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Gender-Related Decrease in Raven's Progressive Matrices Scores in Children Prenatally Exposed to Polychlorinated Biphenyls and Related Contaminants

Y. L. Guo,[1] T.-J. Lai,[2] S.-J. Chen,[2] C.-C. Hsu[2]

[1]Department of Environmental and Occupational Health and [2]Department of Psychiatry, National Cheng Kung University Medical College, 138 Sheng Li Road, Tainan, Taiwan 70428, Republic of China

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Polychlorinated biphenyls (PCBs) are industrial mixtures that have been widely used throughout the world. Major production ceased in the mid-1970s because the chemicals had become a severe environmental problem. PCBs have long environmental half lives and bioconcentrate, therefore contaminating soil, water, wild life, and human tissues. Typical human exposures come from environmental contamination of food supply, especially fresh water fish and meat, and occupational exposures. In certain uses, PCBs can partially oxidize and themselves become contaminated by extremely toxic compounds such as polychlorinated dibenzofurans (PCDFs). Two episodes of intoxication with heat-degraded PCBs have occurred, in Japan and Taiwan respectively. In 1979, over 2000 persons in Taiwan were intoxicated by heat-degraded PCBs that had contaminated their cooking oil (Hsu et al., 1985). Although the exact cause of this episode was not clear, later speculation from epidemiologic investigation was that in one factory, the rice oil was indirectly heated to remove odor and color at the final step of production. Kaneclor 500 (a Japanese PCB mixture) contained in the heating pipe was used as the heat transmitter. Leakage of the pipe introduced PCBs and heat-degraded products such as polychlorinated dibenzofurans (PCDFs) and polychlorinated quarterphenyls (PCQs) into the rice oil. Exposed victims developed chloracne, hyperpigmentation, peripheral neuropathy, and other signs and symptoms which were later called Yu-Cheng ("oil disease") in Taiwan. These symptoms were caused not only by PCBs but by their heat degraded products, PCDFs (Kashimoto et al., 1985).

PCBs, PCDFs, and PCDDs do cross the placenta to affect fetus (Kodama and Ota, 1980). Significant developmental toxicity in animals has been reported for *in utero* PCBs, PCDFs, and PCDDs exposure (Tilson et al., 1990). Neurodevelopmental deficits were demonstrated in children born to Michigan women who reported moderate consumption of Lake Michigan sport fish during pregnancy (Fein et al., 1984), and in 5-10% of North Carolina children exposed to the highest background levels of PCBs (Gladen et al., 1991). The Asian exposures resulted in much more dramatic neurodevelopmental effects. The Yusho episode in Japan caused increased mental retardation in prenatally exposed children (Harada 1976; Kuratsune, 1980). Death, ectodermal defects and developmental delay (Hsu et al., 1985; Rogan et al., 1988) were shown in the children born to affected mothers in Taiwan. Decreased scores in Chinese versions of the Stanford-Binet (SB) Scales and the Wechsler Intelligence Scale for Children, Revised (WISC-R) from age of four to seven years were previously reported (Chen et al., 1992). In addition to the SB scales and WISC-R, the children were also tested with Raven's Colored Progressive Matrices (CPM) and Standardized Progressive Matrices (SPM), the relatively culture-fair tests for cognitive development (Raven 1960).

Correspondence to: Y. L. Guo

Changed androgenic status such as plasma androgen levels and androgen-dependent structures and functions has been reported in male rats prenatally exposed to TCDD (Mably et al., 1992). Cognitive development is sex hormone-dependent, that males develop better spatial abilities and females better verbal abilities. Since CPM and SPM test spatial rather than verbal capabilities, these tests are useful for determining whether prenatal exposure to PCBs/PCDFs caused differential effects on boys and girls. We now report results of CPM and SPM from age six to nine years in Yu-Cheng children and their matched controls.

