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A Review of Potential Metal Toxicity and Mineral Deficiency in Autism

Archana Singh Sikarwar[1*], Hema Balakrishnan[2], Shiow Pyng Tong[2], Koh Vi Vien[2], Jason Yoong[2], Koo Jun Hao[2], Nang Sue Chin[2], Kho Xin Xuan[2], Lim Jiayi[2] and Tye Kar Yee[2]

[1]School of Medicine and Health Sciences, International Medical University, Kuala Lumpur, Malaysia.
[2]School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia.

Authors' contributions

This work was carried out in collaboration between all authors equally. Author ASS designed the study and supervised the work. Authors HB, SPT, KVV, JY, KJH, NSC, KXX, LJ and TKY carried out literature survey, wrote first draft of the manuscript, and the analyses of the study. Author ASS edited the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Autism is a neurodevelopmental disorder that predominantly affects the younger generation. The etiology which contributes to the occurrence of autism is not well defined. However, apart from genetic factors, environmental factors such as metal exposure have been controversial from the last decade. Contamination of several metals was proposed to be responsible for oxidative stress production, mitochondria dysfunction and immune abnormalities which lead to characteristics of autism in children. Objective of review is to analyze the relationship between the most studied toxic metals namely mercury, lead, cadmium and arsenic. Based on the findings, metal toxicity due to lead, mercury and aluminum are clearly exhibited meanwhile insufficient data were available on

**Corresponding author: E-mail: archana_sikarwar@imu.edu.my;*

arsenic and cadmium. In addition, lack of essential minerals in autistic children who were exposed to heavy metals has also precipitated the autistic disorder. However, high quality epidemiological studies with minimal biasness should be conducted to support the correlation of heavy metal with autism.

Keywords: Autism; heavy metals; toxicity.

1. INTRODUCTION

Autistic spectrum disorder (ASD) is a neurodevelopmental disorder that predominantly established in early childhood and is identified by impairments in social interactions, marked abnormal communication skills as well as restricted, repetitive and stereotyped behavior [1]. According to Autism and Developmental Disabilities Monitoring Network (ADDM), among 14 sites in United States, the prevalence per 1000 children was around 6 from 2000 to 2002. However, the number of children affected by autism increased tremendously since 2004 and reached the peak value in 2008 in which the range of prevalence over 1000 children was from 4.8 to 21.2, whereas about 1 in 150 children affected by autism from 2000 to 2002 and almost 2 children suffered from autism disorder among 176 people [1]. Researchers have conducted a survey based on different number of reported sites. Boys were found to have higher risk factor than girls. Centers for Disease Control and Prevention (CDC) have done a government survey on autism prevalence rate in 2009, which showed that 1 in 110 of 8 years old children among 14 communities in United State were affected by autism and similarly, boys carry four to five times higher risk than girls [1,2].

The pathophysiological etiology, which contributes to autism, is currently not well-defined, non-specific and controversial but genetic and environmental factors have been implicated. Autism is linked to genetic susceptibility such as fragile X syndrome which is a hereditary factor that lead to intelligence problem and tuberous sclerosis [3]. Environmental factor is also an inevitable cause of autism. Contamination of several metals like mercury, lead, arsenic, aluminium and cadmium are believed to be responsible for oxidative stress production, mitochondria dysfunction, immune abnormalities and lead to characteristics of autism in children [4]. It is suspected that children with autism may have liver or renal function impairment, hence their bodies accumulate large amount of heavy metals and eventually, causing neurodegeneration [4].

Metals are widespread environmental elements and acute or chronic exposure to these toxins will lead to developmental problems including endocrine disruption, behavioral disturbance and lower intelligence quotient (IQ) [5]. Windham et al. [6] found that the amount of airborne pollutant especially mercury is correlated to the increase risk in autism in an epidemiological study. James et al. [7] explained that infants are at risk of metal toxicity due to low serum level of glutathione as toxic metals are commonly being removed by glutathione conjugation through bile excretion. In addition, children with predominantly all-milk food in everyday diet will indirectly decrease their toxic metal excretion abilities by a factor of three in an animal study.

