

Mercury and autism: Accelerating Evidence?

Joachim Mutter*, Johannes Naumann*, Rainer Schneider*¹, Harald Walach*^{1,2}
& Boyd Haley³

* Institute for Environmental Medicine and Hospital Epidemiology, University Hospital Freiburg, Germany

¹ Samuelli Institute, European Office, Freiburg, Germany

² School of Social Sciences, University of Northampton, United Kingdom

³ Department of Chemistry, Lexington, University of Kentucky, USA

Correspondence to: Joachim Mutter
Institute for Environmental Medicine and Hospital Epidemiology
University Hospital Freiburg, Hugstetter Str. 55
79106 Freiburg, GERMANY
PHONE: ++49-761-270-5489
FAX: ++49-761-270-5440
EMAIL: joachim.mutter@uniklinik-freiburg.de

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Abstract

The causes of autism and neurodevelopmental disorders are unknown. Genetic and environmental risk factors seem to be involved. Because of an observed increase in autism in the last decades, which parallels cumulative mercury exposure, it was proposed that autism may be in part caused by mercury. We review the evidence for this proposal. Several epidemiological studies failed to find a correlation between mercury exposure through thimerosal, a preservative used in vaccines, and the risk of autism. Recently, it was found that autistic children had a higher mercury exposure during pregnancy due to maternal dental amalgam and thimerosal-containing immunoglobulin shots. It was hypothesized that children with autism have a decreased detoxification capacity due to genetic polymorphism. In vitro, mercury and thimerosal in levels found several days after vaccination inhibit methionine synthetase (MS) by 50%. Normal function of MS is crucial in biochemical steps necessary for brain development, attention and production of glutathione, an important antioxidative and detoxifying agent. Repetitive doses of thimerosal leads to neurobehavioral deteriorations in autoimmune susceptible mice, increased oxidative stress and decreased intracellular levels of glutathione in vitro. Subsequently, autistic children have significantly decreased level of reduced glutathione. Promising treatments of autism involve detoxification of mercury, and supplementation of deficient metabolites.

Abbreviations

MTHFR – methylene tetrahydrofolate reductase
Hg – mercury
DMSA – dimercaptosuccinic acid
DMPS – sodium 2,3-dimercapto-1-propane sulfonate
MS – methionine synthetase
ASD – autism spectrum disorders

Introduction

Autism spectrum disorders (ASD), first described in 1943 in eleven children born in the 1930s, have increased worldwide [1,2,3,4]. All forms of mercury are neurotoxic, especially during brain development [5,6]. Thus, some authors

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assume that the increase of autism might be caused by the worldwide increase of mercury exposure through fish and industrial sources, amalgam [7] and additionally, through increased parenteral exposure to ethylmercurithiosalicylate (thimerosal), first introduced by Eli Lilly 1931 as a preservative in vaccinations [1,2,8]. Especially, in the U.S., the prevalence of autism became endemic with an increase of about 5 in 10,000 to 60 in 10,000 after three additional thimerosal-containing vaccines were introduced for newborns in the early 1990s, whereas in most other countries with a much lower autism prevalence, like Germany or Denmark, thimerosal in vaccines was reduced at the same time. In California, the autism rate increased by 634% between 1987 and 2002, which cannot be attributed to shifts in the interpretation of diagnostic criteria, migration or improved diagnostic accuracies [3,4,9]. Other developmental and behavioural disorders like attention deficit disorders (ADD) or attention deficit hyperactivity disorders (ADHD) have also increased up to 1 out of every 6 children in the U.S. [10,11]. It should be noted that in the 1990s, newborns until age of 6 months were regularly exposed to a cumulative thimerosal dose of 187,5 µg [12].

This situation seems to resemble the epidemic of Acrodynia in the last century, which affected up to 1 of 500 infants in some industrial countries. After removing a frequently used teething powder, which contained mercury as calomel (Hg_2Cl_2), acrodynia disappeared. Interestingly, calomel is one of the less toxic forms of mercury when given orally and mercury chlorid (HgCl_2), a more toxic form of inorganic mercury, is about 100-fold less toxic than ethyl mercury to neurones in vitro [13]. Beside exposure to teething powders, it was reported in 1953 that immunisations with thimerosal-containing vaccines preceded the onset of acrodynia in several cases [14].

It was not until 1999 that an elimination of thimerosal in vaccines was recommended by the U.S. Public Health Service and the American Academy of Paediatrics. Despite the recommendation, the CDC recommends thimerosal-containing flu vaccines and tetanus boosters and even the WHO promotes the use of thimerosal in vaccinations in border- or undeveloped countries [15].

