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ABSTRACT. *Objectives.* **To correlate the presence and levels of total mercury (THg) in cord blood and meconium indicating prenatal exposure with developmental milestones at 2 years and to compare these subjects with controls of comparable age using cognitive adaptive test and clinical linguistic auditory milestone scale (CAT/CLAMS).**

Methods. **In 48 of the original Tagum (T) subjects, cord blood and meconium Hg levels, head circumference (HC) at birth, and duration of breastfeeding were correlated with CAT/CLAMS at 2 years. At 2 years, THg levels using cold atomic vapor absorption spectrometry were determined in the hair of 46 T subjects and 88 Saranggani (S) controls; THg levels in blood were tested in 48 T subjects and 45 S controls. These levels were correlated with CAT/CLAMS. Both groups had standard physical and neurologic examinations, hearing screen using transitory evoked otoacoustic emissions, serum glutamate pyruvate transaminase, and routine urinalysis. A prevalidated Socioeconomic Means Test was given to both groups.**

Results. **The Hg level in cord blood was negatively correlated with CAT/CLAMS at 2 years. The HC at birth was negatively correlated with levels of Hg in hair of T subjects 2 years later. HC at birth and 2 years hence were positively correlated with CAT/CLAMS. The following were significantly higher in S controls than in T subjects: expressive language quotient 82.569 ± 2.21 versus 71.57 ± 2.61; CLAMS 87.96 ± 2.43 versus 77.67 ± 2.51; CAT 90.57 ± 2.22 versus 83.15 ± 1.43; and full-scale developmental quotient 89.31 ± 2.14 versus 80.56 ± 1.86. Fifteen percent of T subjects had global delay (full-scale developmental quotient ≤70) versus 5.48% in S controls. Hg levels in hair and blood in both T subjects and S controls at 2 years showed no correlation with CAT/CLAMS. The duration of breastfeeding in both groups likewise showed no correlations with CAT/CLAMS.**

Conclusion. **The study suggests that prenatal Hg exposure is correlated with lower scores in neurodevelopmental screening, but more so in the linguistic pathway. Other confounding factors cannot be eliminated.** *Pediatrics* **2003;111:e289–e295. URL: http://www.pediatrics.org/cgi/content/full/111/3/e289;** ***prenatal hg exposure, developmental follow-up.***

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ABBREVIATIONS. Hg, mercury; MeHg, methyl mercury; THg, total mercury; ppm, parts per million; ppb, parts per billion; HC, head circumference; T, Tagum; S, Saranggani; CAT, cognitive adaptive test; CLAMS, clinical linguistic auditory milestone scale; DQ, developmental quotient; SGPT, serum glutamate pyruvate transaminase; ELQ, expressive language quotient; RLQ, receptive language quotient; FSDQ, full-scale developmental quotient.

There is increasing awareness of the hazards of mercury (Hg) exposure to the fetus and infant during critical periods of neuronal development. Maternal exposure to elemental Hg vapor results when Hg is released during the purification of gold in mining communities or from dental amalgam fillings during mastication. Maternal source of methyl Hg (MeHg) is from dietary intake of seafood or treated grain. Both elemental Hg and MeHg pass through the placenta with ease, and when elemental Hg is changed to polar compounds, it cannot recross to the maternal circulation, resulting in accumulation of Hg in the fetal tissues including the developing brain.[1–10] Inorganic Hg, however, is hazardous to the developing fetus because it accumulates in the placenta, resulting in a "sink effect" that interferes with function.[11,12]

In Japan and Iraq, microcephaly, mental retardation, cerebral palsy, deafness, and dysarthria were reported in infants of mothers with sensory and motor impairment as a result of high-dose MeHg poisoning episodes.[13,14] No cord-blood levels were determined in these infants. In a retrospective study of 24 infants with overt Minamata disease, the median total Hg (THg) concentration in stored frozen umbilical cord tissue was 1.63 μg/g, whereas in the fetus and embryo born of asymptomatic mothers, THg ranged from 0.03 to 1.05 μg/g.[15,16]

Chronic low-level prenatal MeHg exposure from maternal consumption of fish demonstrated more subtle endpoints, including developmental delay and learning deficits. Neurobehavioral dysfunction was estimated to occur when the Hg concentration in maternal blood was approximately 24 μg/L computed from a measured level of >6 μg/g of maternal hair.[17]

