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Review article

Toxic metal(loid)-based pollutants and their possible role in autism spectrum disorder

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction, verbal and non-verbal communication, and stereotypic behaviors. Many studies support a significant relationship between many different environmental factors in ASD etiology. These factors include increased daily exposure to various toxic metal-based environmental pollutants, which represent a cause for concern in public health. This article reviews the most relevant toxic metals, commonly found, environmental pollutants, i.e., lead (Pb), mercury (Hg), aluminum (Al), and the metalloid arsenic (As). Additionally, it discusses how pollutants can be a possible pathogenetic cause of ASD through various mechanisms including neuroinflammation in different regions of the brain, fundamentally occurring through elevation of the proinflammatory profile of cytokines and aberrant expression of nuclear factor kappa B (NF-κB). Due to the worldwide increase in toxic environmental pollution, studies on the role of pollutants in neurodevelopmental disorders, including direct effects on the developing brain and the subjects' genetic susceptibility and polymorphism, are of utmost importance to achieve the best therapeutic approach and preventive strategies.

1. Introduction

Autism spectrum disorder (ASD) is currently defined as a spectrum of lifelong heterogeneous neuro-developmental disorders, characterized by deficits in social interaction and communication, and restricted, repetitive interests and behaviors, onset usually occurs before the age of three years (APA, 2013; Yenkoyan et al., 2017). During the past two decades, the increased worldwide ASD prevalence rate has led to great concern because a worrisome 30% increase in incidence and prevalence in children was reported (Calabrese et al., 2016). It has been shown that the prevalence of children with ASD aged 6–17 was 2% in 2011–2012, while a marked increase from the past 1.16% was reported since 2007 (Blumberg et al., 2013). In the US, the increase in the prevalence of ASD has been even more dramatic over a shorter period (Boyle et al., 2011; Christensen et al., 2016; Baio et al., 2018). In the years 2006–2008, approximately one in six American children had a developmental disability, classified from mild (like language and speech impairments) to severe (like cerebral palsy, ASD, and intellectual disabilities) (Boyle et al., 2011). According to the Centers for Disease Control and Prevention (CDC), about one in 59 (16.8 per 1000) US school-aged children has an ASD diagnosis (Baio et al., 2018).

To date, there is no consensus on the pathogenesis of this disorder. Research has suggested that there are multiple risk factors related to the pathogenesis of ASD. Some suggested idiopathic risk factors are:

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obstetric complications, fetal hypoxia, maternal or paternal age, bleeding during pregnancy, gestational diabetes, diet and medication used during the prenatal period (Kolevson et al., 2007; Meguid et al., 2017). Maternal or paternal age at the time of birth may be associated with ASD due to its link with an increase in the risk of chromosomal abnormalities (Kolevson et al., 2007; Goddard et al., 2016; Martinelli and Staiano, 2017) or mutations in genes involved in fetal neuro-development (Ezra et al., 1995; Rosenthal and Paterson-Brown, 1998; Kourtian et al., 2017; Stessman et al., 2017). These mutations may be spontaneous or caused by environmental factors including exposures to metal-derived toxicants; but collectively mutations have been estimated to be causal in about 7% of those subjects diagnosed with ASD (Kazmaura and Lie, 2002; Tang et al., 2006; Geier et al., 2009a, 2009b, 2016; Shen et al., 2010; Pietropaolo et al., 2017). Furthermore, in a recent study, glutamine was reported as a predictive prognostic marker in ASD patients, and it was reported that an anomaly in the balance between GABAergic and glutamatergic neurotransmission was prevalent in ASD cases (Al-Otaish et al., 2018). Oxidative stress and neuroinflammation also play a significant role in ASD (Rossignol and Frye, 2012).

However, it is also known that environmental factors such as exposure to some toxic chemicals present in the environment and the dysregulation of intracellular trace metals can lead to human brain injury (National Academy of Sciences, 1993; Stork and Li, 2016). This vulnerability is greatest during embryonic and fetal development and maybe especially significant in the first trimester of pregnancy (Grandjean and Landrigan, 2006; Caserta et al., 2013; Costa et al., 2017). The neonate is considered exceptionally vulnerable to toxic metal exposure and reduced uptake of essential elements like zinc (Zn) and manganese (Mn) (Oskarsson et al., 1998; Arora et al., 2017). During these periods, the central nervous system (CNS) is experiencing a rapid growth rate and is highly vulnerable to the effects of both toxins and toxicants (Oskarsson et al., 1998; Ethier et al., 2012; Miyazaki et al., 2016).