It is of public interest to ask, why thimerosal and dental amalgam, which both consists of about 50% of the most toxic nonradioactive element [16] and, in the case of amalgam, additionally of other heavy metals (eg. tin, copper, silver, zinc), have been used since 70 and 170 years, respectively, and, have been allowed to bypass governmental toxicological testing. It must be noted that until today no controlled, randomized study regarding the safety of amalgam or thimerosal exists. Such a future study should consider mercury exposure through pregnancy and vaccinations, because these exposures seem to be crucial in the pathogenesis of autism [17,18]. Furthermore, there is no single study, which compares the health of individuals exposed-versus *never* exposed to mercury (from amalgam or thimerosal) with the exception of the one by Mortada

et al. [19]. As was shown by the recent debate regarding the as yet unrecognized profound adverse side effects of hormone replacement therapy, the lack of a large enough prospective controlled, randomized study may lead to false conclusions. Against this background it is interesting to note that several scientists from the FDA, NIH, and CDC may have been influenced by vaccine manufacturers or dental boards [15, 20–24]. Despite this information, the Institute of Medicine of the U.S. concluded recently that there is no relationship between thimerosal and autism, and that no further studies should be conducted to evaluate the relationship between thimerosal and autism [25]. This was done in spite of several biological studies reporting thimerosal to have toxic properties that made it a major suspect for the recent autism epidemic. There were no biological studies presented that did not show major toxic effects of thimerosal. Thus, it is pertinent to question why the CDC committee suggested no further research and emphasize the importance of carefully paying attention to published and unpublished data and note pertinent conflicts of interest.

Search Strategy

The data base Medline was searched using Ovid Technologies, Version rel 9.1.0 for 1966–30.8.2005 with keywords (mercur\$ or thimerosal or thiomersal or ethylmercur\$) and (autism or neurodevelopment\$ or neurotoxic\$ or autoimmun\$). This search was supplemented from the bibliography of retrieved articles. Also, we searched the internet using google. We performed a multidisciplinary review of the material by researchers with different leanings and preconceptions.

Reduced mercury levels in hair of autistics despite higher mercury exposure?

Holmes et al. [17] and Hu et al. [26] found that mercury levels in the first babies' haircut of 94 autistic children were significantly lower (about 8-fold less) than in 49 normal controls. This was unexpected because the autistic children had been exposed to significantly higher mercury levels through maternal dental amalgam and thimerosal containing immunoglobulins during pregnancy [17]. Considering the mothers with 8 to 15 amalgams, the birth hair ratio was 12 times higher in the normal versus autistic children. In contrast to iatrogenic mercury exposure during pregnancy, no correlation between maternal fish consumption and the risk of autism for their children was reported [17]. It was assumed that autistic children do not effectively excrete mercury from intracellular locations into blood during pregnancy and shortly after birth, thus showing less mercury in first haircut [17]. Further interpretations of the results of Holmes et al. [17] were discussed recently [18,27,28]. In haircuts from 40 older children with autism, other authors found elevated levels of mercury, lead and uranium compared to 40 normal controls [29]. Other toxic metals like aluminium, arsenic, cadmium or beryllium showed no difference [29].

Enhanced susceptibility, exposure and toxicology to mercury

The process of cysteine and glutathione synthesis, which are crucial for natural mercury detoxification, are reduced in autistic children, possibly due to genetic polymorphisms [13,30]. Therefore, autistics have 20% lower plasma levels of cysteine and 54% lower levels of glutathione, which, among others, adversely affect their ability to detoxify and excrete metals like mercury [13,31]. This may lead to higher Hg concentrations in tissues like the nervous system and lead also to a longer half-life of mercury, compared with children with normal levels of cysteine and glutathione [13,18]. As was shown by Bradstreet and colleagues [15,32] in a study involving 221 autistics, vaccinated autistics showed about 6-fold increase in urinary mercury excretion compared with normal controls after appropriate mobilisation with DMSA. Interestingly, lead and cadmium levels did not differ between the groups [15,32].

