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Mercury, Lead, and Zinc in Baby Teeth of Children with Autism Versus Controls

James B. Adams and Jane Romdalvik
Chemical and Materials Engineering, Arizona State University, Tempe, Arizona

V. M. Sadagopa Ramanujam and Marvin S. Legator
Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, Texas, USA

This study determined the level of mercury, lead, and zinc in baby teeth of children with autism spectrum disorder (n = 15, age 6.1 ± 2.2 yr) and typically developing children (n = 11, age = 7 ± 1.7 yr). Children with autism had significantly (2.1-fold) higher levels of mercury but similar levels of lead and similar levels of zinc. Children with autism also had significantly higher usage of oral antibiotics during their first 12 mo of life, and possibly higher usage of oral antibiotics during their first 36 mo of life. Baby teeth are a good measure of cumulative exposure to toxic metals during fetal development and early infancy, so this study suggests that children with autism had a higher body burden of mercury during fetal/infant development. Antibiotic use is known to almost completely inhibit excretion of mercury in rats due to alteration of gut flora. Thus, higher use of oral antiobiotics in the children with autism may have reduced their ability to excrete mercury, and hence may partially explain the higher level in baby teeth. Higher usage of oral antibiotics in infancy may also partially explain the high incidence of chronic gastrointestinal problems in individuals with autism.

Autism is a severe developmental disorder that involves social withdrawal, communication deficits, and stereotypic/repetitive behaviors. The causes of autism are unknown, but both genetic and environmental factors have been implicated. The purpose of this study was to investigate the environmental factor of heavy metals (mercury, lead) toxicity.

A thorough review by Bernard et al. (2001) reported that all of the major symptoms reported in the literature for autism were also reported for cases of infantile mercury poisoning, including especially language/communication problems and social withdrawal. Therefore, they suggested that autism was primarily due to infantile exposure to mercury. Their hypothesis is plausible because mercury exposure at hazardous levels is common in the United States and other countries; the Food and Drug Administration (FDA) estimates that 1 in 6 women in the United States have mercury levels that increase the risk of neurological damage to their children. (Mahaffey et al., 2004) The major sources of mercury exposure for infants are (1) maternal seafood consumption, (2) maternal mercury amalgam dental fillings, and (3) thimerosal (an ethylmercury compound) in childhood vaccines and in anti-RhoD immune globulins given to Rh-negative mothers during pregnancy. Thimerosal was largely but not totally removed from childhood vaccines by 2004.

Mercury toxicity might occur either due to high exposure, or due to a decreased ability to excrete mercury, with the latter case seeming to be the primary issue in autism. The primary mechanism for excreting mercury involves its binding to glutathione and then being excreted in the bile (Ballatori & Clarkson, 1985). Infants are poor excretors because they produce less glutathione (Ballatori & Clarkson, 1984) and because they are usually on all-milk diets (which decreased mercury excretion by a factor of 3 in a study of rats); thus, they are especially vulnerable to mercury poisoning (Rowland et al., 1984).

Infants with autism were even more vulnerable to mercury toxicity, because their glutathione is much lower than in typical children (James et al., 2004; Audhya, 2004) and a higher fraction of their glutathione is oxidized (James et al., 2004). Further, two studies (Konstantareas & Homatidis, 1987; Adams et al., 2003) found that children with autism had much higher usage of oral antibiotics, which (in rats) resulted in a near-total loss of the ability to excrete mercury (Rowland et al., 1980, 1984). The reason appears to be that normal gut anaerobes are able to convert methylmercury (which is rapidly absorbed) into inorganic mercury (which is poorly absorbed and hence mostly excreted). In contrast, most strains of yeast

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Address correspondence to James B. Adams, Arizona State University, PO Box 876006, USA. E-mail: jim.adams@asu.edu

and *Escherichia coli* carry out the reverse reaction, namely, the methylation of inorganic mercury to methylmercury. (Rowland et al., 1975) Thus, high oral antibiotic use would result in a loss of normal gut flora and an increase in yeast and *E. coli*, resulting in a loss of ability to demethylate methylmercury and enhanced methylation of inorganic mercury, resulting in decreased excretion and increased uptake of mercury. This hypothesis is supported by a recent study by Rosseneu et al. (2003) that found that 94% of 80 children with regressive autism and chronic constipation/diarrhea had approximately 10,000 times the normal level of *E. coli* in their stool.