1.1 Metal Toxicity and the Correlation with Autism

Study was started with the aim to explore the relationship between toxic metal and autism among the children. Therefore, based on the analysis of several research articles, we have deduced that there were few toxic heavy metals that were identified in hair and nail sample of autistic children.

Research conducted on 18 children in Dallas, USA (aged between 1 to 4 year old), have identified that the common heavy toxic metal were mercury, chromium, tin, manganese, lead, arsenic, cadmium, cobalt and uranium. However, the most common heavy metal have been identified as lead which is having mean value of 0.63 where the minimum level should be 0.18 µg of metal for every 1 g of hair.

Research conducted in Egypt, among 44 children (aged 3 to 9 years), were found that hair concentration of aluminum, arsenic, cadmium, mercury, nickel, antimony and lead were elevated in autistic as compared to non-autistic children. The mean levels of hair toxic metal concentration have been mentioned in Fig. 1.

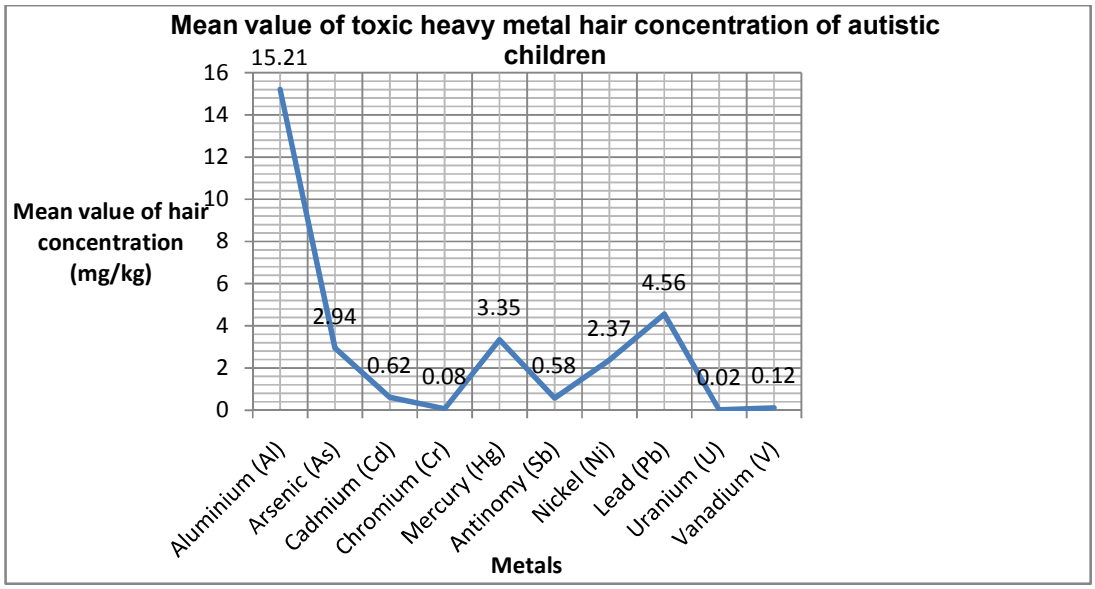

Fig. 1. Mean value of toxic metal in autistic children in 44 children

In this review article, we are mainly discussing about the toxic metals that are commonly related to autism which are mercury, lead, cadmium, aluminium and arsenic.

1.2 Mode of Action of Heavy Metals

Studies have been done in animals especially in fishes which reported that heavy metals have direct effect on sensing cells in the olfactory epithelium [8] which may be reversible if provide them unpolluted conditions [9-11]. Reversibility depends on extent of exposure of heavy metal to an animal [12]. Researchers also reported that certain heavy metals like cadmium, Mercury, Nickel and Manganese may travel along the nerves to central nervous system and exert disruption in signaling pathway [13]. Mirza et al. [14] hypothesized that heavy metals may accumulate in signal generating olfactory cells and hinder with signal processing rather than reception.