Prenatal, neonatal and/or early childhood exposure to environmental factors may contribute or be a relevant factor in the child's development of the symptoms used to place children within the autism spectrum (Bailey et al., 1995; Monaco and Bailey, 2001; Hultman et al., 2002; Daniels, 2006; Sutcliffe, 2008). Interactions of gene and environmental factors, such as exposure to toxic metal pollutants, are associated with several nervous system disorders (Bjørklund, 2013; Pietropaolo et al., 2017). Exposure to environmental toxins and toxicants may also be causal factors for gene mutations or genetic variations, which has been suggested to lead to ASD diagnosis; but given the observed neurodevelopmental differences in twins having ASD diagnoses, these factors are still to be fully elucidated as causing ASD (Santangelo and Tsatsanis, 2005; Daniels, 2006; Wender and Veenstra-VanderWeele, 2017). Environmental factors could act in conjunction either with inherited susceptibilities or by inducing epigenetic changes (Mehler, 2008; Homs et al., 2016; Bjørklund et al., 2017a; Zhubi et al., 2017). For example, epigenetic effects on the regulation of the reelin gene (RELN) and glutamate decarboxylase 67 (GAD1) have been reported in the frontal cortex of the brains of individuals diagnosed with ASD (Wasser and Herz, 2017; Zhubi et al., 2017).

Exposure to environmental toxicants such as: a) lead (Pb); b) all forms of mercury (Hg) including elemental Hg, inorganic Hg compounds (e.g., calomel [Hg_2Cl_2] and mercuric chloride [$HgCl_2$]) and organic Hg compounds (e.g. methylmercury (MeHg) chloride [MeHgCl], MeHg cysteine [MeHgCys] and the sodium salt of ethylmercury (EtHg) thiosalicylate [Na^+ EtHg Thiosalicylate$^-$]); c) toxic aluminum (Al) compounds (e.g., the sparingly soluble hydroxy Al salts and, for those with certain kidney diseases, the highly soluble Al (III) salts like aluminum sulfate [$(Al^{3+})_2(SO4^-)_3$]; and d) arsenic (As), have been found to be associated with disorders ranging from overt toxicity at high levels of exposure down to subclinical dysfunction when exposure is at minimal levels (Gibson, 1904; Landrigan et al., 1975; Harada, 1995; Canfield et al., 2003; Tomljenovic et al., 2014; Strunecka et al., 2016; Kalkbrenner et al., 2018; Wu et al., 2018). Evidence indicates that the interplay between these factors, i.e., Pb, Hg, Al, As, and the presence of certain genetic predispositions or epigenetic effects can lead to the symptoms characteristic of ASD (Hodgson et al., 2014; Tomljenovic et al., 2014; Yassa et al., 2014; Felice et al., 2015; Macedoni-Lukšič et al., 2015). Moreover, a very recent study reported synergistic neurotoxic effects of Al and Hg in primary human neuronal-glial (HNG) cells by a substantial increase of pro-inflammatory signaling pathways through significant induction of NF-kB (p50/p65) in response to Al and Hg alone or in a combination of both (Alexandrov et al., 2018).