Delayed detoxification of mercury severely impairs methylation reactions (like DNA-, RNA-, cobalamin-, protein-, phospholipids-, histones-, and neurotransmitter-methylation), which further adversely affects growth factor derived development of the brain and attention performance. Phospholipid methylation, which is crucial for attention, is impaired in autistic and attention deficit hyperactivity disorders [13]. Ethyl mercury in levels reached ten days after vaccination in an *in vivo* study [33] produced an inhibition of methylation of more than 50% *in vitro* [13,30]. *In vitro* studies have also shown that thimerosal was more than 100-fold more potent than inorganic mercury in inhibiting such essential methylation reactions [30]. Also, inorganic mercury was found to be 10-fold more potent than lead in inhibition of neuronal micro-tubular function, which is crucial for nerve growth and transport of neurotransmitters [34,35]. Inorganic mercury also leads to growth inhibition and denudation of neuronal growth cones by inducing the abnormal aggregation of tubulin [36]. This was seen already 15 min. after exposure to very low levels of inorganic mercury, levels which were about 100–1000-fold lower than found in brains of individuals with dental amalgam or Alzheimer's disease [37]. This observation fits in with earlier reports that the microtubulin protein, tubulin, was on average 80% less viable in Alzheimer's diseased brain than in age-matched normal controls [79] and that this abnormality could be induced in the brains of rats by exposure to mercury vapor [80]. It was also shown *in vitro* that low concentrations of thimerosal, which can occur after vaccination, induce membrane- and DNA-damage and initiate apoptosis in human neurons [38]. Humphrey and co-workers [39] have shown recently that this apoptosis is mediated by mitochondria in an *in vitro* study. Genotoxic effects were also observed in another *in vitro* study [49]. Furthermore, autistics seem to be genetically more susceptible for toxin derived inhibition of methylation processes [13]. As an example, polymorphism of methylen tetrahydrofolate reductase (MTHFR) gene was more frequent in chil-

dren with autism [41]. It was assumed consequently that about 15% of the population may show enhanced susceptibility to mercury exposure [15].

Studies on monkeys have shown that ethyl mercury, like mercury vapour, crosses the cell membrane and is then converted intracellularly to inorganic mercury (Hg^{2+}), which accumulates preferentially in the brain and the kidneys [42]. Intracellular accumulation of mercury was shown to be higher for ethyl- compared to methyl mercury but clearance rate was higher for ethyl mercury [42]. There were no differences in the toxico-kinetics of methyl mercury as compared with *i.m.* thimerosal in animals [43]. In contrast, another study in immature mice found higher mercury levels in blood, brain and kidneys after methyl mercury exposure compared to ethyl mercury exposure [44]. In this study a form of methyl mercury that may be 20 times more toxic than the one found in fish was used [37]. However, it seems to be likely that toxico-kinetic studies in mice and monkeys are not comparable due to metabolic differences. Mice, in contrast to primates, for instance, are able to produce grams of vitamin C, a potent antioxidant, especially when under stress.

Picchichero et al. [33] argue that ethyl mercury administered through vaccines is eliminated rapidly from the blood and rapidly excreted in stool. In this study, only 33 children at age of 2 and 6 months were used for blood mercury assessment, thus potentially overlooking individuals with impaired mercury excretion. Blood levels were obtained days to weeks after vaccination, thus peak levels could not have been measured. The mercury dose was much lower than through vaccination in the 1990s. Nonetheless and somewhat weakly founded, the authors concluded from this data, "This study gives comforting reassurance about the safety of ethyl mercury as a preservative in childhood vaccines" [33]. Others have already criticised this study [45] or mention points of possible conflicts of interests [46].

Despite of that, as described above, levels of ethyl mercury found 8 days after vaccination [33] leads to 50% inhibition of methionine synthetase (MS) *in vitro* [13,30]. An earlier study using rabbits injected with thimerosal containing radioactive mercury showed that from hour 1 post injection to hour 6 the level of radioactive mercury in the blood dropped over 75% while from hour 2 post injection to hour 6 there were significantly increased radioactivity levels in the fetal brain, liver and kidney [81]. This latter study strongly implies that a rapid drop in blood mercury levels from thimerosal injection is due to uptake by other organs of the body and not due to excretion.

Therefore, the implications by others of thimerosal safety based on shorter blood levels half-lives [33] suffers from a lack of logic. Additionally, in a recent study, thimerosal was a potent inhibitor of phagocytosis by mononuclear phagocytes inhibiting the process at low nanomolar levels [82]. Phagocytosis is the first step of the innate immune system and it seems likely that injection of thimerosal would therefore inhibit an

infants immune system as they only have the innate system until the acquired system is built up by aging.