1.2.1 Mercury

Mercury is a toxic heavy metal that is usually related to autism. According to the WHO factsheet titled 'Mercury and Health', even a small amount of mercury exposure may result in serious health problems [15]. This is supported by Charles Lee, who states that mercury exposure can result in serious health consequences as it damages the renal and nervous system besides interfering the brain development in unborn and very young children [16].

To understand better about the relationship between mercury and health problems, mercury cycle should be revised. Various forms of mercury are present and these include the metallic mercury, organic mercury and inorganic mercury. Metallic mercury is also known as elemental mercury and it exists as liquid in room temperature and evaporates easily to form mercury vapours which are readily absorbed and transported to the brain [17]. Metallic mercury can be accumulated in the brain as it passes through the blood brain barrier [17].

Dental amalgam is a mercury-based filling which is made up of 50% metallic mercury [18]. While chewing, metallic mercury released from the filling as mercury vapour which is followed by inhalation of mercury. According to the US Food and Drug Administration, the use of mercury in dental amalgam may cause neurotoxic effects on the nervous system of developing foetus and children [19]. This is in line with a prospective study conducted by Geier and colleagues in 2009, where children, whose mother received more than six dental amalgams filling during pregnancy were 3.2 folds more likely to be diagnosed with autism [20].

A study carried out by Palkovica et al. [21] also reported that dental amalgam fillings should be used cautiously in women during the childbearing age in order to avoid prenatal mercury exposure. This is due to the increased mercury level found in the cord blood as a result of greater number of

maternal amalgam fillings. The adverse health effects of mercury from dental fillings are however not studied in this research. Due to the possible side effects of mercury to human, dental amalgam were even banned from being use in country like Norway (2008), Denmark (2008) and Swedish (2009) [19].

In contrast, the American Dental Association (ADA) has considered the use of mercury in amalgam as safe, as it does not leak from the amalgam [19]. A systematic review conducted by Rasines G. [22] in 2008 finds out that the mercury released from amalgam fillings are not associated with neurotoxicity in children owing to insignificant difference in neurobehavioral and neuropsychological score that were reported in children receiving dental amalgam fillings or composite fillings. Recent survey in 2009, conducted by Ye X and colleagues on 198 children who had amalgam filing and 205 children with no history of amalgam fillings, also showed no differences in renal function, neurobehavioural, neuropsychological or intelligence tests between the groups [23].

Combination of mercury with elements, such as oxygen, chlorine or sulphur results in the formation of inorganic mercury which is also called the mercury salts [24]. It is usually found in the cosmetic products and enters into the body through skin absorption [17]. Unlike the metallic and organic mercury, inorganic mercury does not easily pass through the blood brain barrier and this explains why the neurological damage caused by inorganic mercury is unlikely to occur and less severe [17].

Organomercury is the most toxic mercury among the three types of mercury exposure. It is formed when mercury is combined with carbon [24]. Methylmercury, ethylmercury and phenyl mercury are examples of organomercury. Similar to metallic mercury, methylmercury also passes through the blood brain barrier and its accumulation in the central nervous system leads to neurological disorder [17]. Prenatal exposure of mothers to methylmercury also affects the foetus despite the function of placenta as a barrier to mercury. The condition is even worse, with the fact that neurotoxicity is more expressive in the developing brain as compared to the fully mature brain [17]. Methylmercury poisoning is aroused from the contaminated fish and shellfish consumption as this mercury bioaccumulates in the ascending food chain of the marine life. [17]. Higher concentration of methylmercury is usually found in larger fishes that feed on other smaller fishes due to the longer life-span [25]. Swordfish, sharks and king mackerels that usually contain a mercury level of greater than 1part per million (ppm), are the highest mercury-containing fishes [25].