A decreased ability to excrete mercury is consistent with a recent study by Holmes et al. (2003), which found that children with autism had only one-eighth the normal amount of mercury in their baby hair (assuming that the level in hair is indicative of the level of ability to excrete mercury). In adition, the severity of autism was strongly inversely correlated with the level of mercury, suggesting that the children with the weakest ability to excrete mercury developed the most severe symptoms.

A decreased ability to excrete mercury should result in a higher body burden, and that was demonstrated in a study by Bradstreet et al. (2003). They investigated the effect of giving *meso*-2,3-dimercaptosuccinic acid (DMSA) to 221 children with autism compared to 18 controls, and found that the children with autism excreted 3.1 times more mercury into their urine (which is where DMSA is excreted), but lead and cadmium levels were not significantly different. DMSA provocation testing is probably a measure of both recent and older exposures.

There have also been studies of the level of mercury in the hair and blood of older children with autism. These studies are of limited relevance because mercury has a half-life of only several weeks in the blood, and thus the studies do not reflect levels in early infancy when autism developed. One study in the United States found elevated levels of mercury and other toxic metals in the blood (Audhya, 2004), whereas one study in Hong Kong found no difference in blood or hair levels (Ip et al., 2004). Similar to the Hong Kong study, one study in the United States also did not find any difference in the level of mercury in the hair of older children (age 3–15 yr) with autism versus controls (Adams et al., 2006).

Finally, there have been at least 10 epidemiological studies of the link between thimerosal-containing vaccines and autism, because it was discovered in 1999 that the amount of thimerosal in childhood vaccines was far in excess of FDA guidelines. Five studies by Geier and Geier found a significant link (Geier & Geier, 2003a, 2003b, 2003c, 2004, 2005), four studies failed to find a link, (Andrews et al., 2004; Hviid et al., 2003; Madsen et al., 2003; Stehr-Green et al., 2003), and one study was inconclusive (Verstraeten et al., 2003). Three of the negative studies were in countries with much lower usage of thimerosal in vaccines than in the United States, and they had much lower rates of autism in those countries, so it may not be valid to extrapolate those results to the United States.

There was a recent study by Palmer et al. (2006) That found a strong link between mercury emissions from coal-burning plants and the incidence of autism in counties in Texas. Similarly, a study by Windham et al. (2006) in the San Francisco Bay area found that five air pollutants correlated with the incidence of autism, with mercury having the highest correlation.

In summary, there is evidence to suggest that infants who are autistic have a decreased ability to excrete mercury, due to a combination of decreased glutathione, oxidative stress, excessive use of oral antibiotics, and possibly other genetic or environmental factors. Such a metal efflux disorder for another metal (copper) results in Wilson's disease, and thus it is possible that a decreased ability to excrete mercury may exacerbate or induce the symptoms of autism.

The purpose of this study was to further investigate the mercury/lead body burden of children with autism versus controls by evaluating the amount of mercury/lead in their baby (deciduous) teeth. Baby teeth are formed in utero and during the first few years of life, so they provide a measure of cumulative exposure during that critical period of development. Several studies of the level of lead in baby teeth found them to be a reliable indicator of the severity of symptoms of lead poisoning (Needleman et al., 1974). Previous studies have demonstrated that mercury can be reliably measured in teeth (Eide et al., 1993; Tvinnereim et al., 2000).

METHODOLOGY

This study was conducted with the approval of the Human Subjects Institutional Review Board of Arizona State University. All parents and (where possible) children signed informed consent forms. The autism participants were families of children with autism in the state of Arizona, contacted using the mailing lists of the Greater Phoenix Chapter of the Autism Society of America. The inclusion criteria for the children was that they were born between 1988 and 1999 and were previously diagnosed by a psychiatrist or developmental pediatrician with an autism spectrum disorder (ASD), including autism, PDD/NOS, and Asperger's syndrome.