MATERIALS AND METHODS

In early 1985, 6 years after the Yu-Cheng poisoning episode, all living children born to Yu-Cheng women were identified (Rogan et al., 1988). There were 128 such Yu-Cheng children born to 74 mothers. After parents' informed consent, 118 Yu-Cheng children born to 69 mothers entered for long term follow-up. One hundred and eighteen control children were selected by matching for neighborhood, age (within 15 days for those under one year, and within one month for those older), sex, mother's age (within 3 years), parents' combined educational level (within about 3 years for the total), and occupation (within 1 class of 5 classes from unskilled laborer to professional). To evaluate the innate deductive abilities for subject children, CPM were applied at 6, 7, and 8 years, and SPM were used at 9 years of age. CPM and SPM were adapted to Chinese and the reliability, standardized procedure of test administration, and background data in school-age children in Taiwan were reported (Hsu, 1971, Hsu et al., 1974). A more recent update of the background data in 1986-7 was available for different areas of Taiwan (Feng, 1988). The Yu-Cheng children and their controls were tested annually in late August from 1985 to 1992. The children were tested in their homes, and each Yu-Cheng child and his or her control were tested on the same day by the same tester. The testers were not aware of the child's exposure status although some of the children might still have physical stigmata, i.e., acne scars or nail deformities which might be visible to the testers.

During the 8 year follow-up, parents removed 3 of the Yu-Cheng children, and their controls were not tested further. There was no loss of subjects due to death or illness. We present here the results at ages six through nine. All children were in these data at least once; 91 pairs at age six, 92 pairs at age seven, 82 pairs at age eight, and 67 pairs at age nine. Differences between scores of Yu-Cheng children and controls were calculated using Wilcoxon one-sample test. To examine whether later born Yu-Cheng children were less affected by prenatal exposure, the differences in scores between exposed and control children were compared with the year of birth using regression analysis.

RESULTS AND DISCUSSION

Yu-Cheng children scored lower than their controls in CPM at ages six, seven, and eight; and borderlinely lower in SPM at age of nine (Figure). When the difference of CPM/SPM scores between exposed and controls children were compared with year of birth using regression analysis, no clear pattern of moderation of the effect could be seen in those children born longer after the exposure (Table 1). When grouped by sex, the Yu-Cheng boys had significantly lower CPM/SPM scores compared to their controls, but the Yu-Cheng girls' scores were not statistically different from their controls (Table 2).

Using two widely accepted tools, CPM and SPM, we were able to detect cognitive deficits up to 9 years of age in children with prenatal exposure to PCBs and