According to study by Shea and colleagues in 2004, declined in infants' and children performances in the neurobehavioural tests are found to be due to the prenatal exposure to methylmercury which can be easily passed to the new-born through the placenta and breast milk. [25]Young children are more susceptible to mercury toxicity and their exposure to mercury in the first year of life may cause their brain to be more affected. This explained why these children are unable to perform in the attention, language skills, visual-spatial abilities and memory test [26]. However, conflict of interest has been reported in study carried out by van Wijngaarden et al. [27] which states that no association is found regarding the prenatal exposure of methylmercury with ASD phenotypic behaviours in the study of high fish consumption cohort.

Other type of organomercury is called as ethylmercury which is formed from the dissociation of thiomersal which functions as a preservative in vaccines [17]. Its use as preservative was first introduced by Eli Lily [27]. In the United State (US), 12 times increase in autism cases were reported, after three additional thiomersal-containing vaccines were introduced to newborns in the early 1990s [27]. This is much higher as compared to country like Germany and Denmark which has reduced the use of thiomersal in vaccines. Though autism cases are much lower in these countries, increase in autism is reported despite the removal of thiomersal-containing vaccines since 1992 [17].

A cross sectional study conducted by Gallaghar and Goodman in 2010, male newborns who receive thiomersal-containing hepatitis B vaccination in the first month of life are 3 times more likely to be diagnosed with autism [28]. This association is also reported in study done by Geier and Geier in 2004, where children receiving thiomersal-containing diphtheria-tetanus-acellular pertussis (DTaP) vaccines are associated with a greater risk of neurodevelopmental disorder adverse events as compared to children receiving thiomersal-free DTaP vaccines [28]. Autism, mental retardation, speech disorder, thinking abnormalities, infantile

spasms and ataxia are the neurodevelopmental disorder adverse events studied [29]. Geier and Geier further prove the validity of their study in 2007, where ASD infants who had normal development in their first year of life, undergo regression into autistic disorder after a significant exposure to medicinal sources of mercury [30].

Debate has been going on among researchers on the correlation between thiomersal-exposure and autism in children. Besides the supporting evidence proposed, there are also researches that found no correlation between thiomersal-exposure and autism in children. A study in Canada, by Fombonne and colleagues in 2006, found that the increase in pervasive developmental disorder (PDDs) is not related to thiomersal exposure as the incidence of PDDs are greater in the thiomersal-free birth groups rather than the thiomersal-exposed groups [31]. Another study conducted by Price and colleagues in 2010, also found no evidence to conclude that increasing ethylmercury exposure through thiomersal-containing injection was in line with a greater risk of autisms [32].

A critical review proposed by Parker and colleagues in 2005, which further showed invalid correlation between thiomersal-containing vaccines with ASD. Parker and colleagues reviewed a total of 12 articles published between the years of 1966 to 2004 before they came to the conclusion that the incidence of ASD is not associated with the use of thiomersal-containing vaccines [32]. Ethylmercury is eliminated out of the body efficiently, owing to its 7 days, short half-life. The very low concentration of ethylmercury used in vaccines also cause harm results from thiomersal-containing vaccines to be less likely [33].

Autistic children are associated with reduced cysteine and glutathione synthesis which are crucial for natural mercury detoxification [34]. This was proven in study conducted by James and colleagues in 2004 where 19% lower plasma cysteine and 46% lower plasma glutathione were identified in autistic children [35]. As the ability of autistic children in mercury detoxification and excretion were impaired, higher mercury concentrations can be found in tissues of the nervous system. The longer half-life of mercury in autistics children also increases their susceptibility to mercury exposure. As there is a delayed in mercury detoxification, phospholipid methylation process that is responsible for normal attention is impaired in autistic children [36].