A recent study reported that there is a close relationship between the level of industrial pollutants of As, Pb and/or Hg species and the prevalence of children having ASD diagnosis (Dickerson et al., 2015). This study corroborated a previous study by Roberts et al. (2013) that found that perinatal exposures to the highest versus lowest quintile of diesel, Pb, Mn, Hg, methylene chloride, and an overall measure of metals were significantly associated with ASD. Also, a study in Riyadh area, Saudi Arabia reported significantly higher levels of toxic metals (i.e., Hg, Pb, As and cadmium [Cd] species) in children having ASD diagnosis as compared to the levels of these metal species in neurotypical children (Al-Ayadhi, 2005). Again, in Saudi Arabia, researchers found elevated levels of Hg and Pb together with a significant decrease in the selenium (Se) levels in red blood cells (RBCs) of patients with ASD when compared to neurotypical children (El-Ansary et al., 2017a, 2017b). On the other hand, glutathione (GSH) as the predominant cellular free radical scavenger in the brain is the primary defense against many toxic metals, and low GSH has been reported in ASD patients. Therefore, although high exposure to heavy metals is a problem, low GSH seems to be the primary reason for elevated toxic metals in ASD (Nair et al., 2015; Endres et al., 2017). Also, a decreased ratio of reduced GSH to oxidized GSH (GSH/GSSG) and elevated oxidative stress in the brain of ASD patients may result in increased mitochondrial superoxide production, oxidative protein and DNA damage, and chronic inflammatory response (Rose et al., 2012; Chauhan and Chauhan, 2015).

A recent systematic review and meta-analysis of 48 studies by meta-regression analyses reported a link between ASD and toxic metals in different specimens such as whole blood, red blood cells, serum, plasma, urine and hair of ASD patients. Specifically, they found higher blood and erythrocyte levels for Hg and Pb and reported the role of toxic metals as environmental factors in the ASD etiology (Saghazadeh and Rezaei, 2017). Also, Gump et al. (2017) assessed blood Pb and Hg levels in a biracial cohort of 9–11-year-old children (N = 203) using neurodevelopmental and psychological functioning assessments. Increased Pb levels in these children were associated with deviant behaviors, unstable emotionality, and difficulties in communication. Increased Hg levels were associated with various autism spectrum behaviors for children with sustained vagal tone during acute stress. A large Mothers and Children's Environmental Health (MOCEH) study of 458 mother-child pairs found associations between prenatal and early childhood Hg exposure and autistic behaviors at five years of age using the Social Responsiveness Scale (Ryu et al., 2017). The variations of the level of toxic metals in ASD subjects are presented in Table 1.

A small number of studies, however, have demonstrated a significant decrease in levels of heavy metals in the hair of children who have ASD (Holmes et al., 2003; Kern et al., 2007; Skalny et al., 2017a, 2017b, 2017c). Kern et al. (2007) have proposed that this observation may be indicative of altered mechanisms of heavy metal excretion and their subsequent sequestration in the organism.

Exposure to some environmental toxic metals can lead to an initial stimulation of the immune cells. This may lead to an increase in the serum neurokinin A level with a subsequent enhancement in the release of this tachykinin from these cells that have been found in children with ASD (Mostafa et al., 2016a). A recent study of 47 ASD patients with 46

Table 1
Possible impact of toxic metals in patients with autism spectrum disorder.

