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Review

The relationship between mercury and autism: A comprehensive review and discussion

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ABSTRACT

The brain pathology in autism spectrum disorders (ASD) indicates marked and ongoing inflammatory reactivity with concomitant neuronal damage. These findings are suggestive of neuronal insult as a result of external factors, rather than some type of developmental mishap. Various xenobiotics have been suggested as possible causes of this pathology. In a recent review, the top ten environmental compounds suspected of causing autism and learning disabilities were listed and they included: lead, methylmercury, polychorinated biphenyls, organophosphate pesticides, organochlorine pesticides, endocrine disruptors, automotive exhaust, polycyclic aromatic hydrocarbons, polybrominated diphenyl ethers, and perfluorinated compounds. This current review, however, will focus specifically on mercury exposure and ASD by conducting a comprehensive literature search of original studies in humans that examine the potential relationship between mercury and ASD, categorizing, summarizing, and discussing the published research that addresses this topic. This review found 91 studies that examine the potential relationship between mercury and ASD from 1999 to February 2016. Of these studies, the vast majority (74%) suggest that mercury is a risk factor for ASD, revealing both direct and indirect effects. The preponderance of the evidence indicates that mercury exposure is causal and/or contributory in ASD.

Contents

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1. Introduction

Autism spectrum disorders (ASD) is defined by persistent deficits in social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities [1]. Although an ASD diagnosis is defined behaviorally by the American Psychiatric Association, other features, more physical or health related, are associated with an ASD diagnosis.

ASD is considered to be heritable with complex inheritance and genetic heterogeneity [2]; however, a consensus is emerging that the total fraction of ASD attributable to genetic inheritance may only be 30–40% [3]. Chromosomal microarray testing reveals that approximately 80% of children with ASD have a normal genome [4]. Of the remaining 20%, approximately half of those have various polymorphisms of unknown significance and the other half of those have de novo mutations with little or no commonality. These findings suggest that non-genetic factors have a significant role in the etiology of ASD.

In addition, many brain pathology studies indicate marked and ongoing neuroinflammation in ASD [5–14]. This type of reactive pathology is suggestive of insult and with concomitant neuronal damage [15] rather than some type of developmental mishap as has been suggested [16,17]. A developmental mishap does not explain the evidence of neuroinflammatory reactivity and neuronal damage within the brain in ASD which includes: (1) activated microglia (immune macrophages within the brain); (2) activated astrocytes (a broad class of cells that support neurons within the brain); (3) elevated levels of glial fibrillary acidic protein (GFAP; an intermediate filament protein that is expressed by astrocytes possibly to maintain structural integrity, known to be upregulated in response to injury); (4) increased oxidative stress (e.g., elevated neurotrophin-3, elevated 3-nitrotyrosine, and oxidized glutathione levels, etc.); (5) elevated levels of 8-oxo-guanosine (a product of oxidative damage to DNA); (6) elevated proinflammatory cytokines (e.g., tumor necrosis factor alpha, interleukin 6, and granulocyte-macrophage colony-stimulating factor); (7) aberrant expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB, a protein complex that regulates transcription and reflects the cellular response to stress); and (8) neuronal cell loss [8,15,18–21]. Nor does it explain the classic regression found in autism that occurs around 15–22 months of age where these children lose previously acquired neurological function, such as language and other interactive skills and abilities [22].

Various xenobiotics have been suggested as causal agents in the pathology of ASD. In a highly-cited review, Grandjean and Landrigan [23] identified five industrial chemicals as developmental neurotoxicants based on epidemiological evidence: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. In an Environmental Health Perspectives editorial, Landrigan et al. [3] note that neurodevelopmental disabilities affect over 10% of children born in the US each year and listed the top ten environmental compounds suspected of causing autism and learning disabilities: lead, methylmercury, polychorinated biphenyls, organophosphate pesticides, organochlorine pesticides, endocrine disruptors such as phthalates, automotive exhaust, polycyclic aromatic hydrocarbons, polybrominated diphenyl ethers (brominated flame retardants), and perfluorinated compounds. Both teams specify "methylmercury" rather than the broader class "mercury", possibly because more studies exist on the methylmercury form (found in fish), and possibly because ethylmercury (found in Thimerosal-containing vaccines) and mercury vapor (released from dental amalgams) are unpopular targets.

Of the numerous studies that have been conducted over the last three decades that examine the relationship between mercury exposure and ASD, the majority of the studies found that mercury is a risk factor for ASD. However, there are also several studies that suggest mercury is *not* a risk factor for ASD, therefore evaluating the totality of the evidence is not easy.

This review will focus on mercury exposure and ASD by conducting a comprehensive literature search of original studies in humans that examine the potential relationship between mercury and ASD from 1999 to February 2016, including studies of human tissue levels of mercury, studies of biomarkers for mercury exposure, and epidemiological studies. The literature search includes published original research studies on mercury and ASD, from PubMed and Google Scholar; however, references cited in identified publications were also searched to locate additional studies. Search words included: autism, autism spectrum disorders, ASD, pervasive developmental disorders, PDD, mercury, Hg, Thimerosal, metals, methyl-mercury, ethyl-mercury, inorganic-Hg, mercury chloride.

This review will categorize, summarize, and discuss the published research that addresses this topic. Each section of this paper will present an area of scientific inquiry on the issue and the studies which have been published on it. An associated table(s) in each section will briefly describe the pertinent studies and their findings. This review will begin with studies that examine brain biomarkers and mercury levels in children with ASD.

2. Brain biomarkers and mercury levels in children with ASD

Many studies show production of numerous auto-antibodies which react with specific brain proteins and brain tissues in children with ASD. These auto-antibodies can also act to alter the function of the respective brain tissue [24]. In addition, studies show that anti-brain antibodies are associated with more severe cognitive and behavioral profiles in children with ASD [25]. Moreover, recent studies (see Table 1) have found that certain brain auto-antibodies correlate with mercury levels in children with ASD [26,27].

This finding is biologically plausible since studies show that mercury exposure, especially to the mercury-based compound Thimerosal, can cause autoimmune dysfunction. For example, Voldani et al. [28] conducted a study that demonstrated certain dietary peptides, bacterial toxins, and xenobiotics, such as Thimerosal, can bind to lymphocyte receptors and/or tissue enzymes, resulting in autoimmune reaction in children with autism. Havarinasab et al. [29] also found that Thimerosal can induce (in genetically susceptible mice) a systemic autoimmune syndrome.