Review

Heavy Metal Toxicity: A Potential Risk Factor for Autism

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Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors.[1-3] The hereditary origins of ASD remain unclear, with debates over whether it arises from multiple gene interactions or rare mutations. In the United States, autism affects 1 in 68 children, with a prevalence of one in 42 for boys and 1 in 189 for girls. This results in a gender ratio of about five boys for every girl.[4]

Numerous studies have established a correlation between autism and heavy metals. An epidemiological study revealed that the presence of airborne pollutants, particularly mercury (Hg), was associated with an elevated risk of autism.[5] Another investigation demonstrated a significant correlation between blood Hg levels and the diagnosis of autism.[6] Additionally, a study found that children with autism had double the Hg levels in their baby teeth compared to typical children.[7,8]

HEAVY METALS

While heavy metals are naturally present on Earth, they can pose serious toxic threats to all living organisms and the environment.[9,10] The increased

ABSTRACT

Autism spectrum disorder (ASD) encompasses a diverse range of conditions characterized by difficulties in social skills, repetitive behaviors, speech, and nonverbal communication. It is important to note that ASD does not have a single identifiable cause; rather, it arises from the complex interplay between genetic susceptibility and exposure to environmental factors. Impacting approximately 1% of all children, autism spectrum disorder is linked to toxic heavy metals and other potential environmental hazards that may contribute to its development, in conjunction with intricate genetic elements. This review aims to establish a connection between heavy metals and autism, presenting findings from experimental studies that investigate the relationship between heavy metal exposure and autism.

Keywords: Autism spectrum disorder, heavy metals, neurotoxicity

use of industrial products has led to a significant rise in human exposure to heavy metals over the past 50 years.[10] Heavy metal toxicity is a substantial concern, carrying various health risks. Despite lacking any biological role, the toxic effects of these metals persist in harmful forms within the human body, impacting its proper functioning.[11]

In the medical context, the definition of heavy metals disregards the atomic weights of the elements. Over sixty elements fall under the classification of toxic (heavy) metals. Examples include the commonly known Hg, manganese (Mn), iron (Fe), cobalt, nickel, copper, zinc (Zn), cadmium (Cd), arsenic (As), chromium, lead (Pb), silver, and selenium as heavy metals.[7-10]

Environmental Risk Factors for Autism

The etiology of ASD is not fully understood, reflecting the complex interaction between genetics and the environment. While genetics is a well-established risk factor, environmental contributions have gained recognition. Various environmental factors linked to ASD risk include

advanced parental age, assisted reproductive technologies, nutritional factors, maternal infections and diseases, environmental chemicals and toxicants, medications, and other conditions. Investigations focus on their impact during three crucial time windows for brain development: periconception, prenatal, and early postnatal periods. Potential protective factors against ASD development have also been explored. Recommendations for clinicians to mitigate ASD risk or severity have been proposed. Advances in molecular biology and big data approaches provide opportunities to unravel the gene-environment interplay leading to ASD development. Autistic children exhibit deficiencies in metabolizing sulfur compounds, leading to reduced detoxification of heavy metals and increased toxicity. Impaired methylation and redox homeostasis, with heightened vulnerability to oxidative stress, resemble the effects of heavy metal exposure. ASD, characterized by brain and immune dysfunction, intersects with aluminum a neurotoxin and potent immune adjuvant. Aluminum's neurotoxicity involves inducing oxidative stress and releasing deoxyribonuclease (DNase), a significant DNA damage inducer. Lead, another heavy metal, induces oxidative stress, and lipid peroxidation, alters synaptic pruning, disrupts dopaminergic function, interferes with glutamate (an excitatory neurotransmitter crucial for neuronal development), reduces hippocampal expression of protein kinase C, and causes volume loss in vital prefrontal cortex portions.[12-17]

THE LINK BETWEEN HEAVY METALS AND AUTISM

Autism formation may be affected by various impressions and one of them is the chemicals.

Some studies prove that toxicant factors may affect neuronal and behavioral development at critical developmental stages. The pathogenetic mechanisms of environmental chemical factors can involve neurotoxicity but can also extend to pathways of immune dysregulation, altered lipid metabolism, and mitochondrial dysfunction.[18,19]

There is sufficient evidence that maternal exposure to heavy metals such as Pb, Hg, Cd, and As causes an increase in neurodevelopmental disorders and restricts fetal and infant growth even at low-level exposures.[20]

Researchers investigated symptoms of the relationship between children with autism with their toxic metal body burden and red blood cell

glutathione levels. Both genetic and environmental factors have been implicated. One environmental factor that has received significant attention is the body burden of Hg, Pb, and other toxic metals.[21]

Children are vulnerable to the neurotoxic effects of chemicals, especially during the prenatal period, when there is an immature blood-brain barrier which means that rendering the developing brain more vulnerable to drugs or toxins entering the fetal circulation from the mother, neuronal growth, migration, and myelination processes that occur on a specific and rapid schedule. Moreover, some toxic substances can pass through the placental barrier and easily access the developing brain and interfere with these important processes, possibly leading to adverse outcomes.[20]