The impaired ability of autistic children in mercury excretion was proven by Holmes and colleagues in 2003. This study was conducted to measure the mercury level in the first baby haircuts of autistics children. A significant reduction in mercury levels, was reported which was about 8-folds lower, is found in autistic children as compared to normal children [37]. This was in accordance to the fact that autistic children have impaired ability in excreting mercury. Study conducted by Adams et al in 2009 were also reported that children with lower mercury level in the first babies' haircut had 2.5-fold higher chance of getting ASD when compared to those with higher mercury level [37]. Hair mercury analysis can be used to test for autism as children with more severe autism have a lower mercury level in their hair [35].

1.2.2 Lead

One of the most common causes of autism is childhood lead poisoning [38]. Harmful effects on the development of widespread brain areas including those implicated in mental, communication, and social functioning have been identified in lead poisoning in the childhood [38]. In 1976, a study conducted by Cohen et al. [39] has noticed elevated blood lead levels in children with autism. The toxic effects of lead are usually attributed to multiple mechanisms. One of the key factors is the ability of lead to mimic calcium action in the body [38]. Lead is capable to compete with or substitute for calcium in activating both protein kinase C (PKC) and calmodulin. It was reported that inhibition of brain microvascular formation and function can happen with lead concentrations that are effective in activating PKC. This will impair the development of nervous system in children who are exposed to considered amount of lead. Besides that, improper activation of calmodulin may alter the activity of secondary messenger pathways, which plays crucial roles in long-term potentiation in synapses, spatial learning, and memory processes [40].

Several studies have been conducted to determine the correlations between lead exposure and autism. Hair and nail analysis were often used to detect long-term exposure to lead because lead is accumulated and stored in tissues. Investigation shows that increasing order of toxic metals lead concentration in the hair and

nail samples and their correlation with degree of severity [38]. Study was conducted to measure the levels of 10 toxic metals in hair samples of autistic children as compared to non-autistic children through hair mineral analysis, and correlate the levels of these toxic metals to severity of autism. A total of 44 autistic test group (aged 3 to 9 years) were compared to a similar control group, consisting of a total of 106 non-autistic children [41]. The result showed that there was a statistically significant positive correlation between lead and verbal communication ($p=0.020$), and between lead and general impression ($p=0.008$) [41]. Association was found between higher concentration of lead in hair with impaired verbal communication and general impression. Brockel et al. claimed that children with autism are commonly found to have problems with communication and learning skills. They are typically associated with symptoms, such as retarded childhood development, decreased cognitive ability, learning and behavioral disabilities, attention deficit hyperactivity disorder (ADHD), impetuosity, and responding incoherently [41]. Researchers found out that there is sufficient evidence to state that a biomarker related to heavy metal toxicity especially lead has relationship with the severity of autism where elevations in urinary porphyrins which have relationship with lead were significantly associated with Childhood Autism Rating Scales [41]. On top of that, evidence has been stated by Abdullah et al. [42] in his article on Toxic trace elements in the hair of children of autism, that children with autism had significantly ($p< 0.001$) higher in hair concentration level of lead compared to other heavy metals such as antimony, arsenic, beryllium, cadmium and aluminums. Investigation showed that increasing order of toxic metals lead concentration in the hair and nail samples and their correlation with degree of severity. In several cases, they have noted temporal association between elevated blood lead levels and the emergence of autistic symptoms [38]. Blood analysis was used by researchers to correlated lead with autistic symptoms. In several cases, researchers also noted temporal association between elevated blood lead levels and the emergence of autistic symptoms [38]. It was stated that lead poisoning have been implicated with autism and reported an association between increased exposure to the lead exposure and teacher parents' ratings of children behavior especially in distractibility, impulsive behavior, poor concentration and non – persistence [43].