In the whale-eating community of Faeroe Is-

TABLE 1. Socioeconomic Means Test SMT

Indicators	Saranggani (n = 88)	Tagum (n = 47)	P Value
Economic indicators			
Radio	100%	98%	.343
Electric fan	97%	98%	.818
Liquified petroleum gas	40%	39%	
TV	42%	50%	
Refrigerator	35%	54%	
Video hi-fi stereo	26%	33%	.277
Salary levels			
<1000	11%	9%	
1001–2000	16%	11%	
2001–3000	32%	47%	
3001–4000	11%	9%	
4001–5000	10%	4%	
5001–10,000	10%	11%	
>10,000	10%	9%	
		0	0
Average salary (in pesos)	4958.40	4760.13	.836
Health care practices			
Attend health guidelines	94%	94%	.56
Follow health guidelines	100%	100%	
Buy affordable medicines	98%	100%	.43
Train as comm. health worker	26%	59%	.00023
Seek advice from health workers	99%	93%	.117
Follow advice of health workers	97%	98%	.575
Complete prescribed medication	98%	100%	.430
Child-rearing practices			
Encourage to play with blocks and draw	82%	91%	.111
Put together 2-3 pieces of puzzle	42%	100%	.002*
Recite nursery rhyme to child	82%	83%	.556
Read fairy tales to child	18%	17%	.556
Encourage child to talk	80%	61%	.018*
Follow simple instructions	97%	91%	.183
Allow child to watch TV, listen to radio alone	100%	78%	.000*
Encourage child to walk, run, tiptoe, play, kick, etc	98%	96%	.425
Hug and comfort child	100%	100%	
Bring child to park, etc	100%	98%	.343
Allow child to dress up, pick up toys, eat with family	99%	100%	.657
Comfort and pacify fussy child	75%	100%	.0000*
Maternal/child health			
Delivered by			
Doctor	13%	98%	.000
Traditional attendant/midwife	87%	2%	.000
Breastfeeding			
Prevalence	76%	93%	.0019*
Duration	11.25 mo	19 mo	.007
Community health-related activities			
Member of health organization	89%	65%	0.0015
Awareness of health services	98%	100%	0.43
Implement health messages	99%	93%	0.117
Disseminate health information	98%	91%	0.105
Discuss drug abuse with family	83%	67%	0.035
Discuss sex with family	88%	70%	0.012

* Significant difference between T subjects and control in child-rearing practices ($P < .05$).
Prevalidated and developed in 1995 by HAMIS (Phil. DOH supported by German Technical Cooperation).

land,[2,3,7] maternal hair Hg levels at 10 to 12 parts per million (ppm) in 112 children showed that at 7 years, subtle effects on brain function, particularly attention, language, and memory, were detected when matched with children of 805 mothers with hair Hg levels <3 ppm. Because Hg that enters the hair follicles from capillary blood binds strongly to the sulfhydryl group in the structural protein of hair, hair, whether from the mother or newborn, is a more satisfactory measure than blood level because of the rapid removal of Hg from circulation. Hg in hair at birth and up to 36 months has been suggested to be an indication of prenatal exposure, whereas hair levels beyond that period are generally reflective of postnatal exposure.[7]

Currently, neurodevelopmental problems in children secondary to maternal MeHg consumption of fish during pregnancy are considered to be the most sensitive indicators of adverse effects of MeHg exposure.[18] Postnatal exposure from breast milk may add to the Hg burden in the neonate, whose ability to excrete Hg is lower than more mature individuals.[19] However, the study by Grandjean et al[20] in 1995 showed that breastfeeding confers an advan-

tage to the infant in terms of neurobehavioral development, thereby compensating for the increased exposure to Hg.