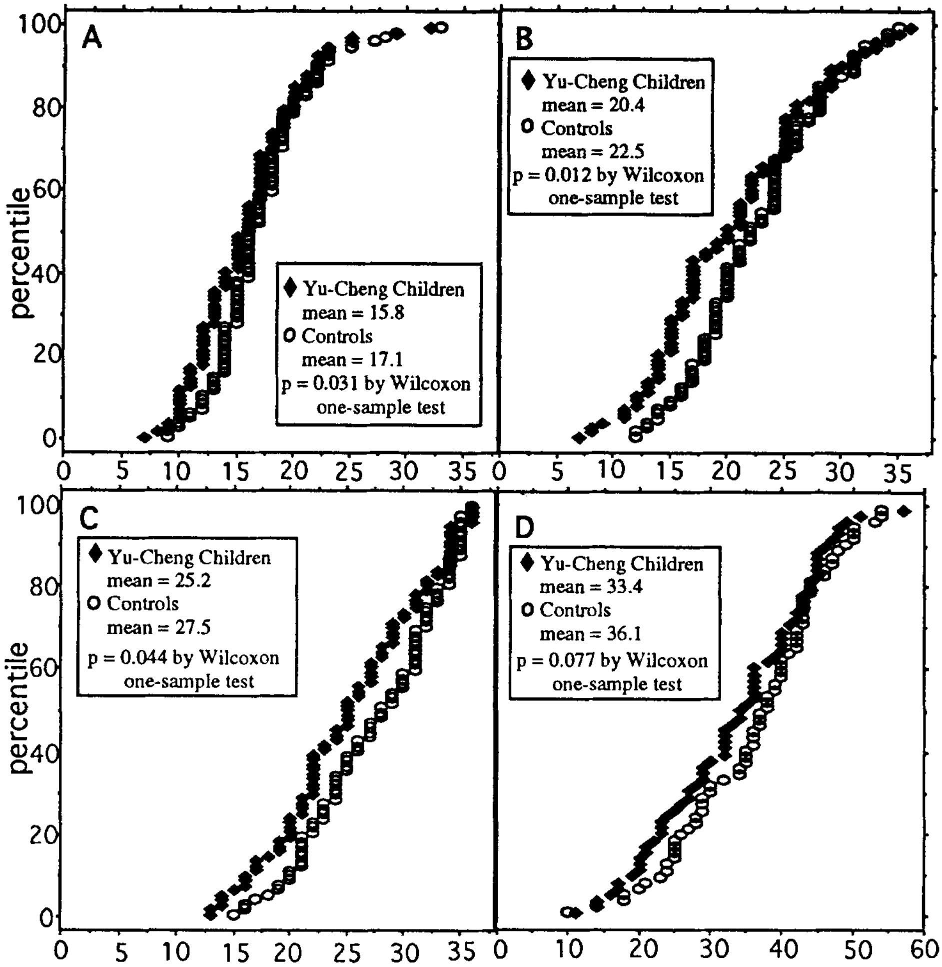

Figure. Scores of Colored Progressive Matrices in Yu-Cheng children and controls at 6 (A), 7 (B), 8 (C) years of age, and Standardized Progressive Matrices at 9 (D) years of age.

PCDFs. We saw no evidence that the deficits in these children were decreasing as they aged. In the children born later after mothers' intoxication, no clear pattern of moderation in effect of the reduced CPM scores were seen. The reduction of CPM and SPM scores was sex-dependent, that the Yu-Cheng boys were more affected than the Yu-Cheng girls compared with their controls.

Table 1. Lack of predictability of birth date on the differences in CPM and SPM scores. Results of regression analysis are shown using y=difference of test scores (control minus exposed) and x=year of birth. None of the slope coefficients for CPM and SPM at different ages was statistically significant, indicating that year of birth does not affect the difference between exposed and control children.

	slope	SE of slope	t-value	p-value	R-square
CPM at 6 yr	-0.18	0.40	0.47	0.64	0.002
CPM at 7 yr	-0.61	0.46	1.32	0.19	0.019
CPM at 8 yr	-0.07	0.47	0.14	0.89	0.0002
SPM at 9 yr	0.71	0.92	0.77	0.44	0.009

Table 2. CPM and SPM in Yu-Cheng and control girls and boys.

	Tests performed	N*	Yu-Cheng children (mean ± SE)	Controls (mean ± SE)	Mean of difference	paired T-value	p-value
Girls	CPM at 6 yr	48	16.2 ± 0.7	16.9 ± 0.6	-0.6	-0.8	0.45
	CPM at 7 yr	48	21.0 ± 1.0	21.9 ± 0.9	-0.9	-0.9	0.37
	CPM at 8 yr	41	26.3 ± 1.0	27.4 ± 0.9	-1.1	-1.3	0.22
	SPM at 9 yr	34	32.4 ± 1.9	34.1 ± 2.1	-1.8	-0.9	0.40
Boys	CPM at 6 yr	43	15.3 ± 0.7	17.3 ± 0.7	-1.9	-2.0	0.05
	CPM at 7 yr	44	19.7 ± 0.9	23.2 ± 0.8	-3.4	-2.9	0.006
	CPM at 8 yr	41	24.1 ± 0.9	27.7 ± 0.9	-3.6	-3.1	0.004
	SPM at 9 yr	33	34.4 ± 1.8	38.0 ± 1.2	-3.5	-1.9	0.07

*number of pairs of study children

Raven's Progressive Matrices are considered to be relatively culture fair and evaluate the general intelligence factor, i.e., Spearman's "g" factor (Raven 1983; Raven et al., 1985). They indicate a person's ability to form comparisons and to reason by analogy as well as to show to what extent he or she is capable of organizing spatial perceptions into systematically related wholes. Very simple oral instructions are required in the tests. The finding of reduced CPM/SPM scores was consistent with previous assessment in this group, in which WISC scores were reduced in Yu-Cheng children at 6 and 7 years of age (Chen, 1992).