Parents of the participants with ASD asked friends and neighbors to act as controls for the study. The criteria for the controls were that they: (1) be mentally and physically healthy individuals born between 1988 and 1999, without any developmental delays, illness, or other medical conditions, and (2) be unrelated to a person with ASD. Table 1 lists the characteristics

TABLE 1
Characteristics of Participants

Parameter	Autism	Controls
Number	16	11
Number with autism/ASD	15/1	n/a
Male/female	81%/19%	45%/55%
Age when tooth fell out	6.1 ± 2.2 yr	7.0 ± 1.7 yr

of the participants. The autism group had a smaller percentage of females than control, which is a limitation of this study. Obviously, none of the tested teeth had any mercury amalgam or other type of filling.

Comparison of differences between the groups was done using a two-sided *t*-test assuming unequal variances, with a level of $p = .05$ being used as the criterion for statistical significance.

Teeth Digestions for Mercury (Hg) Metal

All laboratory processing was performed under clean, contaminant-free conditions, to minimize external metal contamination. All glassware was soaked in 10% nitric acid and washed with water, and thoroughly rinsed with milli-Q deionized water prior to use. In between sample analyses, 2% ultrapure nitric acid blanks were also analyzed to clean the system and to check whether there was any carryover from the previously analyzed sample.

Each tooth sample was weighed accurately and digested with a known volume (2–4 ml) of ultrapure hydrochloric acid (HCl) for 4–6 days at 50°C in a screw-capped polypropylene tube wrapped with Parafilm to close the cap very tight. The sample was cooled to room temperature and stored in a freezer until analyzed.

Analysis of Mercury (Hg)

Each digested sample was suitably diluted and analyzed for mercury (Hg) metal using cold vapor atomic absorption spectrophotometry (CV-AAS) at room temperature (Eide et al., 1993; Tvinnereim et al., 2000).

Cold Vapor Atomic Absorption Spectrophotometry

Mercury (Hg) metal concentrations were determined by cold vapor atomic absorption spectrophotometry (CV-AAS). An LDC analytical manual mercury module cold vapor generator attached in series with a Mercury Monitor 3200 model elemental mercury detector (Thermo Separation Products, Riviera Beach, FL) was routinely used. The mercuric ion (2+) in the tissue digestate was reduced to elemental mercury (zero charge) by using a mixture of stannous chloride, sodium chloride, hydroxylamine hydrochloride, and sulfuric acid. The reaction was rapid and quantitative. The elemental mercury vapor was then bubbled with purified air using a hydrocarbon trap and was allowed to pass through a beam of light having an absorption maximum wavelength of 253.7 nm. The absorbance at this wavelength was proportional to the concentration of mercury.

The mercury calibration standards (0, 50, 100, 250, 500, 750, and 1000 ng/L) were prepared by serial dilutions of the reference standard (2000 mg/L, Aldrich Chemical Co., Inc., Milwaukee, WI) in 2% ultrapure nitric acid. The absorbance was recorded for each standard. The absorbance for a 1:20 (v/v) diluted digested tooth sample was also recorded and the experiment repeated twice. In order to avoid cross contamination due to possible accumulation of trapped Hg, the system was purged using a 2% ultrapure nitric acid blank in between samples. From the mercury calibration curve, the concentration of Hg in the 1:20 diluted tooth sample was calculated.

Sensitivity of the Method for Hg

The 2% nitric acid blank had absorbance readings of 0.0001 to 0.0002, which correspond to 1–2 ng/L, showing that the chemical reagents, acids, and water used for the analyses did not introduce any error due to possible Hg contamination. A diluted (1:20) digestate sample (0.1 g of tooth) from normal children gave absorbances in the range of 0.0025 to 0.040 absorbance units, which was at least 10- to 200-fold higher than the 2% nitric acid blank values. Thus, this technique is sensitive and selective, and well tested for the measurements of Hg metal in teeth in the micrograms per gram range (Tvinnereim et al., 2000).

Analysis of Lead (Pb) Metal

Our laboratory has been certified for the routine measurements of lead (Pb) metal in human tissues, paint chips, and dust samples for the last 20 yr. Each tooth digestate sample was further diluted suitably with 0.5 *N* ultrapure nitric acid prior to analysis. Samples diluted 1:5 (v/v) and 1:10 (v/v) were analyzed using a Perkin Elmer model 5100 graphite furnace atomic absorption spectrophotometer (GFAAS). The calibration standards for Pb were 0, 5, 10, 20, and 40 ppb (μg/L) and the wavelength used was 283.3 nm. This method is sensitive and selective, and reliable for the measurements of Pb metal in teeth in the micrograms per gram range (Tvinnereim et al. 2000).