In contrast to astrocytes or hepatocytes, neurons are unable to synthesize cysteine, the rate limiting amino acid for glutathione synthesis [47]. Thus, neurons are most sensitive to mercury toxicity since, as mentioned above, glutathione is the major intracellular agent in mercury- and heavy metal detoxification [18]. It is well known that thimerosal and inorganic mercury deplete intracellular glutathione levels, which subsequently leads to increased oxidative stress, neuronal cytotoxicity and death [47–50]. The toxic effects of ethyl mercury seem to be similar to those of methyl mercury as indicated by James et al. [47]. Of 13 children treated with a thimerosal containing topological “antiseptic” for umbilical cord infection, 10 died [83]. This antiseptic was used world-wide on adolescents and adults with very little reported negative effects. This strongly implied that infants were much more susceptible to thimerosal toxicity than older humans and question any decision to inject this material into infants.

Autoimmunity and inflammation

An autoimmune pathogenesis of autism, triggered by bacterial antigens, dietary peptides and mercury was proposed by Vojdani et al. [51]. Autopsied brains of autistics demonstrated chronic activation of microglia and astrocytes, thus indicating an autoimmune processes [52]. Note that mercury is a potent inducer of haptene mediated autoimmune reactions [7,16], in particular when given repetitively, which is the case in children exposed early to iatrogenic mercury during pregnancy (through maternal amalgam and thimerosal) and then, again after birth through vaccinations. In autoimmune sensitive mouse strains, vaccinations with thimerosal in doses and timing equivalent to the paediatric immunisation schedule of the U.S. in 2001 lead to profound behavioural and neuropathologic disturbances, which are comparable to autism [53]. In a preliminary report, the autoimmune reaction persists long after mercury can no longer be detected [54]. It is important to note that thimerosal doses applied in this study were lower than the ones given to newborns in the 1990s in the U.S. It was also shown, that the risk of thimerosal sensitisation is increased in individuals with gene deletions of the glutathione S-transferases M1 and T1 [55]. Recently, it was shown on genetically metal-susceptible mice that, in contrast to methyl mercury, thimerosal leads to strong autoimmunity [56,57]. Mercury also increases neurotoxicity of glutamate [37]. Interestingly, microglial activation and enhanced glutamate cytotoxicity has been described in many neurodegenerative diseases. As a side note, the risk of multiple sclerosis, another autoimmune disease, may be enhanced through additional vaccinations with thimerosal containing Hepatitis B vaccines [58].

Synergistic toxicity and the role of steroids

In vitro studies point to the possibility that neurotoxicity of mercury or thimerosal is enhanced through mercurials but also through neomycin and aluminum-hydroxid (also used in vaccines) and testosterone, while estrogen decreases the toxic effects [59]. In another study, estrogen is shown to decrease the toxicity of inorganic mercury on neurones [50]. These observations may explain the 4 to 1 ratio of boys to girls in autism [60] and leads to possible therapies. It was also proposed that lead might play a pathogenetic role in neurodevelopment disorders and autism. Combination of lead and mercury resulted in a synergistic increase of toxicity in vitro, respectively [61].

Epidemiological studies

It should be noted that epidemiological studies and studies using mercury levels in blood and urine, which do not consider genetic susceptibility factors, autoimmunity reactions and mercury exposure during pregnancy (amalgam, thimerosal), are not able to detect a statistically significant effect, even if there is one.

Nevertheless, some studies have shown a correlation between mercury exposure and the risk of autism. Using data from the Vaccine Adverse Events Reporting System (VAERS), Vaccine Safety Data (VSD), Biological Surveillance Summaries of the Centers for Disease Control and Prevention (CDC) and the U.S. Department of Education datasets, a significant correlation was found between the risk of neurodevelopmental disorders and the cumulative thimerosal dose given parenterally, which exceeds (11–150 fold) the EPA and FDA established maximum permitted levels for the daily oral ingestion of methyl mercury [11,21,62–65].

In a first analysis (“Generation Zero analysis”) of the Vaccine Safety Datalink datasets (VSD), Verstraeten et al. had described a significant increase of autism risk in children at one month, with the highest mercury exposure levels compared with children with no exposure [22]. In four subsequent separate generations of the analysis, which involve the exclusion of children with no thimerosal exposure and less than two polio vaccines, the statistical significance disappeared [21,22,66]. The prevalence of autism in Amish People, a population which deny vaccination to their children and with low incidence of caries, seem to be very low in comparison to the general prevalence in the U.S. in a preliminary report [67]. However, also other cultural, environmental or behavioural factors might explain this fact.