Toxic metal	Negative studies with an increased level of metals in ASD patients	Positive studies with an increased level of metals in ASD patients	Possible mechanisms of action
Lead (Pb)	Adams and Romdalvik (2007); Fuentes-Albero et al. (2015); Macedoni-Lukšič et al. (2015)	Blaurock-Busch et al. (2011); Priya and Geetha (2011); Blaurock-Busch et al. (2012); Adams et al. (2013); Alabdali et al. (2014); Yassa et al. (2014); Dickerson et al. (2015); Fuentes-Albero et al. (2015); Khaled et al. (2016); Kim et al. (2016a); Mostafa et al. (2016b); Saghazadeh and Rezaei (2017), Wu et al. (2018), Qin et al. (2018)	Cognitive and neurobehavioral deficits in later life, alter neurochemistry, and elevate the affected persons'risk of being arrested for a crime in adulthood; stimulation of autoimmunity and neuroinflammation; induction of the serum anti-ribosomal P antibodies production.
Mercury (Hg)	Holmes et al. (2003); Kern et al. (2007); Skalny et al. (2017a); Skalny et al. (2017b)	Bradstreet et al. (2003); Ip et al. (2004); Al-Ayadhi (2005); Palmer et al. (2006); Adams and Romdalvik (2007); Mostafa and Refai (2007); Geier et al. (2008); El-Baz et al. (2010); Blaurock-Busch et al. (2012); Wright et al. (2012); Yassa (2014); Hodgson et al. (2014); Yau et al. (2014); Mohamed et al. (2015); Mostafa and Al-Ayadhi (2015); Kern et al. (2016); Khaled et al. (2016) Geier et al. (2017a); Geier et al. (2017b); Jafari et al. (2017); Ryu et al. (2017); Ye et al. (2017)	Impairment of GST; restricted effect on detoxification or sequestration of Hg; higher antineuronal antibodies; immune, sensory, neurological, and motor dysfunctions.
Aluminum (Al)	De Palma et al. (2012); Skalny et al. (2017a)	Adams et al. (2006); Blaurock-Busch et al. (2011); Albizzati et al. (2012); Al-Farsi et al. (2013); Shaw and Tomljenovic (2013); Metwally et al. (2015); Mohamed et al. (2015); Dickerson et al. (2017)	Interaction of Al with numerous glycolytic enzymes, and induction of a great suppression of cellular energy synthesis and elevate the potential neurotoxic activities in children, polymorphisms in the glutathione-S-transferase (GST) genes; direct binding of Al3 + ion by oxygen-based ligands; activation of microglia to produce TNF-α, IL-6, iNOS, NOS-2, neuroinflammatory PICs and ROS.
Arsenic (As)	Fido and Al-Saad (2005); Kern et al. (2007); De Palma et al. (2012); Rahbar et al. (2012) Adams et al. (2013); Dickerson et al. (2016) Skalny et al. (2017a); Skalny et al. (2017c)	Al-Ayadhi (2005); Obrenovich et al. (2011); Blaurock-Busch et al. (2011); Dickerson et al. (2015); Li et al. (2017)	Modification of brain morphology, degeneration of gliosis, neuronal, up-regulation of Bax and Bak expression, as well as depression of Mcl-1 in the cerebral cortex; impaired neurite growth due to suppression of AMPK kinase activation; inhibition of Wnt/β-catenin signaling pathway.

neurotypical individuals reported a positive association between PGE2, COX-2, and mPGES-1 and ascertains the potential role of PGE2 pathway and neuroinflammation in the etiology of ASD, and the possibility of using PGE2, COX-2 and mPGES-1 as biomarkers of autism severity (Qasem et al., 2018). The combination of corticotrophin-releasing hormone (CRH), neurotensin (NT) and environmental pollutants could hyperstimulate the already activated mammalian target of rapamycin (mTOR) as well as stimulate mast cell and microglia activation and proliferation and, thereby, increase the affected child's risk for ASD onset (Mostafa et al., 2008; Angelidou et al., 2010; Theoharides et al., 2013). In conclusion, the vast majority of the research suggests that children with ASD have increased levels of Pb, Hg, and Al and that there are mixed results for As (Table 1).

2. Lead

2.1. Lead and the environment

Lead (Pb) is a non-essential toxic metal, which is widely distributed in the environment because of its use in many different applications, particularly as: a) the yellow pigments in paints, b) a constituent in tin toys, c) the projectile in small caliber ammunition, and d) an anti-knock agent in automobile and aircraft fuels. Lead exposure levels have been a matter of public health concern in many countries for decades (Fuentes-Albero et al., 2015; Tan et al., 2016; Laidlaw et al., 2017). For example, in Singapore, the level of Pb in soil significantly increased from 2 mg/kg in the 1900s to more than 55 mg/kg in the 1990s (Chen et al., 2016a). The total emissions of Pb in China during the period 1990–2009 were nearly 200,000 t (Li et al., 2012). It is still used in several products whose utilization and consumption result in human exposure. Of these products, those that represent a minor hazard to developing children are, for example, Pb-acid car batteries, ammunition, and fishing sinkers. Lead-containing paint, leaded gasoline, and Pb-contaminated water, on the other hand, are serious hazards to developing children, due to their widespread prevalence in daily life (Bellinger, 2012). A study involving 25.5 million children demonstrated that environmental Pb exposure is associated with the total loss of 29 million IQ points (Wechsler scale) (Bellinger, 2012). In general, IQ loss due to Pb-contaminated foods in the European population varies from 0.1 to 0.49 IQ points (Bierkens et al., 2012).