In 1997, we studied 78 consecutive mother–infant pairs in Tagum, an artesanal gold mining and processing community. Maternal exposure was from Hg vapor and from fish. Our objectives were to determine the toxicodynamics of THg transfer from the mother to the fetus and its effects on the newborn.[21] None of the mothers showed clinical signs of Hg toxicity. The prevalence rates were as follows: mother's blood, 6.4%; colostrum, 6.4%; cord blood, 16.70%; infant's hair, 31.57%; and meconium, 46.75%. The mean Hg levels among those with detectable levels were 24 parts per billion (ppb; range: 20–30) in mother's blood ($n = 5$), 53.3 ppb (range: 20–130) in cord blood ($n = 12$), and 48.64 ppb (range: 20–200) in meconium ($n = 36$), reflecting the absence of a placental barrier with accumulation in fetal tissues. At birth, the significant findings were in the head circumference (HC). The average HC was significantly smaller than that of the average for Filipino newborns (32.54 ± 1.83 cm vs 35.98 cm; $P < .001$), whereas there was no significant difference in mean birth weight (2989 ± 564 g vs 3015 g; $P = .691$).[22] Furthermore, those found positive for Hg in hair, cord blood, and meconium had smaller HCs on correlation and quartile analysis.

Additional studies are needed to fill gaps in knowledge. Early deviations from normal have to be documented, especially in terms of timing of onset and type of clinical manifestations. Manifestations as a result of fetal exposure are different from the clinical features in older individuals and may not be completely reversible. There is also the potential for emergence of neurologic effects later in life after earlier low-dose MeHg exposure. The objectives of this study were to follow-up at 2 years of age the toddlers of asymptomatic mothers, with baseline data at birth proving fetal exposure to Hg, to determine when and what indicators appear with fetal Hg exposure and the type of developmental problems that can be detected by a simple but reliable instrument for assessment and to compare the developmental scores of case and control subjects at 2 years.

METHODS

Subjects

Only 48 of the original 78 cohort from the Tagum I study[21] (T subjects) were available for follow-up at 2 years of age (mean: 27 months of age). The reasons for the 39.7% attrition were primarily related to inaccessibility of areas of residence to postal service, radio announcements, and house-to-house search because of security reasons. A few relocated to undetermined areas for better livelihood.

Eighty-eight 2-year-old children (mean: 22 months) from Saranggani, a small coastal coconut plantation and fishing community at the southeastern tip of the Philippines with no known source of industrial, chemical, or pesticide pollution were used as controls (S controls). The mean age was lower because all the 2-year-olds were included to increase the number. Saranggani faces the open Celebes Sea, 250 km from where the main rivers in Tagum empty. The area is rich in predatory species of fish. However, Hg levels have not been studied in the marine life in this area.

Both T subjects and S controls belong to the same ethnic group, with the same dialect and similar dietary habits. A prevalidated Socioeconomic Means Test[23] (Table 1) was administered by a board-certified pharmacist of the team who interviewed parents. The 2 groups are similar in socioeconomic characteristics and child-rearing practices. The few significant differences are shown in Table 1. Of note is that more T mothers breastfed, and the duration of breastfeeding is significantly longer in T than in S subjects.

Two children from S controls and 1 child from T subjects were eliminated from the cognitive adaptive test and clinical linguistic auditory milestone scale (CAT/CLAMS) correlation analysis because of bilateral otitis media. Ten S controls left before administration of CAT/CLAMS. A written consent was obtained from all of the mothers.

Neurodevelopmental Screening

All of the members of the team were blinded as to the original levels of Hg in our Tagum I study. The T subjects were seen in the Tagum Regional Hospital. One board-certified neonatologist did all of the physical examinations and history taking. A board-certified neurologist did each individual standard neurologic examination after which she acted as a quiet independent observer while another board-certified neonatologist, trained and experienced in developmental screening using Capute CAT/CLAMS,[24–33] did the neurodevelopmental screening.

CAT/CLAMS is a highly recommended tool for 1- to 36-month-old children. It has been found to have a significant correlation with the Bayley Scales of Infant Development-Mental Scale with a sensitivity of 0.66, specificity of 0.79, and positive predictive value of 0.80.[27,28] The mean for our country is 100 developmental quotient (DQ). The test evaluates 2 streams of development namely: longitudinal language pathway based on sequential milestone language (CLAMS) acquisitions mainly provided by the mother, and visual motor problem-solving tasks (CAT), which are performed directly with the child. The test is uniquely suited for discriminating between global delay and unequal deficits in either language or visual motor skills because cognition and language pathways are separately assessed. Scoring of the Capute's CAT/CLAMS is based on the child's performance on test items corresponding to developmental milestones. The scores are divided by the child's chronological age to determine the DQs.

