Environmental Research 109 (2009) 728–733

Contents lists available at ScienceDirect

Environmental Research

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

Neuropsychological function in school-age children with low mercury exposures

Pamela J. Surkan[a,b], David Wypij[c], Felicia Trachtenberg[d], David B. Daniel[e], Lars Barregard[f], Sonja McKinlay[d,*], David C. Bellinger[b,g]

[a] Department of International Health, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21025, USA
[b] Department of Environmental Health, Harvard School of Public Health, Landmark Bldg, 401 Park Drive, Boston, MA 02115, USA
[c] Department of Biostatistics, Harvard School of Public Health, 655 Huntington Ave, Boston, MA 02115, USA
[d] New England Research Institutes, 9 Galen Street, Watertown, MA 02472, USA
[e] School of Psychological Sciences, University of Northern Colorado, Colorado, USA
[f] Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital and Academy at Göteborg University, Sweden
[g] Harvard Medical School, Children's Hospital, 300 Longwood Ave, Boston, MA 02115, USA

ARTICLE INFO

Article history:
Received 3 July 2008
Received in revised form
8 April 2009
Accepted 16 April 2009
Available online 22 May 2009

Keywords:
Mercury
Children
Neurodevelopment
Semi-parametric models

ABSTRACT

The EPA reference dose for methylmercury (MeHg) was established using data from populations with greater exposures than those typical of the US. Few data are available on potential adverse health effects at lower levels. We examined relationships between hair mercury (Hg) levels and neuropsychological outcomes in a population of US children. This study included data from 355 children ages 6–10 enrolled in the New England Children's Amalgam Trial. Data on total hair Hg levels, sociodemographic information and neuropsychological function were collected. We evaluated associations between hair Hg and neuropsychological test scores with linear regression methods and used generalized additive models to determine the shape of associations that departed from linearity. Models controlled for relevant covariates, including the potential beneficial effects of consuming fish.

In adjusted models, we observed no significant linear relationships between hair Hg level and any test score. Significant departures from linearity were identified for WIAT Math Reasoning and WRAMVA Visual-Motor Composite scores. The association was positive for hair Hg levels below 0.5 μg/g and negative for levels between 0.5 and 1.0 μg/g. Overall, test scores of children with hair Hg levels $\geqslant$1.0 μg/g appeared to be lower than those of children with levels $<$1.0 μg/g, but few children had levels in this upper range and these differences did not reach statistical significance. Hair Hg levels below 1.0 μg/g in US school-age children were not adversely related to neuropsychological function.

1. Introduction

Intake guidelines for methylmercury (MeHg), such as the reference dose (Rice, 2004) and the provisional tolerable weekly intake (JointFAO/WHO Expert Committee on Food Additives, 2004), have been derived on the basis of studies of adverse health effects in populations that consume large quantities of seafood (Kjellström et al., 1989; Grandjean et al., 1997; Myers et al., 2003). Although the findings of these epidemiologic studies are somewhat mixed, the weight-of-evidence indicates that higher prenatal exposures to MeHg are associated with neuropsychological deficits in children (National Research Council, 2000; Axelrad et al., 2007). MeHg exposures in the US population, in which consumption of seafood is relatively modest, are considerably lower than those in these other studies. For example, the mean maternal hair Hg levels in the Faroese and Seychellois birth cohort studies were 4.3 and 6.9 μg/g, respectively (Grandjean et al., 1999; Myers et al., 2003). In contrast, among US women of child-bearing age, the mean, median, and 95th percentile of hair Hg levels are 0.47, 0.19 and 1.73 μg/g, respectively (McDowell et al., 2004). The median hair Hg level among children 1–5 years of age is 0.11 μg/g (McDowell et al., 2004). MeHg is incorporated into hair in proportion to the MeHg in blood. Since hair grows approximately 1 cm per month, hair Hg reflects exposure during the past months or year, depending on hair length (McDowell et al., 2004).