Analysis of Zinc (Zn) Metal

Our laboratory has been analyzing zinc (Zn) metal in human tissues for the last 20 yr. Each tooth digestate sample was further diluted suitably with 0.5 *N* ultrapure nitric acid prior to analysis. Samples diluted 1:20 (v/v) and 1:40 (v/v) were analyzed using a Perkin Elmer 5100 model flame atomic absorption spectrophotometer (flame AA). The calibration standards for Zn were 0, 50, 100, 200, and 300 ppb (μg/L) and the wavelength used was 213.9 nm. This method is sensitive and selective, and reliable for the measurements of Zn metal in teeth in the micrograms per gram range (Tvinnereim et al., 2000).

RESULTS

Table 2 lists the results of the measurements of mercury, lead, and zinc in the teeth. The teeth of the children with autism had a 2.1-fold higher mean level of mercury, and a 3.1-fold higher median level of mercury. The teeth of the children with autism had levels of lead that were slightly higher than the

TABLE 2
Baby Tooth Analysis in Children with Autism Versus Typical Control Children

Component	Autism	Controls
Hg, mean	0.15 ± 0.11**	0.07 ± 0.06
Hg, median	0.14	0.05
Pb, mean	0.38 ± 0.32	0.29 ± 0.14
Pb, median	0.3	0.26
Zn, mean	100 ± 20	98 ± 16
Zn, median	93	96

Note. Units are μg/g.
**Significant difference from control ($p < .05$).

controls, but the difference was not statistically significant. The teeth of the children with autism had very similar levels of zinc compared to the control children.

Table 3 lists the results of the medical history questionnaire. The autism group had similar levels of maternal seafood consumption, number of maternal dental fillings present during pregnancy, and number of maternal dental fillings placed during pregnancy (very rare, only one instance in the autism group and one in the control group). Both groups also had very few instances of mercury-based fillings in other teeth at the time the tooth was tested (one child in the autism group had two mercury amalgam fillings, and one child in the control group had one mercury amalgam filling in the non-tested teeth). This is important for quality of the data, as mercury fillings in other teeth could affect the level in the tooth tested.

TABLE 3
Medical History of Children with Autism Versus Controls
Values Listed are Averages and Standard Deviations

Parameter	Autism	Controls
Maternal fish consumption (servings/month)	2.2 ± 2.9	2.4 ± 2.7
Maternal Hg fillings	4.8 ± 4.4	5.3 ± 3.6
Maternal Hg fillings placed during pregnancy	0.1 ± 0.3	0.1 ± 0.3
Number of Hg fillings in child's mouth	0.1 ± 0.5	0.1 ± 0.3
Anti-Rho D immunoglobulin	0%**	36%
Antibiotic use during pregnancy[a]	0.3 ± 0.5	0.2
Antibiotic usage 0–6 mo[a]	1.1 ± 1.3**	0.4 ± 0.5
Antibiotic usage 7–12 mo[a]	2.5 ± 1.7***	1.1 ± 1.1
Antibiotic usage 13–24 mo[a,c]	3.8 ± 5.4	2.3 ± 2.3
Antibiotic usage 24–36 mo[a]	3.0 ± 4.5	1.4 ± 1.3
Antibiotic usage 36–48 mo[a]	1.2 ± 1.3	1.2 ± 1.8
Total antibiotic usage 0–12 mo[a]	3.6 ± 2.4***	1.5 ± 1.5
Total antibiotic usage 0–36 mo[a]	10.8 ± 9.5*	5.1 ± 4.3
Severity of paint consumption[b]	0.3 ± 0.6	0.1 ± 0.3

[a]Units for antibiotic usage are in rounds, where each round was defined as approximately 10 days.
[b]Severity scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe.
*Trends towards significant difference from control (p<.1).
**Significant difference from controls (p<0.05).
***Very significant difference from controls (p<0.01).

The children with autism had markedly higher levels of antibiotic usage at ages 6–12 mo and possibly at ages 0–6 mo. They also had quantitatively higher levels of oral antibiotic usage at ages 12–24 mo and 24–36 mo, but those differences were not statistically significant. At ages 36–48 mo both groups had similar antibiotic usage levels. Overall, summing the total oral antibiotic usage for multiple time periods, there was markedly higher oral antibiotic usage for the time 0–12 mo and possibly for 0–36 mo. The parents reported that the vast majority of the usage of oral antibiotics was for otitis media (ear infections).