Lead paint was used for a long time in homes in the US before it was banned in 1978. However, greater concerns are associated with Pb in gasoline and solders used in electronic devices, particularly in the Swedish population, where accurate epidemiological surveys were periodically conducted (Strömberg et al., 1995, 2003, 2008; Macauley et al., 2003). Lead compounds, such as tetraethyl Pb and tetramethyl Pb, were initially used in gasoline to increase its octane rating. The sale of leaded gasoline for use in automobiles was phased out from the late 1970s and banned in the US in 1996 in accordance with the Clean Air Act. However, Pb compounds are still being used as an anti-knock agent in high-octane aviation gasoline in the US. The use of this leaded gasoline in automobiles and aircraft has resulted in Pb-contaminated soil, and the ingestion of dust from that Pb-contaminated soil still represents a major source of Pb exposure. The third hazard for growing children, although not so prominent as the previous two, comes from water contaminated with Pb by the use of Pb pipes and Pb-based copper-pipe solders in drinking-water distribution systems. Moreover, foods or beverages processed with Pb-contaminated water also represent a possible hazard for public health.

2.2. Lead and autism spectrum disorder

When biologically adsorbed by humans, Pb is a potent neurotoxin with several adverse effects on health. Increased Pb exposure in early childhood is often associated with relevant modification in neurochemistry, growth retardation, neuro-toxicity, impaired cognitive

development in infancy, and deficits in attention and executive functions (Bellinger et al., 1986; Binns et al., 2007; Li et al., 2016; Mostafa et al., 2016b; Ye et al., 2017; Wu et al., 2018). Moreover, Pb exposure-mediated effects in early life have been reported in Table 1 as a) lead to cognitive and neurobehavioral deficits in later life (Winneke et al., 1983; Finkelstein et al., 1998; Sanders et al., 2009; Zahran et al., 2009); b) alter neuro-chemistry (Binns et al., 2007); and c) elevate the affected person's risk of being arrested for a crime in adulthood (Cecil et al., 2008; Wright et al., 2008).