1.2.3 Cadmium

Commonly studied heavy metal in cases of autism is cadmium. Cadmium is one of the metals that known to affect the development of infant brain particularly during the first three months of growth. Therefore, several studies have been conducted to determine the relationship between heavy metals and autism.

Children with ASD might have inabilities in eliminating the toxins from the body. Thus, toxins build up in body and result in increased free radical body which eventually affects the nervous system. However, detoxification and excretion of heavy metals depends on their conjugation to glutathione, whose levels are significantly reduced in autistic subjects [43]. Low level of glutathione can be part of the reason that reduces the ability to remove toxic metals. Study was further supported by the studies of Yorbik et al which compare the urine levels of heavy metals such as cadmium, chromium and lead in 30 autistic children with 20 healthy subjects using atomic absorption spectrometry. The results have shown that the cadmium level in urine of autistic children is significantly decreased as compared to that of healthy subjects [44].

However, other studies indicates there is no correlation between autism and heavy metal. A study has been conducted to understand the toxicological status of children with autism compared to neurotypical children where the levels of toxic metals are measured in total blood, red blood cell and urine. Cadmium is detectable for whole blood and urine but hardly spotted in RBC as the level was below the detection limit which is 0.001 mcg/g. Children with autism had significantly lower level of cadmium in whole blood except urinary level is being the most sensitive. However, compared to other metals, cadmium levels are considered low in blood and urine because cadmium is primarily excreted in bile. Thus, study suggests that there is not much difference of cadmium body burden in children with autism and neurotypical children [45]. In a case study by Abdullah et al. [42] conducted 40 autistic children who were tested for heavy metal toxicity in their hair sample, the p value were not significant, hence does not contribute to autism. Hence, more studies need to be done to confirm the relationship between cadmium and autism in children.

1.2.4 Arsenic

It has been believed that autism spectrum disorders are in part caused by environmental exposure to heavy metals such as arsenic. Arsenic is a sulfhydryl-reactive metal found to be toxic to the nervous system even at low exposure levels. The more toxic form, inorganic arsenic, is found to be carcinogenic and affects neurodevelopment. Inorganic arsenic exists in soil and rocks. It is highly water soluble thus readily mobile in the environment. Organic arsenic, though less toxic compared to the inorganic counterpart, can be harmful to neurodevelopment too [45]. Human can be exposed to inorganic arsenic in many ways including:

- Arsenate which widely contaminates drinking water source
- Consuming crops grown in arsenic-contaminated soil
- Bioaccumulation in the human body from high frequency consumption of seafood (eg shellfish) over a long period [45].

Arsenic exposure in human is assessed using the blood concentrations. Concentrations of the metal in urine samples indicate more recent exposures (for past several days). Arsenic levels in hair or fingernails would represent exposure from the past several months [45]. As mentioned earlier, the exact causes of autism spectrum disorders have remained obscure; among them one postulation suggested is the epigenetics theory. Autism is among the monogenetic brain disorders associated with DNA methylation and histone modification defects [46]. The epigenetic dysregulation of the gene expression is considered to be one of the pathophysiological factors contributing to neurodevelopmental disorders such as autism [47]. Arsenic has been viewed to induce epigenetic alterations of the gene expression. For example, arsenite exposure is reported to induce DNA hypo and hypermethylation [48]. Studies have been conducted to investigate the possible correlation between arsenic exposure and autistic spectrum disorder. Rahbar et al. [47] in a Jamaican age and sex-matched case control study did not find a significant association between ASDs and total blood arsenic concentrations. This was the first study to take into account the confounding factor diet such as consumption of fruits and vegetables, drinking water source and seafood consumption [45]. In another study, Fido and Al-saad used 40 older children with autism as subjects. They found that there was no difference of arsenic levels in haircuts in between the group of autistic children and the control group of 40 normal controls [49].