The determination of the transitory evoked otoacoustic emissions (Otodynamic Co, Herts, United Kingdom) was done by a trained technologist in the common waiting, examining, and blood letting area, which limits acceptability of results. One resident doctor collected all of the blood samples from the antecubital vein into heparinized glass vacuum tubes (Becton Dickinson, Franklin Lakes, NJ) and frozen immediately. Blood for hemoglobin determination was sent to the laboratory for examination.

TABLE 2. Correlation of HC at Birth With CAT/CLAMS in T Subjects ($n = 47$)

Developmental Scales	Correlation Coefficients
RLQ	0.299 (P=.058)
ELQ	0.275 (P= .08)
CLAMS	0.386 (P=.013)
CAT	0.309 (P=.052)
FSDQ	0.377 (P=.017)

Significant correlation $P \leq .1$.

TABLE 3. Correlation of Hg Levels in Cord Blood and Meconium With CAT/CLAMS

Developmental Scales	Cord Blood ($n = 44$)		Meconium ($n = 44$)	
	r	P	r	P
RLQ	−159	.152	0.072	.321
ELQ	−0.284	.031	0.254	.048
CLAMS	−.0171	.0134	0.236	.061
CAT	−0.001	.496	0.212	.086
FSDQ	−0.119	.223	.232	.067

Significant correlation $P < .1$.

TABLE 4. Mean Hg Levels in T Subjects and S Controls

	T Subjects	S Controls	*P* Value
Mean Hg in hair (ppm)	1.28 ± 0.30 (n=46)	0.66 ± 0.05 (n = 88)	.051
Mean Hg in blood (ppb)	2.6 ± 0.27 (n=48)	3.25 ± 0.22 (n = 45)	.07

Upper limits hair 2 ppm, blood 7.5 ppb.
Significant difference $P \leq .05$.

Blood for serum glutamate pyruvate transaminase (SGPT) was collected in nonheparinized Vacutainer, spun down, and frozen for determination in Manila. Routine urinalysis was done in Tagum Regional Hospital.

The frozen blood samples for Hg analysis were packed in frozen refrigerant in insulated containers during transport to Manila and kept in a freezer until air lifted to the Minamata Institute under similar transport conditions. Forty-three of the 88 Vacutainer from S controls cracked and the contents spilled during shipment to Japan, reducing the blood samples from 88 to 45. Hair was obtained from the occiput using clean scissors. Samples were wrapped in Saran Glad Wrap (Life System Medical Distributor, Manila, Philippines) and stored dry until analysis. Two hair samples from T subjects were lost in transit, reducing the samples from 48 to 46.

Glassware was cleaned with acidic permanganate solution (0.5% $KMnO_4$ in 1 N H_2SO_4) and rinsed with Hg-free water. For total Hg analysis, the different samples (blood and hair) were pretreated with HNO_3-$HClO_4$-H_2SO_4 mixture and then digested by heating at 230°C to 250°C on a hot plate for 20 minutes. After cooling, each sample was filled with Hg-free water up to the 50-mL mark and analyzed by semiautomated cold vapor atomic absorption spectrometry (Sanso-Seikusho Co, Kimamo, Japan). International standards were run with the determinations. With this modified system developed by the National Institute for Minamata Disease in Japan, the sensitivity and accuracy are substantially improved and the analysis of a sample can be completed within 1 minute with a detection limit of 0.5 mg Hg or 0.5 ppb.[33] All samples for Hg level determination were done by 2 of the coauthors in the laboratory of the Minamata Institute in Japan. SGPT levels were determined at the Philippines Children's Medical Center.

Statistical Analysis

Among T subjects, variables measured at birth were correlated with variables measured 2 years later. Average differences were noted. Correlation analysis was used to determine relationships between variables. Pearson product correlation coefficients were used for continuous variables such as HC, expressive language quotient (ELQ), receptive language quotient (RLQ), and full-scale developmental quotient (FSDQ), whereas Spearman rank correlation was used for ordinal data and normal data such as Hg levels. Percentages were used to determine prevalence.

For comparing mean scores between case and control, t test was used. For testing the association between nominal variables, χ^2 test or Fisher exact probability test was used. Odds ratio was used to compare the risk of attaining lower-than-normal scores in the 2 areas of residence.

