

Autism Spectrum Disorder: Role of Heavy Metals

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopment disorder characterized by altered communication, cognitive development, behavioral pattern and social skills. Autistic children are poor detoxifiers of heavy metals and hence are more prone to the toxic effects of heavy metals. The following review summarizes the current knowledge of the role of heavy metal in the pathogenesis of ASD.

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Introduction

Autism spectrum disorder (ASD) is a complex neurological and neurodevelopment disorder that begins at an early age and lasts throughout the person's life. It affects various actions of the person which includes communication, behavior pattern, social skills, speech and social interactions [1, 2]. They have behavioral characteristics like lack of interest in making eye contact, unwillingness to talk, unusual tone of voice, not sharing their enjoyable moments and repetitive behavior [3]. Since it constitutes numerous symptoms hence the name autism spectrum disorder [4]. People with autism have atypical cognitive profile such as impaired cognition and atypical visual information processing [5]. It is believed to be primarily a hereditary disorder which mostly affects children [6]. However various environmental factors may contribute to the pathogenesis of autism one of which is exposure to heavy metals. Heavy metal exposure is very common and children are more susceptible towards its risk over adults. Several studies have shown association between autism and heavy metals exposure [7]. Autistic children are poor detoxifier as they have a lower level of glutathione which is important for the detoxification of heavy metals [8]. Metals like mercury, lead, cadmium and arsenic containing sulfhydryl groups are more likely to cause autism. Other metals like aluminum, lead, antimony and mercury also increases the risk of autism [9]. Here we review the latest evidence on role of heavy metals on autism spectrum disorder.

Heavy metals and autism spectrum disorder

Lower level of glutathione has been reported in autistic individuals which increases their susceptibility towards metal toxicity [10, 11]. Metallothioneine also helps in detoxifying heavy metals. It has also been

associated in the development of neurons, maturation of GI tract, proper immune function and helps in delivering of zinc to cells. Dysfunction or decreased level of metallothionein may lead to ASD [12, 13].

Lead: Lead poisoning in children is one of the most common cause of neurodegeneration. In case of pediatric lead poisoning the effects spreads over different areas of the brain including those implicated in communication, cognitive and social functioning. In elevated blood lead levels has been reported in autistic children [14]. Lead competes with ions like calcium, transcription factors and proteins. During pregnancy, the demand for calcium increases. Calcium may compete off accumulated lead from the bones which gets transferred to the blood and crosses the placental barrier to the fetus. A study done on Egyptian autistic children showed direct correlation between plasma lead levels and severity of the disease. Lead may lower frustration tolerance, weakens reaction control and leads to reduced intellectual development in the children [15].

Aluminium: Human exposure to aluminium can cause autism. Pediatric vaccines include aluminium adjuvant is indirect measure of infant's exposure to aluminium and has been associated with ASD. It has been found that not the amount of aluminium but the location of the metal in different areas of brain is in direct relation to autism. Aluminium content in the vaccines passes the blood brain barrier and gets accumulated in the brain tissues. It is present in both grey and white matter as viewed using aluminium selective fluorescent dyes. Aluminium may get associated with inflammatory cells in the vasculature and meninges. In the central nervous system, it has been found in both neuronal and glial cells [16, 17]. Aluminium enters the autistic brain tissues with the pro-inflammatory cells which get loaded with aluminium in lymph or in the blood. At the site of injection aluminium and monocytes interacts which later gets differentiated to macrophages. The macrophages escort aluminium to the brain cells and triggers autism primarily by preventing synaptic pruning [16]. It is a neurotoxin but then also given in injection as it is an adjuvant to immune cells. Aluminium may also stimulate proinflammatory cytokines resulting in neuroinflammation associated neurodegeneration in autism [18].