Few data are available on potential adverse health effects of hair Hg levels typical of the US population. However, two recent studies did suggest that deficits in infant development are evident within the range of typical US maternal hair, maternal blood or cord blood Hg levels at delivery (Oken et al., 2005, in press; Jedrychowski et al., 2006). Furthermore, data on potential health effects associated with childhood, contrasted with fetal exposures, are very limited. Although the fetus is considered to be the most

Abbreviation: Hg, Mercury; MeHg, Methylmercury

* Corresponding author. Fax: +1 617 926 8246.
E-mail address: SMcKinlay@neriscience.com (S. McKinlay).

0013-9351/$ - see front matter
doi:10.1016/j.envres.2009.04.006

susceptible subgroup of the population (National Research Council, 2000), cross-sectional studies conducted on Amazonian children and children from French Guiana suggested that maternal hair and/or cord blood Hg levels greater than approximately 10 μg/g at the time of delivery or interview (used as a proxy for prenatal exposures) were associated with reduced neuropsychological performance in school-age children, but few associations were found in relation to children's concurrent hair Hg levels (Grandjean et al., 1999; Cordier et al., 2002).

The goal of the present analyses was to evaluate the relationships between hair Hg levels measured in childhood and cognitive outcomes in a population with Hg exposures that are typical of those observed in the US population.

2. Methods

2.1. Study design and participants

This study included baseline data from the 5-year New England Children's Amalgam Trial (NECAT), a randomized trial conducted between 1999 and 2005 for the purpose of studying potential effects of dental amalgam on child neurodevelopment (Children's Amalgam Trial Study Group, 2003; Bellinger et al., 2006). Children aged 6–10 were eligible to participate if they spoke English, had at least two dental caries on posterior occlusal tooth surfaces, and did not have previous amalgam fillings. Children were also excluded if a parent/guardian reported they had medically diagnosed psychological, behavioral, neurological, immunosuppressive, or renal disease. Although data were originally collected for an amalgam trial to study elemental Hg, the focus of our analyses was on hair Hg, which reflects primarily MeHg.

Initially, 598 eligible children were identified from the Boston, Massachusetts area and Farmington, Maine, a rural area. Parental consent and child assent were obtained for 534 children (89%; 291 from Boston, 243 from Maine). The institutional review boards of the New England Research Institutes, the Forsyth Institute, and hospital-affiliated dental clinics (affiliated with Franklin Memorial Hospital in Maine, and the Cambridge Health Alliance, Boston University Medical Center, or Children's Hospital in Massachusetts) approved this study. Total Hg level was determined in a sample of the child's hair collected at baseline. Sociodemographic information was also collected from parents/guardians.

2.2. Measurement of Hg exposure

Approximately 50–100 strands of hair, cut as close to the scalp as possible, were collected at the child's baseline visit. This visit was conducted before a child was randomized to the amalgam or non-amalgam group. Therefore, at the time hair Hg was measured none of the children had ever had any exposure to elemental Hg from amalgam fillings. Hair samples were sent to the University of Rochester Medical School (Department of Environmental Medicine, Rochester, NY) for analysis. Total Hg was measured in hair by cold vapor atomic absorption spectrometry (CVAAS) (Magos and Clarkson, 1972). The laboratory has performed well in inter- and intra-laboratory comparisons (Boischio and Cernichiari, 1998). Comparisons have also been performed between the CVAAS method and independent methods (X-ray fluorescence spectrometry and gas chromatography with atomic fluorescence detection) with good agreement between the three methods (Cernichiari et al. 1995).

The detection limit was 0.75 ng Hg. Hair samples were dissolved in 10 ml volume, with an aliquot (typically 3 ml) removed for analysis. Detectable concentration (μg Hg/g hair) varied with hair mass, with larger samples (e.g. longer hair) having a lower detectable concentration. Forty-seven percent of the samples were below the detectable concentration (0.22 μg/g on average). Samples below the detectable limit were imputed as detectable concentration/$\sqrt{2}$ (Horning and Reed, 1990). Due to inaccuracy of imputing from very high detection limits, samples with hair mass <6.3 mg were excluded from all analysis and descriptive statistics. A hair mass of 6.3 mg corresponds to a detection limit of 0.40 μg/g, the median H–Hg content of the detectable samples. Of the 534 children enrolled, 16 did not have baseline hair samples and for 32 children the hair sample weighed <6.3 mg. Thus, for the purposes of analyses, a hair Hg level was available for 486 children (91% of 534).