In a study, autism and heavy metals relationship was observed. Some non-inherited factors such as exposure to environmental pollutants are associated with neurodevelopmental disorders like autism. Studies reported that endocrine-disrupting compounds (EDCs), including some heavy metals, have reverse effects on fetal neurodevelopment. The study aimed to measure the amniotic fluid (AF) levels of EDCs and metals as well as the receptor transactivation induced by AF and investigate the possible link between prenatal exposure to EDCs and heavy metals and ASD risk.[21-23]

Among the measured 59 elements and metals, 16 elements including Fe, Cu, Zn, and Se were detectable in all AF samples, while eight elements, including Hg and Ag, were not detectable in any AF samples. The metals of interest such as Cr, Pb, As, Mn, and Cd were detected in 98.9%, 34.1%, 22.7%, 18.2%, and 12.5% of the AF samples, respectively. The present study showed that environmental EDCs, such as heavy metals, and their biological activities can be detected in AF, indicating that EDCs can cross the placenta and increase the potential fetal exposure to these environmental contaminants. Endocrine-disrupting compounds might modify ASD risk by influencing the hormone receptor function.[21-24]

Another study focused on the relationship between Hg and autism exposure and autism by conducting a comprehensive literature search of original studies in humans that examine the potential relationship between Hg and ASD from 1999 to 2016, including studies of human tissue levels of Hg.[25]

When looking at human tissue studies that examine the relationship between Hg and symptom severity in ASD. In the studies that examine blood

(whole blood and red blood cells) and nails, results show that the higher the Hg levels, the worse the autism symptoms.

According to a study conducted by the National Institutes of Health, baby teeth contain heavy metals in different levels between children with autism and children without autism. Researchers used twins to check genetic influences and focus on possible environmental effects of autism. The differences in metal uptake between children with and without autism were especially notable during the months just before and after the children were born. The scientists determined this by using lasers to map the growth rings in baby teeth generated during different developmental periods. Baby teeth from children with autism contain more toxic Pb and less of the essential nutrients Zn and Mn, compared to teeth from children without autism. They also observed a lower uptake of Mn in children with autism, both before and after birth. The pattern was more complex for Zn. Children with autism had lower Zn levels earlier in the womb, but these levels then increased after birth, compared to children without autism. Also, scientists said that larger replication groups are needed to confirm the relationship between heavy metals and autism.[26-29]

Another study aimed to assess the levels and possible environmental risk factors and sources of exposure to Hg, Pb, and aluminum in children with ASD as compared to their matched controls. One hundred ASD children were studied in comparison to 100 controls. All participants were subjected to clinical evaluation and measurement of Hg, Pb, and aluminum through hair analysis which reflects past exposure. The mean levels of Hg, Pb, and aluminum in the hair of autistic patients were significantly higher than controls. Mercury, Pb, and aluminum levels were positively correlated with maternal fish consumption, living near gasoline stations, and the usage of aluminum pans, respectively. Levels of Hg, Pb, and aluminum in the hair of autistic children are higher than controls. Environmental exposure to these toxic heavy metals, at key times in development, may play a causal role in autism.[30-33]

Another research study indicates that insufficient maternal Fe intake during conception is linked to an increased risk of autism in the offspring. Iron plays a crucial role in the functioning of all cells, facilitating oxygen delivery, electron transport, and enzymatic activity. Cells with high metabolic rates are particularly vulnerable to dysfunction during Fe deficiency. Pregnancy increases Fe requirements as the mother's blood volume expands, and the fetus undergoes growth and development. Iron deficiency is associated with adverse pregnancy outcomes, and the rapidly developing fetal brain is especially susceptible. Maternal Fe deficiency, hypertension, smoking, or glucose intolerance can contribute to fetal Fe deficiency. Low maternal gestational Fe intake is correlated with autism, schizophrenia, and abnormalities in offspring brain structure. Newborns with Fe deficiency exhibit compromised recognition memory, slower processing speed, and poorer bonding, persisting even after postnatal Fe repletion. Preclinical models of fetal Fe deficiency confirm acute and long-term compromises in Fe-dependent processes, including monoamine neurotransmission, neuronal growth and differentiation, myelination, and gene expression.[34-36]

In conclusion, the content outlined in this review redirects the discourse on the significance of nutrition in safeguarding childhood brain health. Rather than solely emphasizing postnatal nutrition, it underscores the importance of prenatal and even preconceptional nutrition. The argument advocates for policies that encourage maternal nutritional well-being before pregnancy, with a subsequent emphasis on providing essential nutrients such as Fe during pregnancy. This comprehensive, life-cycle approach to nutrition can be viewed as an investment in the mental health of future generations and a broader investment in society.

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