Mercury: Methyl mercury present in the diet due to environmental exposure to mercury, results in the neurodevelopmental impairments in the children who are exposed to mercury at prenatal stage [19]. The relationship between the mercury poisoning and autism has been established by measurement of urinary excretion of an organic compound known as porphyrins [20]. Porphyrin is a biomarker to the mercury toxicity. Children having autism has been found to have elevated levels of urinary concentrations of pentacarboxyl and coporphyrins which occurs due to disordered porphyrin metabolism [21]. The level of mercury toxicity associated urinary porphyrins was high in the autistic children then control subjects [22]. Another study, compared neurotypical and autistic children of same age to examine the association between the mercury exposure in children and the porphyrin levels. It also founded that the levels of urinary porphyrins concentration were high in children with autism. These findings showed that the disordered porphyrin metabolism is a salient feature of autism [23]. Severity study was also done in both the normal and autistic children to know the levels of mercury and its effect. The different severity levels were low functioning autism high functioning autism and medium functioning autism. The study showed a significant increase in the level of mercury in the hair and nail of the autistic subjects when compared with the healthy group [24].

Cadmium: It is recognized as toxicant which has adverse effects on fetal growth. Its effects have mostly been studied in animals where it has been associated with change in behavior and learning ability of the offspring. The percentage of cadmium absorption increases during pregnancy and it gets accumulated in the placenta. Due to accumulation, it inhibits the expression of the placental genes responsible for the transfer of glucocorticoids to fetus through the placenta. This causes toxicity to the cells and affects fetal development. It is associated with the learning difficulties and affects intelligence levels. Studies have also reported high cadmium in the children whose development is slower than the healthy children [25].

Arsenic: It is a toxic heavy metal which is harmful even on low exposure. It has sulfhydryl reactivity which increases its effects. It also crosses placenta during pregnancy and affects fetal neurological development. Arsenic gets accumulated in the keratinized tissues of body and its level is higher in the autistic child than the healthy one [26].

Selenium: Some studies indicate that in autistic individuals the antioxidant status is diminished due to an increase in the levels of reactive oxygen species and reduction in the antioxidants. Defects in the metabolism of cellular antioxidants which maintains the intracellular redox status may potentiate autism. Selenium dependent enzymes a family of 25 unique proteins also known as selenoenzymes play a significant role in the maintenance of intercellular reducing conditions, especially in the brain. Brain consumes oxygen at a higher rate and that is accompanied by high ROS production and thus the activity of selenoenzymes is of utmost importance to maintain the redox state. Selenoenzymes are inhibited irreversibly by many electrophiles which diminishes its functions. A decrease in the concentration of the selenium is observed in the hair and nail samples of the patients suffering from autistic disorder [27, 28].

Titanium: Anatase titanium dioxide is the nanosized particles which affects the gene expression in central nervous system and are associated with the development and functions of the nervous system. A study on mice investigated the effects of maternal exposure to nanoparticles of titanium dioxide using cDNA microarray analysis. Apoptotic genes were increased in the brain of the new born, while titanium was found to reduce the genes associated with brain development. The genes responsible for oxidative stress also varied in 2 to 3 weeks old mice brain. Titanium dioxide also produced reactive oxygen species (ROS) during photocatalysis. The study showed that the maternal exposure to anatase TiO₂ nanoparticle bring about alteration in the genes related to the development of the brain and may also be associated with neuronal death [29].

Zinc: It has been suggested in recent studies that deficiency of zinc in early childhood may lead to autism. Zinc plays an important role in the formations of different proteins. Zinc is also associated with the transfer of impulses from one neuron to another neuron. Deficiency of zinc in early development stages leads to impaired synaptic maturation and neuronal circuit formation [30]. Zinc levels in neurons is an important factor which interacts with the proteins that are encoded by the genes involved in the formation as well as stabilization of the synapses during early developmental stages. Zinc deficiency has been associated with development of autism [31].

Conclusion: Autism is a neurodevelopmental disorder growing at a fast rate and extending worldwide. Our knowledge regarding its etiology and pathogenesis is still evolving. It has a very complex etiology with both genetic and environmental components playing major role. Among the environmental factors heavy metal toxicity plays a major role. Exposure to heavy metals like lead, mercury, aluminum, arsenic selenium, cadmium, titanium and deficiency of zinc has been shown to potentiate this developmental disorder. More epidemiological evidence and animal studies are essential for a better understanding of the molecular mechanism involved in heavy metal associated ASD.

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