Furthermore, a study on the relationship between ASD prevalence and environmental Pb concentrations as an air pollutant has indicated that Pb combined with Hg and As exposure, have synergistic effects on ASD prevalence (Dickerson et al., 2016). Qin et al. (2018) in a study with 34 blood samples of ASD children revealed higher Pb levels compared to neurotypical children. Moreover, in a study of 2473 school-age children, the results indicated that even low levels of blood Pb at 7–8 years of age could induce ASD or contribute to autistic behaviors at 11–12 years of age (Kim et al., 2016a). Higher levels of Pb in blood samples of ASD children were found in a study with 40 ASD children in Egypt compared with neuro-typical children as well as with healthy siblings of the ASD children (Khaled et al., 2016). In another study, researchers found a relationship between urban residential proximity to pollutant sources releasing toxic metallic air pollutants, such as As, Pb, or Hg, and a higher prevalence of children with ASD (Dickerson et al., 2015). Also, patients having an ASD diagnosis had remarkably high Pb and Hg levels in their red blood cells as well as low levels of enzymatic and non-enzymatic antioxidants (e.g., GSH and vitamin E) compared to the levels reported in neurotypical children (Alabdali et al., 2014; Fuentes-Albero et al., 2015). A significant elevation in the Pb and Hg levels in hair and nail samples from the ASD-diagnosed subjects were related to the severity of their impairments (Priya and Geetha, 2011). Moreover, a positive relationship has been reported between increased blood Pb levels and brain-specific auto-antibodies in children diagnosed with ASD. A study of patients from areas with low levels of Pb pollution reported that individuals with a severe ASD diagnosis had higher blood Pb levels compared with the levels found in individuals with mild to moderate ASD diagnosis (Mostafa et al., 2016b). Furthermore, it is reported that Pb stimulates auto-immunity and neuroinflammation in patients with ASD (Mostafa et al., 2016b). In particular, it has been shown that elevated levels of blood Pb in some ASD children could induce serum anti-ribosomal P antibodies production (Mostafa et al., 2016b). Adams et al. (2013) reported toxic metal levels in 55 ASD children compared with 44 neurotypical children. Their age was between 5 and 16 years. They found significantly increased levels of Pb in red blood cells compared to neurotypical children (+41%) as well as increased levels in urine (+ 74%) (Adams et al., 2013). However, Adams and Romdalvik (2007) did not report a significantly increased level of Pb in the ASD children's teeth samples at around six years of age. Yassa (2014) conducted a study on 2–10 years old ASD children in Upper Egypt and found a significantly higher level of Pb in the blood and hair samples of ASD children compared with neurotypical counterparts. Blaurock-Busch et al. (2011) reported a significantly higher level of Pb concentration in both hair and urine samples of children with ASD compared with neurotypical children. In another study, a significantly higher level of Pb (4.56 mg/kg) was reported in the hair samples of ASD children when compared with neurotypical counterparts (3 mg/kg) (Blaurock-Busch et al., 2012). Fuentes-Albero et al. (2015) conducted a study on 35 ASD children vs. 34 non-autistic Spanish children to assess the Pb concentration level in their urine. They found a not statistically relevant tendency to higher urine Pb level in the neurotypical group (Fuentes-Albero et al., 2015). In another study, it was reported that there is no statistically significant reduction in blood Pb levels between ASD and non-ASD children, although the increasing trend of blood Pb was observed in ASD children (Macedoni-Lukšič et al., 2015). Saghazadeh and Rezaei (2017) reported in a meta-analysis of 32 previous studies that there were overall higher blood Pb concentrations in ASD children compared with neurotypical children. Three independent studies evaluated the erythrocyte Pb levels in 138 of ASD patients and reported that they had higher erythrocyte Pb compared with neurotypical individuals. Also, a meta-analysis of five studies showed no difference in urine Pb levels of 199 ASD patients. Lead concentrations in hair were found to be higher in ASD patients in developing but not “developed” countries (Saghazadeh and Rezaei, 2017). However, the different results about the Pb levels in ASD children could be because of socio-demographic variables, different geographic exposure to Pb, clinical aspects of the examined sample such as located close to industrialized areas with low income social class and air pollution, living in old houses with Pb-containing paint, leaded gasoline, and Pb-contaminated water as well as children with ferropenic anemia, pica behavior. In summary, Table 1 shows that some studies did not find significant differences in Pb levels in ASD vs. controls, whereas the majority of the studies did find significantly higher levels of Pb in ASD vs. controls. Some of the studies showing no correlation/statistical significance between Pb levels and ASD had small sample sizes, such as Adams et al. (2008) which found that the Pb levels were 24% higher in ASD vs. controls, but the difference was not statistically significant. Therefore, it appears that Pb levels are generally increased in ASD vs. controls.

2.3. Lead and neurotoxicity

Lead is capable of inducing a neuroinflammatory response. In particular, Pb exposure modulates expression of IL-6, TGF-β1, and IL-18 in certain brain regions (Kasten-Jolly et al., 2011). Perinatal exposure to lead acetate also resulted in a significant increase in IL-1 and TNF-α expression in the cerebral cortex (Li et al., 2014). Moreover, increased hippocampal TNF-α expression is associated with impaired learning and memory in animals (Li et al., 2009). It has also been demonstrated that Pb up-regulates the expression of MAPK, extra-cellular matrix (ECM) receptor and vascular endothelial growth factor (VEGF). These changes are accompanied by altered regional expression patterns of pro-inflammatory cytokines (IL-1β, IL-18, and IL-33) (Kasten-Jolly et al., 2012). The role of NF-kB, AP-1, JNK, and MAPKK pathways in Pb-induced neuro-toxicity and neuroinflammation was also recently demonstrated (Ramesh et al., 2001).

The microglial response is one of the mediators of Pb-induced neuro-inflammation. In particular, it has been demonstrated that chronic Pb exposure in immature rats is associated with glial activation and IL-1β and TNF-α overproduction in the hippocampus and increased IL-6 expression in the forebrain. It is notable that glial activation and pro-inflammatory cytokine expression are associated with impaired axonal markers levels (Strużyńska et al., 2006). More recently, it has been demonstrated that Pb-induced production of pro-inflammatory cytokines (TNF-α, MCP-1, IL-6, COX-2) during glial activation is associated with the up-regulation of ERK, Akt, and NF-kB signaling pathways, and subsequently, it leads to neuronal death (Kumawat et al., 2014). Another study also detected a significant up-regulation of IL-1β, TNF-α, and iNOS synthesis during Pb-induced microglia activation (Liu et al., 2012a).