2.3. Neuropsychological endpoints

With the aim of studying the effects of hair Hg on a broad range of neuropsychological endpoints, outcome variables included the Full-Scale, Verbal, and Performance IQ scores on the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 1991); the Reading Composite, Basic Reading, Reading Comprehension, Math Composite, Math Reasoning, and Numerical Operations scores on the Wechsler Individual Achievement Test (WIAT) (Psychological Corporation, 1992); the Visual-Motor Composite, Drawing, Matching, and Pegboard scores on the Wide Range Assessment of Visual Motor Ability (WRAVMA) (Adams and Sheslow, 1995); the General Memory Index on the Wide Range Assessment of Memory and Learning (WRAML) (Sheslow and Adams, 1990); perseveration errors on the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993), the Stroop Test of Color-Word Interference (Trenerry et al., 1989); the time to complete Part B of the Trail-Making Test (Spreen and Strauss, 1998), and Finger Tapping counting the mean of 5 trials with the dominant hand (the WPS Electronic Tapping Test). With the exception of the Trail-Making Test, higher scores on the neuropsychological tests indicated better performance. All data on neuropsychological endpoints were collected at baseline.

2.4. Statistical modeling

Because maternal IQ is an important predictor of child cognitive abilities, we restricted our study to include only the 379 children with information on maternal IQ. We also excluded 24 observations missing information on birthweight or lead exposure, covariates included in the analyses. This resulted in a sample size of 355. For a multiple linear regression model which already adjusts for a moderate number of covariates having an R^2 of 10–30%, a sample size of 355 provides 80% power to detect an increase in R^2 of 2% or greater, and 90% power to detect an increase in R^2 of 3% or greater when adding a linear effect of hair Hg to the model (nQuery Advisor, Statistical Solutions, Saugus, MA).

For descriptive purposes, we estimated relationships between demographic factors and neuropsychological test scores of children with continuous hair Hg, by calculating group comparisons using a likelihood ratio test for categorical variables and Spearman's correlations for continuous variables. Spearman's correlations were also used to assess unadjusted associations between continuous hair Hg levels and

Table 1
Associations between hair mercury levels and demographic and other child characteristics ($N = 355$).

		Hair mercury level (μg/g)	
	%	Mean (SD)	p-Value[a]
Gender			0.71
Male	46.8	0.31 (0.36)	
Female	53.2	0.32 (0.24)	
Age (years)			0.22
6–7	53.5	0.29 (0.27)	
8–9	37.2	0.35 (0.35)	
10–11	9.3	0.28 (0.23)	
Race			<0.001
Non-Hispanic white	72.4	0.29 (0.27)	
Non-Hispanic black	16.9	0.30 (0.22)	
Hispanic	3.1	0.39 (0.36)	
Other	7.6	0.52 (0.52)	
Education of primary caregiver			0.72
<High school	10.4	0.28 (0.19)	
High school graduate	80.3	0.32 (0.31)	
College graduate	9.3	0.33 (0.27)	
Marital status			0.96
Married	37.2	0.30 (0.30)	
Not married	62.8	0.29 (0.30)	
Fish consumption			0.003
At least once a week	33.8	0.36 (0.32)	
At least twice a month	22.3	0.37 (0.35)	
Monthly or less	29.0	0.27 (0.27)	
Never	14.9	0.21 (0.15)	
	Mean (SD)	Spearman correlation	p-Value
Birth weight (g)	3374 (538)	−0.05	0.31
Socio-economic status[b]	52.9 (30.6)	0.03	0.61
Primary caregiver IQ[c]	96.5 (12.1)	−0.00	0.94
Blood lead level (μg/dl)	2.19 (1.63)	0.04	0.47
Hair mercury level (μg/g)	0.31 (0.30)	–	–

[a] p-Values measuring associations between hair mercury level and categorical variables were calculated with a likelihood ratio test comparing the groups.
[b] Computed using the method of Green (1970).
[c] Measured with the Kaufman-Brief Intelligence Test (K-BIT).