.5%
Years living in Mexico	335	21.4 ± 8.1***	281	19.4 ± 8.6
Ever smoke	335	45.1	281	43.4%
BPb at delivery, mom (µg/dL)	332	8.8 ± 4.3[δ]	278	8.3 ± 3.9
Birthweight (g)	333	3153 ± 422	282	3119 ± 417
Gestational age (wk)	333	39.2 ± 1.5	275	39.2 ± 1.5
BPb at delivery, child (µg/dL)	280	6.8 ± 3.5[δ]	232	6.5 ± 3.7

*p<.1, **p<.05, ***p<.01; [δ]Mother & infant BPb at delivery correlated at r=0.87

Table 2. Developmental test scores, BPb, *DAT* genotype in study children.

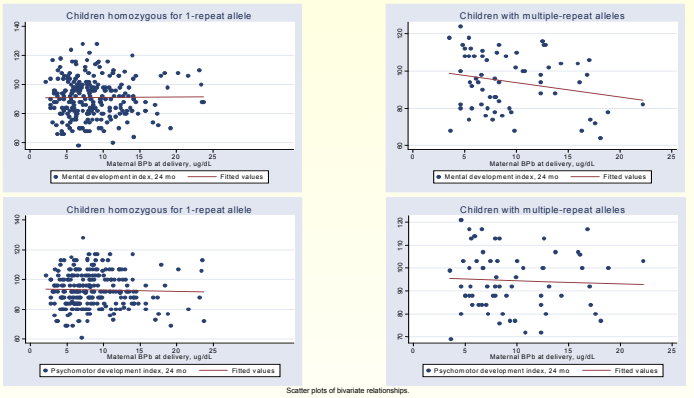
		N	Mean ± SD	Range
Bayley Scales of Infant Development, 24 mo	Mental Development Index	341	91.7 ± 14.0	58 – 128
	Psychomotor Development Index	342	93.1 ± 11.9	61 – 128
McCarthy Scales, 48 mo	General Cognitive Index, GCI	314	93.3 ± 13.2	51 – 128
	Verbal Scale	314	45.6 ± 7.4	28 – 68
	Perceptual Scale	314	50.5 ± 9.1	30 – 74
	Quantitative Scale	314	42.2 ± 9.0	22 – 69
	Memory Scale	314	46.9 ± 7.7	26 – 97
Blood lead concentration 24 mo (µg/dL)		307	8.2 ± 4.3	2.5 – 38.6
Blood lead concentration 48 mo (µg/dL)		263	8.1 ± 3.7	2.5 – 30.3
DAT genotype				
Short-repeat		347	80.7%	
Long-repeat		83	19.3%	

Table 3. Adjusted main effects of lead exposure and *DAT* genotype on cognition.

		Prenatal BPb	Concurrent BPb	*DAT* genotype
BSID, 24 mo	MDI	-0.2 ± 0.2**[1]	-0.2 ± 0.2	-0.7 ± 1.7
	PDI	-0.2 ± 0.2	-0.02 ± 0.2	0.5 ± 1.7
McCarthy Scales, 48 mo	GCI	-0.1 ± 0.1	-0.2 ± 0.2	0.5 ± 1.5
	Verbal Scale	-0.03 ± 0.1	-0.2 ± 0.1*	0.2 ± 1.0
	Perceptual Scale	-0.02 ± 0.1	-0.2 ± 0.1	-0.5 ± 1.1
	Quantitative Scale	-0.1 ± 0.1	-0.1 ± 0.1	2.8 ± 1.1**
	Memory Scale	-0.01 ± 0.1	-0.1 ± 0.1	0.05 ± 1.0

[1]Values given as β±SE; *p<.1, **p<.05, ***p<.01; models adjusted for performance at previous testing, maternal IQ, total years of schooling, marital status at enrollment, child sex, child's height at the time of testing, assignment to placebo or calcium.

Figure 1. Prenatal lead exposure and cognitive development at age 24 mo.



Scatter plots of bivariate relationships.

Table 4. Pre and post-natal lead exposure and child development, by *DAT* genotype.

Developmental Test		Short-repeat alleles	Long-repeat allele
Mental Development Index, 24 mo	Maternal BPb, delivery	-0.2 ± 0.2[1]	-1.0 ± 0.4**
	Child BPb, 24 mo	0.2 ± 0.2	-0.3 ± 0.5
Psychomotor Development Index, 24 mo	Maternal BPb, delivery	-0.3 ± 0.2	-0.05 ± 0.5
	Child BPb, 24 mo	-0.1 ± 0.2	-0.2 ± 0.6
McCarthy Scales GCI	Maternal BPb, delivery	-0.1 ± 0.2	-0.3 ± 0.4
	Child BPb, 48 mo	-0.1 ± 0.2	0.3 ± 0.4

[1]Values given as β±SE; *p<.1, **p<.05, ***p<.0; models adjusted for performance at previous testing, maternal IQ, years of school,,marital status at enrollment, child sex, child's height at the time of testing, assignment to placebo or calcium.

Discussion

- Prenatal BPb was associated with Bayley Scales of Infant Development at 24 months; *DAT* genotype and concurrent BPb were not.
- Children with higher prenatal Pb exposure and long-repeat *DAT* allele scored more poorly on the MDI than children with short-repeat genotype. There were no differences on PDI.
- Prenatal BPb was not associated with McCarthy Scales scores.
- 48-mo BPb was related to lower scores on the Verbal Scale, after adjustment for covariates.
- Long-repeat alleles in the *DAT* genotype were associated with improved Quantitative scale scores, after adjustment for covariates.
- There were no interactions between BPb and *DAT* on McCarthy Scale scores (sample size?).
- Children with *DAT* long-repeat genotype appear to have improved developmental scores.
- *DAT* long-repeat polymorphism also appears to make children more susceptible to the effects of prenatal lead exposure on cognitive development. Mechanisms of susceptibility are unclear.
- Long-repeat *DAT* polymorphism is linked to increased DAT availability and increased DA clearance from synapses; prenatal Pb exposure may impair the function of the DA system.

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