RESULTS

Two-Year Neurobehavioral Follow-up of T Subjects

HC at birth was positively correlated with CLAMS and FSDQ, whereas RLQ, ELQ, and CAT had moderate correlation ($P < .1$; Table 2). The HC at birth was negatively correlated with Hg level in hair at 2 years of age ($r = -0.275$; $P = .043$).

There were significant negative correlations between Hg in cord blood and ELQ and CLAMS. However, the opposite was seen in the correlation analysis with Hg in meconium. ELQ, CLAMS, CAT, and FSDQ ($P < .1$) were positively correlated with levels of Hg in meconium (Table 3).

Levels of Hg in hair and blood at 2 years were examined to determine current levels and their correlations with levels at birth and CAT/CLAMS. There were no significant correlations between cord-blood Hg levels and the Hg levels at 2 years in hair ($P = .74$) and blood ($P = .835$). Likewise, there were no significant correlations established between Hg levels in meconium and Hg level at 2 years in hair ($P = .16$) and blood ($P = .882$). Hg levels in hair and blood at 2 years showed no correlations with CAT/CLAMS.

TABLE 5. CAT CLAMS Scores in T Subjects and S Controls

Developmental Scales	T Subjects (n = 47)	S Controls (n = 76)	*P* Value
RLQ	77.19 ± 3.04	83.41 ± 2.95	.1658
ELQ	71.57 ± 2.61	82.569 ± 2.21	.0018
CLAMS	77.67 ± 2.51	87.96 ± 2.43	.0056
CAT	83.15 ± 1.43	90.57 ± 2.22	.0059
FSDQ	80.56 ± 1.86	89.31 ± 2.14	.0025

Significant difference $P = .05$.

Comparison of 2-Year-Old T Subjects and S Controls

Hg Levels in T Subjects and S Controls

The mean level of Hg in the hair in 46 T subjects was significantly higher than the average level in 88 S controls ($P = .051$). Seven of the T subjects had levels over the upper limit of 2 ppm set by the Minamata Institute, whereas there was only 1 of 88 S controls ($P = .007$). The mean Hg level in the blood of 45 S controls was slightly higher than the 48 T subjects but not significantly so ($P = .07$). Blood Hg levels in both groups were below the upper limit of 7.5 ppb[30] (Table 4).

The scores on both CAT and CLAMS in the 2 groups were borderline low, with T scores significantly lower in all scales and subscales, except for RLQ (Table 5). Sixty-one percent of T subjects had CLAMS lower than 90 DQ (lower limit of normal) compared with 43% of S controls ($P = .044$)

Table 6 shows that there was a higher incidence of T subjects than S controls with scores <70 DQ in CAT, CLAMS, and FSDQ. However, it was in the CLAMS that there was a significantly higher incidence of low scores in T subjects than in S controls ($P = .00026$). The odds ratio showed that T subjects had almost 5 times (4.81) the risk of lower language ability than S controls. A total of 15.22% of T subjects had global retardation (FSDQ <70) versus 5.48% of S subjects, although P was .07.

Correlation of HC at 2 Years and CAT/CLAMS Scores

The mean HCs for T subjects (mean: 27 months of age) was 47.41 ± 1.31 cm and for S controls (mean: 22 months of age) was 46.31 ± 2.835 cm. No percentile values can be determined because there are no growth curves representative of our child popula-

TABLE 6. Odds Ratio: Incidence of <70 CLAMS, CAT, and FSDQ in T Subjects and S Controls

Developmental Scales	Controls (n = 73)	Subjects (n = 46)	P Value	Odds Ratio	95% Confidence Interval
CLAMS	14.86% (11)	45.65% (21)	.00026	4.8109	2.0273–11.4164
CAT	6.85% (5)	8.51% (4)	.4979	1.2651	0.3218–4.9743
FSDQ	5.48% (4)	15.22% (7)	.0737	3.0963	0.8525–11.2443

tion. Correlation analysis showed that for T subjects, the HCs at 2 years were positively correlated with the scores on the neurobehavioral scales, except for ELQ. This was not shown in S controls (Table 7).