PCBs and related compounds were cleared slowly from human body. Although children born longer after mothers' intoxication were expected to be less affected, this was not shown in our data. A similar picture of lack of moderation was seen in previous report on WISC-R test, in which the reduced cognitive functioning persisted in Yu-Cheng children born up to 6 years after mothers' intoxication.

In control children, boys scored higher in CPM and SPM than girls of the same age. This was because the Matrices tested spatial abilities rather than verbal abilities. Gender-related differences in cognitive abilities have been reported and believed to be cross-cultural (Mann et al., 1990). Girls performed better in tests of verbal abilities and boys in tests of spatial abilities. When compared with their controls, Yu-Cheng boys were more affected than Yu-Cheng girls (Table 2). Sex hormones play important roles in this differential development during a critical period in prenatal growth. Boys born to mothers who took diethylstilbestrol (DES), a nonsteroidal synthetic estrogen, during pregnancy had reduced hemispheric laterality and lowered spatial ability (Reinisch and Sanders, 1992). In primates, manipulations of steroid hormones during the critical period of brain differentiation altered the development of gender differences in cognitive abilities (Bachevalier and Hagger, 1991). PCB congeners are estrogenic or anti-androgenic (Platonow et al., 1972; Lione 1988; Korach et al., 1988). TCDD modulates the levels of receptors to glucocorticoids and estrogens, and exhibits a broad spectrum of antiestrogenic activities (Safe et al., 1991). Therefore gender-dependent reduction in CPM and SPM scores in Yu-Cheng children could be due to disturbance in sex hormone by prenatal PCB/PCDF exposure.

Serum levels of PCDFs were not previously measured for the mothers of our subjects. However, Kashimoto et al. (1985) reported blood levels of PCBs and PCDFs of a group of 113 Yu-Cheng patients directly exposed during a similar period of time as our subject children's mothers as 39 and 0.076 ppb respectively. In 1991, analysis of serum levels in a random subgroup of Yu-Cheng children in this study (Guo et al., 1994; Ryan el al., 1994) showed a median levels of 106 ng/kg lipid, 160 ng/kg lipid, and 1.3 ng/kg whole weight for 2,3,4,7,8-PnCDF, 1,2,3,4,7,8-HxCDF, and total PCBs respectively which were much higher than those (19, 23, and 0.17 respectively) of a pooled serum sample of matched control children. We did not find correlation between children's serum levels of toxicants and reduced CPM scores, this can be due in part to the small number of serum samples analyzed. There was also a lack of correlation between children's serum PCB/PCDF levels and mothers' levels at the time of pregnancy, since duration of breast-feeding was a more important determinant, than the mothers' levels, of children's serum levels (Ryan et al., 1994).

Socio-economic factors were in the matching criteria, and both groups of children were from rural areas. Parents' educational levels were very similar, and up to 12 years of age, education for children were mandatory. None of the exposed families had any psychiatric history, none of the exposed mothers had ever smoked, and only two exposed mothers had ever drunk regularly. The Raven's Progressive Matrices required minimal verbal explanation and judgments from the testers. Therefore, although the testers might be able to know who the Yu-Cheng children were, we do not expect this to make any significant change in the children's scores. We can not rule out the possibility that the test performance might have been affected by the child or the family's emotional burden of being the victims of toxic exposure. However, if this is the case, the girls should be affected at least as much as, or likely more severely than, the boys. The fact that we saw more reduced scores in boys than in girls strongly argue against the possibility that reduced CPM/SPM scores were due to emotional stress from the toxic exposure.

Although many animal studies have been done on the toxicity and mechanisms of PCBs and related compounds, the two Asian outbreaks represent the only known cases of clinically obvious PCB/PCDF poisoning in relatively large groups of women and children. We plan to continue following the prenatally exposed Yu-Cheng children in order to evaluate the courses of the disease process.

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