Geier et al. indicated that there was no significant association between arsenic and ASD severity. In the study, autistic subjects of 1 to 6 years old had their autism severity measured by the Childhood Autism Rating Scale (CARS) score. The arsenic concentrations in their haircuts were tested. The strength of the study was that it included only children with moderate to severe autism. However the sample size was small, though it was statistically adequate enough to establish an association between heavy metal concentrations and autism severity [50]. However, some studies obtained conflicting results. The study done by Obrenovich et al. [53] indicated significantly higher levels of arsenic in the hair of children with an ASD compared to the controls ($p<0.0001$). The source of arsenic was not known [51]. Eleonor et al. [54] found raised hair concentrations of arsenic in autistic children compared to those non-autistic. [52] Al-ayadhi evaluated 77 Riyadh autistic children and significantly higher levels of arsenic were found in the hair of the autistic group [53]. It would be interesting to source more studies investigating exposure of arsenic in the prenatal/fetal period. The studies looked at above only measure levels of arsenic in postnatal period (children). There have been evidences that environmental chemicals can cause insults *in utero*, leading to dysregulation of the fetal epigenome which would then possibly exert an effect on the neurodevelopment of the child [54]. In fact, arsenic was shown to be able to easily cross the placenta [45].

1.2.5 Aluminium

According to the 1970-2205 California Department of Developmental Services (CDDS) and United States Individuals with Disabilities Education Act (IDEA) aluminium adjuvants have shown increasing trends that correlate positively to the rise in the autism [55]. The cumulative aluminium adjuvant and total number of immunization correlates strongly with autism trends. Aluminium exhibited neurotoxin activity that induces neuroimmune disorder and cellular oxidative stress [56]. Lucija et al. [57] in their study demonstrated that childrens from countries with highest exposure of Aluminium from vaccine has highest prevalence of autism ($p<0.001$). Besides that, several publication demonstrated interaction of aluminium with vaccines and other pharmaceuticals including antibiotics and

antipyretics such as acetaminophen [57]. The exposure of aluminium among children especially those with insufficient serum sulfate and glutathione demonstrated higher prevalence rate of autism [58]. Besides that, newborn showed infinite increase in the risk of autism due to hepatitis B birth dose. A U.S.-based study published in 2010 determined that a three-fold increased risk to autism was associated with neonatal administration of Hepatitis B (Hep-B) vaccine prior to 1999, compared with either no vaccination or a delay until after the first month of age. Notably, Hep-B contains both aluminum and mercury [59].

2. DISCUSSION

The exposure of environmental toxin and the influence for the neuro developmental disorders such as autism have been studied in many cases. In a PUBMED search, 58 empirical reports of autism and metal toxicity were reported where 43 suggest the correlation and 13 reports deny the correlation between metal toxicity and autism. However, the tendencies for null results were not reported and it cannot be said that there is no evidence for a link between metal toxicity and autism [60]. However, there are several controversies and conflict of interest in the correlation between toxic metal and autism. Recent studies suggested that controversies in the research of metal associated with autism may exist due to the significant limitations in the studies, retrospective design, publication biases, limited sample size, and the utilization of non-standard tool to diagnose autism [61]. It has been studied that it has pharmaceutical companies offer the significant monetary support to the researchers whose findings do not support link between toxic metals in vaccine. Therefore, the findings in the research are significantly affected due to the professional ethics of the researcher and pharmaceutical companies [60]. Besides that, other factor that precipitates autism with heavy metals is polymorphism in genes that increases the susceptibility of autism [60].

In addition, toxic metals affects the absorption of the trace element, interacts with the essential elements and affects the threshold level besides the toxicity effect which may contribute to the neurodevelopmental condition such as autism [60]. For instance, toxic metals namely cadmium, lead and mercury interacts with nutritionally essential metals [55]. Lead may interact with calcium and causes the impairment in the cognitive development in children [60]. Besides that, it has been observed that children's presented with autistic disorder have very low level of essential metals such as calcium, iron, iodine, magnesium, manganese, zinc, and selenium. However, the level of copper have exceeded the reference range and it is confirmed in a finding by Faber et al. [60] who stated that the incidence of zinc deficiency and copper intoxication is high in children with Autism Spectrum Disorder. This is further supported by Al- Ayadhi who stated that compared to the hair sample of normal children, hair sample of children with Autistic Spectrum Disorder shows significant lower concentration of essential trace elements such as calcium, manganese, iron and chromium [62].