Hg Hair Levels and CAT/CLAMS

The RLQ, ELQ, and CLAMS scores of the 88 S controls with mean hair Hg level of 0.66 ppm were significantly higher than the scores of the 7 T subjects with mean hair level of 4.51 ppm (upper limit, Minamata Institute >2 ppm[33]). The scores of the remaining 29 T subjects with mean hair level of 0.72825 was not significantly different from S controls and the subgroup of T subjects with Hg levels under the upper limit. However, in Fig 1, we can discern a tendency to a dose-response relationship in the sphere of communication.

Breastfeeding

Ninety-three percent of T subjects breastfed, whereas 76% of S controls breastfed their infants (P = .0019). The average duration of breastfeeding was 19 ± 4.04 months in T subjects and 11.25 ± 1.72 months in S controls (P = .007; Table 1). There was no correlation of developmental scores with the duration of breastfeeding in the 43 T subjects and 65 S subjects who breastfed and were subjected to CAT/CLAMS.

Others

There were no sensory or motor abnormalities including tone and deep tendon reflexes on basic neurologic examination in both groups. The age of motor milestone achievements were also normal. The average hemoglobin in T subjects was significantly higher at 11.8 ± 3.29 g/L than the 10.48 ± 1.58 g/L in S controls (P = .006). SGPT and urinalysis were done because there are reported changes in liver mitochondria on nuclear microscopy and the kidneys are involved in Hg excretion,[6,32] but the former are gross tests of organ integrity. SGPT levels were not significantly different between T subjects and S controls (66.23 and 59.87, respectively; P = .613). Both values were within the normal limits for our laboratory. No abnormalities were seen in the routine urinalysis. No difference was seen in the hearing screen between the 2 groups.

TABLE 7. Correlation of HC at 2 Years With CAT/CLAMS Scores

Developmental Scales	Subjects		Controls	
	r	P	r	P
CAT	0.4588	.0015*	0.00642	.959
CLAMS	0.3039	.0378*	0.04415	.7269
ELQ	0.19596	.1868	−0.01915	.8796
FSDQ	0.38429	.0077*	0.02394	.8511
RLQ	0.29881	.0413*	−0.01395	.9122

* Significant correlation $P \geq .1$.

DISCUSSION

There were limitations beyond control in this study. The fallout rate among the original T subjects was 40%. In addition, some of the control blood samples spilled when test tubes cracked during transport, and some subjects left before all of the tests were completed. We also had no samples at birth from our control group.

HCs at birth among T subjects were not only significantly smaller but also negatively correlated with levels of Hg in hair at 2 years. Furthermore, CAT/CLAMS scores on T subjects were positively correlated with HC at birth and 2 years. Therefore a small HC at birth may suggest that this is a factor that may have an impact on future cognition and language ability. Among infants with Minamata disease, microcephaly was 1 of the prominent features.

Correlation of Hg levels in cord blood with CAT/CLAMS and all subscales at 2 years showed that there was a tendency to a negative correlation with all of the DQs, but significance is only with ELQ and CLAMS, pointing to some degree of dissociation between effects on language skills and cognitive adaptive development. Deleterious effect on language was also noted in the Faeroe Island study. However, except for RLQ, levels of Hg in meconium (n = 44) correlated positively with all of the DQs in CAT/CLAMS. These findings suggest that T subjects with Hg in meconium were able to excrete Hg, lessening the developmental impact. Furthermore, in the Tagum I study, 46% of cord-blood samples that were positive for Hg had no Hg in meconium, whereas 80.6% positive in meconium were negative in cord blood (Fisher exact probability test P = .507). Meconium levels were not significantly correlated with Hg levels in cord blood (P = .769). In all meconium samples positive for Hg, there were no detectable levels in mother's blood. Therefore, the absence of measurable Hg in maternal blood does not mean that there is no Hg in the fetus. Although determination of the Hg levels in neonatal hair, cord blood, and meconium are important, none of them gives the total fetal burden. The findings suggest that Hg levels in cord blood may have more predictive value for adverse outcome than meconium.