Lead exposure can induce significant microgliosis and astrogliosis in the hippocampus of young mice, probably as a result of exposure triggering a TLR4-MyD88-NFkB signaling cascade (Liu et al., 2015). While significantly increased BrdU-incorporating progenitors occurred following Pb exposure, no significant increase of BrdU/DCX labeled neuronal differentiation was observed in the dentate gyrus. Instead, Pb exposure led to the detection of abnormal increases in the level of newly formed astrocytes (or astrogliogenesis) in the hippocampus (Liu et al., 2015). Also, there is an increase in the expression level of MyD88 after exposure to Pb-containing species, which was partially blocked when the MyD88 inhibitory peptide was added to the Pb-containing test solution (Benedetti et al., 2014; Liu et al., 2015). This may suggest that MyD88 inhibitory peptide might dampen both the activity and

expression of MyD88 in the hippocampus (Benedetti et al., 2014; Liu et al., 2015).

Additionally, certain studies proposed that glia possess a protective effect against Pb toxicity. In particular, Pb-induced up-regulation of GSH synthesis may be considered as a compensatory response (Strużyñska et al., 2001). Moreover, it has been demonstrated that glial activation in response to Pb exposure may also have a protective effect against glutamate excitotoxicity through modulation of glial glutamate transporters (Strużyńska, 2009) and glutamine synthesis (Strużyńska et al., 2005). However, a more recent study demonstrated microglial dysfunction under Pb exposure (Sobin et al., 2013).

Oxidative stress has been shown to mediate Pb neurotoxicity (Baranowska-Bosiacka et al., 2012a). In particular, it has been demonstrated that perinatal Pb exposure resulted in a significant decrease in superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione-disulfide reductase (GSR) activity in certain brain regions (hypothalamus, corpora quadrigemina, and corpus striatum) (Wang et al., 2006). Brain levels of essential metals (copper (Cu), Zn, and Mn) were also significantly reduced in response to Pb treatment (Baranowska-Bosiacka et al., 2012b). Inhibition of antioxidant enzyme activity is also associated with oxidative DNA damage and DNA fragmentation in the brain (Khalaf et al., 2012). Lead was shown to induce oxidative damage and cell death of human brain microvascular endothelial cells, resulting in blood-brain barrier disruption, thus increasing brain susceptibility to toxic agents (Tobwala et al., 2014). The role of oxidative stress in Pb neurotoxicity is also confirmed by the observation of decreased brain damage in animals supplemented with antioxidants (Antonio-García and Massó-Gonzalez, 2008).

Lead exposure also induces endoplasmic reticulum stress (unfolded protein response) in the CNS, predominantly in astrocytes. In particular, Pb is capable of binding 78-kD glucose-regulated protein (GRP78) with subsequent activation of IRE1/ATF6 and/or IRE1/JNK (Qian and Tiffany-Castiglioni`, 2003). Noteworthy, Pb binding to GRP78 is associated with oxidative stress in Pb-exposed glia (Qian et al., 2005). In turn, using quercetin as an antioxidant, the flavonoid significantly reduced endoplasmic reticulum stress via modulation of PI3K/Akt and IRE1/JNK pathways (Liu et al., 2013a).

The N-methyl-D-aspartate receptor is known to be the target for Pb neuro-toxicity, and at least it partially mediates the inhibitory effect of Pb on neurotrophin brain-derived neurotrophic factor (BDNF) (Neal et al., 2010). This may ultimately result in altered synaptic formation, plasticity, and function during development (Baranowska-Bosiacka et al., 2012a).

Other mechanisms may also be involved in Pb-induced neurotoxic effects. In particular, Pb was also shown to inhibit creatine kinase and pyruvate kinase in the brain cortex, thus disrupting energy homeostasis in the CNS (Lepper et al., 2010). Another study using pseudo-catalytic derivatization analysis demonstrated that exposure to Pb species affected the lipid profiles in the samples of the mouse brain that were previously analyzed and revealed evidence of behavioral disorder (Jung et al., 2017).