Other epidemiological studies did not find an association between thimerosal containing vaccines and autism in United Kingdom [68] and in Denmark [69–71]. Most of these studies did not use controls, which were never exposed to mercury [72]. Additionally, maternal mercury exposure during pregnancy was not measured. We analyse a prominent example below.

Madsen et al. [69] compare the number of newly recorded autism cases prior to 1992, when thimerosal-containing vaccines were used, with those after 1992, when such vaccines were no longer produced in Denmark. The authors observe a rise in autism rates after removal of thimerosal, and thus conclude that thimerosal plays no role in the aetiology of autism [69]. Some important methodical flaws must be noted in this context:

1. Autism counts were based on hospitalized, inpatient records in the first cohort and then changed in the middle of the study period (1995) to include outpatient records. Therefore, the purported increases after 1994 may be explained by the additional recruitment of an existing autism population that did not require hospitalisation.
2. After 1992, the registry added in patients from a large Copenhagen clinic, which accounted for 20% of the caseload in Denmark. The patients from this clinic were excluded prior to 1992.
3. The diagnostic category changed after 1993 from "psychosis proto-infantilis" of ICD-8 (code 299) to "childhood autism" of ICD-10. Another paper using the same inpatient registry reports that the psychosis proto-infantilis category includes *inpatient* cases that do not fulfil the criteria for autism [73].
4. Many of the children were between 7–9 years old, and most were over 4 years old, when recorded. But the onset of autism must occur, by definition in the diagnostic criteria, before three years of age. The most widely used approach to assessing autism trends is to use year of birth as the "incidence time"
5. Another recent study performed by Madsen et al. [74] reported Danish autism rates of 6 per 10,000 for children born in the 1990s. These Danish rates are very low in the 1990s compared to the U.S. [12]. Madsen et al. [69] report also inpatient rates for the pre-1993 "psychosis proto-infantilis" at well below 1 per 10,000. This low rate would contradict the single published survey of autism rates from Denmark, which indicated an autism rate of over 4 per 10,000 as far back as the 1950s [75].
6. Additional confounders were present in the U.S. with high prevalence of autism that were not present in Denmark: Between 1970–92, the only childhood vaccine given in Denmark until 5 months of age was the monovalent pertussis vaccine. In the United States, children were exposed to multiple doses of diphtheria, pertussis, tetanus, polio, hepatitis B and haemophilus influenza B (Hib) vaccines before five months of age in the 1990s. Additionally, Denmark did not administer thimerosal-containing Rho-D immunoglobulin during pregnancy, which may increase the risk for the development of autism [17].

The epidemiological studies that seem to support the missing of a causal link between thimerosal and autism, are thus inconclusive, and some of them are fraught with methodological flaws or inconsistencies. They cannot be used to lay the topic at rest. The situ-

ation rather calls for a joint effort to clarify the points in question. Meanwhile, given the lack of effective treatment options in autism, one might want to use the evidence reviewed here for an experimental form of treatment.

Promising treatments of autistics

According to preliminary results, chelation of heavy metals is now the preferred treatment therapy developed by the Autism Think Tank of the Defeat Autism Now Foundation, which now considers autism as a curable disease based on the observed reversal of diagnosis of numerous children after such treatment [76]. Enhanced detoxification through hyperbaric oxygen therapy and transdermal usage of Dimercaptopropansulfonate (DMPS) seem to be effective treatment options for autistics according to Buttar [77] and Harch [78]. Furthermore, preliminary results suggests that substitution of metabolites important for intracellular glutathione synthesis and methylation, which lacks in autistic children due to mercury exposure and genetic sensitivity [31], like methylcobalamin, s-adenyl-methionine and tetrahydrofolic acid, leads to improvement of symptoms in a about 80% of autistic children [13,31]. Subsequently, these agents were able to normalise the blood levels of glutathione and cysteine in autistic children [31].

Conclusion

Taken together, all the above mentioned data from experimental, clinical and partly from epidemiological studies appear to show that repetitive mercury exposure during pregnancy (through thimerosal and dental amalgam), and after birth, through thimerosal containing vaccinations in genetically susceptible individuals is one potential pathogenetic factor in autism. Other metals and toxicants, partly present in vaccines, and the hormonal situation might have synergistic effects with mercury. This has not been officially acknowledged. Therefore it is mandatory to perform further studies that address this issue with sound methodology and through research uninfluenced by commercial, professional or political interests. Given the widespread use of mercury in medical products, even a small frequency of pathological side effects have a significant impact to public health. Therefore, for preventive purposes, it is mandatory to avoid further use of mercury in medical products in industrial and undeveloped countries.

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