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TOXICOLOGY OF NEURODEVELOPMENTAL DISORDERS

The role of mercury in the pathogenesis of autism

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder of unknown etiology in most cases. Studies of monozygotic twins report an average 60% concordance rate, indicating a role for both genetic and environmental factors in disease expression.[1] Recent reviews in environmental health have suggested that early exposure to hazardous substances may underlie some cases of neurodevelopmental disorders, including ADHD, learning disabilities, and speech/language difficulties.[2] In 1999, thimerosal used as a vaccine preservative was identified as a widespread source of organic mercury exposure in infants.[3] Mercury (Hg), a heavy metal, is considered highly neurotoxic.[4] The amount of mercury in vaccines, while small, exceeded USEPA safety guidelines on a cumulative basis.[3] Certain individuals may exhibit severe adverse reactions to low doses of Hg which are otherwise largely benign to the majority of those exposed.[5] Some individuals with idiopathic autism spectrum disorder may represent such a sensitive population. As summarized in this paper, disease characteristics suggest this possibility: (a) ASD traits are known to arise from mercury exposure; (b) onset of ASD symptoms is temporally associated with administration of immunizations; (c) the reported increase in the prevalence of autism in the 1990s closely follows the introduction of two mercury-containing vaccines; and (d) elevated mercury has been detected in biological samples of autistic patients. Since ASD may now affect as many as one in 150 US children,[6] and since thimerosal is still used in many products worldwide, confirmation of thimerosal as an environmental agent in autism pathogenesis has important societal and patient implications.

Thimerosal is comprised of 49.6% ethylmercury (EtHg) by weight. Until early 2001, it was a component of most Hepatitis B, *Haemophilus influenzae* type B (HiB), and Diphtheria/Tetanus/Pertussis (DTP or DTaP) vaccines. These vaccines were routinely administered to infants at birth and at ages 2, 4, 6, and 15–18 months. The cumulative amount of mercury injected in the first 6 months of life was 187.5 μg.[3] Although the pharmacokinetics of EtHg have not been well studied, its toxicity is believed to be similar to MeHg,[3] for which pharmacokinetic models have been developed to estimate the risk of adverse outcomes based on Hg levels in standard biomarkers of hair or blood. Using such a model, the EtHg from the recommended vaccines is predicted to raise hair mercury levels above USEPA guidelines of 1 ppm for up to one year and, in some infants, to elevate Hg levels to 10 ppm, which is the lowest threshold for adverse outcomes in children exposed prenatally to MeHg.[4,7] That thimerosal-containing vaccines can significantly raise blood Hg levels in infants has been demonstrated *in vivo*.[8] Endpoints for adverse effects at low doses of MeHg have been in domains characteristic of ASD and include lowered performance on tests of attention, memory, language, and fine motor skills.[9–11] A CDC analysis of computerized HMO medical records found statistically significant associations between increased exposure to thimerosal from infant immunizations and attention deficit disorder, speech/language delay, and tics.[12] Traits characteristic of these disorders are common features of ASD.[10,11]

A review of medical literature has shown that exposure to mercury, whether organic or inorganic, can give rise to the symptoms and traits defining or commonly found in ASD individuals.[13] Mercury can cause impairments in social interaction, communication difficulties, and repetitive and stereotyped patterns of behavior, which comprise the three DSM-IV autism diagnostic criteria. Additionally, mercury can induce features prominent in ASD such as sensory abnormalities, emotional/psychological changes, movement disorder, impairments in abstract or complex thinking, severe sleep disturbances, and self injurious behavior. Males are more affected than females in both conditions. Physiological abnormalities more common in ASD populations and known to be caused by mercury exposure include gastrointestinal problems, autonomic nervous system disturbance, unusual EEG activity, immune system alterations, irregularities in neurotransmitter systems, and non-specific brain lesions.

The discovery and increase in the reported prevalence of autism parallels the introduction and spread of thimerosal-containing vaccines. Autism was first described in 1943 among children born in the 1930s.[14] Thimerosal was first added to childhood vaccines in the 1930s.[3] Prior to 1970, classic autism was estimated to occur in approximately 1 in 2000 children, while the average prevalence reported by studies from 1970 to 1990 is 1 in 1000.[15] This period was a time of increased immunization in the developed world. By 1995, the National Institutes of Health reported an autism prevalence of 1 in 500 children,[16] and in 2000 the CDC identified approximately 1 in 250 children with classic autism in one New Jersey town.[6] It was in the early 1990s that the thimerosal-containing HiB and Hepatitis B vaccines became part of the routine infant schedule.[3]

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The onset of autistic symptoms generally follows the administration of thimerosal in vaccines, and symptom emergence is consistent with expression of mercury toxicity. As noted previously, mercury exposure from vaccines began at birth and continued at approximately 2, 4, 6, and 15 months. The great majority of autistic children appear normal at birth,[1] but subtle abnormalities in movement have been observed as early as 4 months of age[17] and sensory-motor disturbances detected at 9–12 months.[18] The full array of diagnostic impairments is generally evident by 15–24 months.[18] Symptoms of mercury toxicity can arise suddenly in especially sensitive or sensitized individuals,[5] but expression is usually gradual.[19] Autistic symptoms usually emerge gradually although there are instances of sudden onset.[10]

Nearly all American children are immunized but less than 1% have ASD. This pattern is consistent with response to low dose mercury exposure, which is characterized by wide interindividual variation.[4] Acrodynia, a severe disease of early childhood prevalent 50 years ago, illustrates this phenomenon. Acrodynia was caused by small amounts of mercuric chloride in teething powders. Although use of the powders was widespread, only a small percentage of children developed the disease.[5] Occasionally siblings of acrodynia patients succumbed as well, and a genetic link was suggested.[5] Studies on mice and rats have demonstrated the role of genetics in interindividual differences in Hg sensitivity, with most strains resistant, some strains high responders, and still others intermediate.[20] Some high responder strains are those prone to autoimmune disorders. ASD is highly heritable[1] and occurs more frequently than expected in families with autoimmune diseases.[21]

Clinicians treating autistic patients have reported elevated mercury levels in urine post challenge with standard heavy metal chelators and improvement in function after mercury removal from chelation.[22,23] In one case study, the only known mercury exposure was from vaccines. These preliminary reports suggest that mercury may persist in tissue in some autistic individuals and may contribute to autistic symptoms.

These findings support a hypothesis that mercury in vaccines may be a factor in the pathogenesis of autism. Understanding of the underlying biological mechanisms of thimerosal toxicity in populations genetically susceptible to mercury's effects might lead to effective medical treatments for autistic individuals. A positive finding of a thimerosal role would also give added impetus to the removal of this non-essential compound from health and medical products in which it can still be found. These products include many pediatric vaccines used in developing nations, all US influenza vaccines, all mono- and divalent diphtheria and tetanus vaccines, some immunoglobulins routinely given to pregnant Rh-negative women, and some over-the-counter ear drops and nasal sprays.

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