The children with autism were reported to have a higher incidence of eating paint (two mild cases, one moderate case, vs. one mild case in the controls), but the difference was not statistically significant.

The typical group in our study had a significantly higher reported usage of anti-Rho-D immune globulins during pregnancy (4 of 11 vs. 0 of the 15 children with autism). Since the incidence in the general population is much lower than in our control group, this difference is likely due to the small size of our control group. It was not possible to determine the mercury content of those shots retrospectively.

DISCUSSION

The two- to threefold higher level of mercury in the baby teeth of children with autism is important because it strongly suggests that they had a higher body burden of mercury during several years of prenatal/infant development. Since mercury is a potent neurodevelopmental toxin that produces many of the symptoms observed in autism (Bernard et al., 2001), this higher body burden of mercury may have exacerbated or produced the development of autism in some of the children in this study.

It is important to point out that similar measurements of the level of lead in baby teeth correlate strongly with the severity of the symptoms of lead poisoning (Needleman et al., 1974).

Two of the major sources of mercury exposure, namely, maternal seafood consumption (Sweet & Zelikoff, 2001; Ratcliffe et al., 1996) and maternal dental fillings, were similar in the children with autism versus the controls. Regarding their third major source of exposure, thimerosal (a mercury-based preservative) in childhood vaccines, as discussed in the introduction, there is a disagreement in the literature about whether or not children with autism were more likely or not to have received thimerosal-containing vaccines. It was not feasible in this retrospective study to obtain sufficient vaccination records

to determine if there was a difference in the amount of thimerosal-containing vaccines received by the children with autism versus typical children.

Exposure from maternal dental amalgams is relatively constant, whereas exposure from seafood or vaccines occurs in brief bursts that will be more toxic than a similar dose given over a longer period of time. It is important to realize that the tooth measurements represent an average over several years of prenatal/infant development, so there were likely time periods when the exposure was even higher, and hence even more toxic during that time.

The major difference in the medical histories of the children with autism was that they had a much higher usage of antibiotics, especially during the first 12 mo of life. This is important since a study of rats found that oral antibiotics almost completely stop the excretion of mercury (Rowland et al., 1984). Specifically, oral antibiotics will reduce the amount of normal gut flora (which demethylate methylmercury) and may increase the amount of yeast and *E. coli* (which methylate inorganic mercury), resulting in both higher absorption and decreased excretion of mercury. Other factors, such as the lower levels of glutathione and higher levels of oxidative stress reported in children with autism, will also contribute to a decreased ability to excrete mercury and hence result in a higher body burden.

Finally, the increased usage of oral antibiotics may cause other problems as well. A study by Haley (2005) found that one antibiotic, neomyosin, enhanced the toxicity of thimerosal to neurons in a cell culture. High oral antibiotic usage might also be related to the chronic gastrointestinal problems reported in approximately 50% of children with autism. Those gut problems may produce pain and suffering that worsen behavior and attention, and hence exacerbate some of the symptoms of autism.

Our results of roughly twofold elevated mercury in children with autism are consistent with a study Nataf et al. (2006), who found two- to threefold higher levels of urinary precoproporphyrins (a specific marker for body burden of mercury) in 106 children with autism versus in typical children.

It is interesting to note that the median mercury level in the control teeth was 50 ppb, which is similar to the level of mercury (40–50 ppb) found by Burbacher et al. (2005) in the brains of infant monkeys following dosing of the monkeys with thimerosal in a manner designed to mimic the U.S. childhood vaccination schedule. If baby teeth levels correlate with brain levels, then this suggests that the children with autism in this small study had median brain levels of mercury in the rage of 140 ppb, which is approaching the range of what has previously been calculated as necessary to result in mercury induced neurological disorders by Takeuchi and Eto (1975). They found that levels of 260–630 ppb were able to induce Minamata disease, which was a severe form of mercury poisoning.

In conclusion, the results of this small study suggest that children with autism have a higher body burden of mercury, probably due to a decreased ability to excrete mercury that is likely in part due to high usage of oral antibiotics. The results of this small study warrant further investigation in a much larger study.

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