It has been identified that selenium protects from mercury and methylmercury toxicity. It has been established that mercury toxicity is prominent in the children of autism. This is further supported by Jory and Woody et al. [63] in their study where lower level of selenium. Apparently, the ability to adapt to the environment is affected by low level of selenium concentration in the children. Besides that, Fagala and Wigg mentioned that selenium is a vital component of glutathione peroxidase which appears to protect from toxicity from metal such as lead, mercury and cadmium [61]. Therefore, we can identify that, autistic children with selenium deficiency are highly susceptible to the metal toxicity which causes them to become regressive, unable to concentrate, and display some learning disorders [57]. In addition, toxic metal exposure will affect the absorption and utilization of the nutrient elements in our body. For example, lead substitutes zinc on hem enzymes and cadmium causes replacement of zinc n metallothionin [58]. Hence, low level of zinc have been associated to fear, verbal communication impairment, and nervousness which may enhance the effect of lead which supports the positive correlation between lead and verbal communication ($p= 0.020$).

Besides that, the accumulation of the cadmium, aluminium, and lead in the kidney, liver and brain that results from and exacerbates magnesium deficiency which leads to the considerable oxidative damages to crucial organs such as brain [64]. The incidence rate of magnesium deficiency in autistic children in a metallomic analysis is 27% in male children of 0-3 years old compared to female children of 0-3years which is 22.9% [65]. Magnesium deficiency is associated with individuals on the autism spectrum disorder,

in the case of Nitric Oxide (NO), is involved in synaptic plasticity, immunity, neurotransmission, electrolytic stability, neuromodulation, gastrointestinal and hepatic function [66]. High intake of vitamin B6 also lowers the level of magnesium [67].

Besides that, low level of iodine in the hair of children with autism suggests that iodine could be important in the etiology of autism preferably through its effect on thyroid function [68]. It has been reported that high incidence of thyroid abnormalities among the parents of autistic children and reduced thyroid- stimulating hormone (TSH) level in children with autism (n=41) [68]. The finding shows that low level of iodine causes impairment in thyroid function which causes some of the autism symptoms such as impairment of the languages and mental retardation [68].

Superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) are the primary enzymes involved in direct elimination of reactive oxidative stress which is involved in the pathophysiology of autism. However these enzymes require micronutrients such as selenium, manganese, copper and zinc [69]. The deficiency of manganese affects the detoxification and elimination of the environmental toxin. Brain is highly vulnerable to oxidative stress due to the limited antioxidant capacity and especially children are more susceptible to autism Children are more vulnerable than adults to oxidative stress because of their naturally low glutathione levels from conception through infancy [69].

Therefore, toxic metal toxicity in addition to nutritional inadequacies potentially heightens the toxicity of metals. Nutritive elements such as trace metals are deficient among the autistic children which further contribute to the autism spectrum disorder [60].

3. CONCLUSION

A strong correlation of mercury and few other toxins have been shown in the pathogenesis of autism, similarly the lack of excess essential minerals have been identified to precipitate the incidence of autism spectrum disorder among children. There is no conclusive data about metal toxicity and the relationship with autism. Increase environmental exposure at children developmental stage plays a significant role in the etiology of autistic disorder. However, further research is needed on a wider scale particularly in toxic metals such as cadmium and arsenic because they have significant role in the autistic spectrum disorder. Therefore, high quality epidemiological studies with minimal biases should be conduct to support the correlation of toxic metal with autism.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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