Care was taken in the selection of controls because cognitive development may vary with ethnic group, socioeconomic status, and child-rearing practices. Our T subjects and S controls were comparable in most of the areas that would affect neurobehavior. However, there were a number of significant differences between the 2 groups, 1 of which is the mean

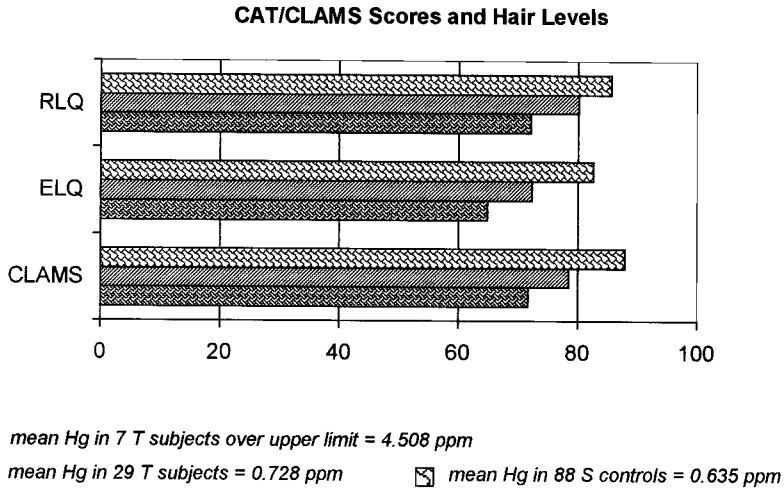

Fig 1. X axis = scores; Y axis = developmental scales.

age of 22 months in S controls versus 27 months in T subjects. We corrected for chronological age in the computation of CAT/CLAMS scores. The prevalence and duration of breastfeeding among T subjects were significantly greater and may add to the postnatal Hg burden. However, there was no correlation between duration of breastfeeding and CAT/CLAMS. Hemoglobin was significantly higher in T subjects despite similar iron supplements that were started at 6 months and may be related to lower iron density in complementary foods because of less meat intake in the fishing community. The presence of parasitic disease was not determined in the study.

Although T mothers were exposed to both elemental and organic Hg, S controls may have been exposed to MeHg from fish. Their blood Hg level was somewhat higher than T subjects. However, the mean Hg in hair was significantly lower in S controls than T subjects and was only 203 times their mean blood level (normal <250).[34] In T subjects, the mean hair level was 492 times their mean blood level, suggesting a high level of prenatal exposure in these subjects, who all were below the generally accepted cutoff age of 36 months over which Hg in hair may be considered to be postnatal in origin.[35]

Although the scores were borderline low in both groups, there is enough evidence in this study to indicate that T subjects are more likely to have future problems based on the evaluation of 2 spheres of development: language abilities and the nonlanguage visual-motor cognitive component. Moderate global delay (FSDQ ≤70) or mental retardation was present in 15.22% of T subjects and 5.48% of S controls (P = .07). It is of interest that there was a dissociation between the 2 pathway scores because the mean cognitive quotient was higher than the linguistic score. Although both pathways were affected adversely by Hg, it is possible that the effect on the domain of language might be greater. However, CLAMS is subject to the shortcomings of all data obtained from parents. Therefore, the scale stresses expressive language because production of words is more objectively measured than is receptive comprehension. In this study, ELQ scores were lower than RLQ in T subjects. The odds ratio showed that T children have almost 5 times the risk of lower language ability than S children. Currently, language delay is recognized as 1 of the best predictors of development and later intelligence[36] because there are striking regularities inherent in early language development. Certainly, hearing impairment should be eliminated in communicative disorders especially because Hg exposure may have deleterious effects on hearing. Our hearing screening showed no hearing loss >3 frequency levels of 40 dB or worse in the better ear, which is the current international definition of hearing impairment.[37] Basic neurologic examination and gross motor milestone acquisition were normal, but gross motor development has not been found to be predictive of cognitive status.[38]

Because the Hg levels in hair and blood at 2 years in both groups were not correlated with CAT/CLAMS but in the T subjects were negatively correlated with documented indicators of Hg presence at birth, our findings suggest that it is prenatal exposure and not necessarily current exposure to Hg that may lead to developmental delay. The role of other pollutants and nutritional deficiencies that may work in a concerted manner have not been eliminated. We were not able to derive the reference dose (safe dietary intake level of Hg) because of the limited number of subjects. However, because Hg freely crosses the placenta, the current strict recommendation of the US Environmental Protection Agency of 0.1 mg/kg/d of MeHg is favorable for fetal development.[18]

CONCLUSION

The study suggests that prenatal Hg exposure is correlated with lower scores in neurodevelopmental screening but more so in the linguistic pathway. Other confounding factors cannot be eliminated.

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