Finally, Pb has the potential to engender developmental neurotoxicity via the activity of epigenetic mechanisms (Senut et al., 2012). In particular, it has been demonstrated that Pb exposure affects DNA methylation, resulting in altered neuronal differentiation in embryonic stem cells (Senut et al., 2014). Also, Pb exposure during early human development induces sex-dependent and gene-specific DNA methylation differences in the methylated regions of PEG3, IGF2/H19, and PLAGL1/HYMAI in adulthood (Li et al., 2016).

3. Mercury

3.1. Mercury as a pollutant in the environment

Mercury (Hg) is a universal environmental contaminant that bioaccumulates as MeHg species in the food chain (Cardenas et al., 2017). The main sources of Hg exposure are currently seafood (Dadar et al., 2014, 2016) and dental amalgams (Bjørklund et al., 2017d). Hg salts have immunomodulatory and allergenic properties (Stejskal et al., 1996), stimulate autoimmunity in genetically susceptible animals (Pelletier et al., 1988) and can also induce or promote the development of autoimmunity in humans (Stejskal and Stejskal, 1999; Prochazkova et al., 2004; Stejskal et al., 2013, 2015). Furthermore, Hg-containing compounds can induce immuno-stimulation, delayed-type hypersensitivity (type IV hypersensitivity), and autoimmunity, through the pathways that involve changed immune cytokines production (Kern et al., 2014; Berlin et al., 2015). In patients diagnosed with ASD, Hg seems to be one of the main environmental triggers for neuroinflammation and autoimmunity (Ezra et al., 1995; Blaylock, 2009; Dickerson et al., 2016; Kirby et al., 2016; Mostafa et al., 2016a; Li et al., 2018). Methylmercury species are also associated with severe neurological disorders in children exposed prenatally when their mothers consumed seed grain or seafood contaminated with significant levels of Hg (Bjørklund et al., 2017b; Van Wijngaarden et al., 2017).

As with Pb, children's nervous systems are sensitive to Hg. Even low-level exposure to Hg-containing substances can cause damage during fetal development. For example, the Hg-related childhood disease acrodynia, also known as “Pink Disease”, caused by the use of teething powders containing mercurous chloride (Hg_2Cl_2), and other cases of Hg poisoning in children provide evidence that children are more susceptible to Hg poisoning than adults (von Muhlendahl, 1991; Yeates and Mortensen, 1994; Bjørklund, 1995; Shandley and Austin, 2011; Lai et al., 2016). About one in 500 of the children who were treated with Hg-containing teething powders developed acrodynia, and of those about 20% died from it (Warkany and Hubbard, 1951; Bjørklund, 1995; Shandley and Austin, 2011). The history of acrodynia indicates that a small part of the population is genetically very vulnerable to Hg. Interestingly, newer research has shown that the grandchildren of the acrodynia victims have an increased incidence of ASD (Shandley and Austin, 2011). The researchers consider that sensitivity to Hg may be a heritable/genetic risk factor for ASD. In their study, it was found that individuals with a confirmed hypersensitivity to Hg have a significantly greater risk of having a descendant with ASD (Shandley and Austin, 2011).

Mercury is considered one of ten high-priority pollutants in the environment by the World Health Organization. Intensive industrial development has resulted in a nearly 3-fold increase in Hg emissions into the environment. It is supposed that atmospheric Hg levels are increased by 1.5% annually (Rice et al., 2014). Currently, annual anthropogenic emissions of Hg are estimated to be 2320 Mg (Pirrone et al., 2010). Due to the negative health effects of Hg exposure, it has been calculated that each kg of Hg emissions into the atmosphere results in economic loss of about € 22,937–52,129 (Nedellec and Rabl, 2016).

There are a variety of sources by which an individual may be exposed to Hg-containing compounds. Sources including Hg compounds are: a) ingredients in various drugs, bleaching creams, antiseptics, spermicides, and disinfectants; b) preservatives in cosmetics, toothpaste, contact lens solutions, vaccines, contraceptives, and immunotherapy solutions; c) fungicides and herbicides; d) alloys used in dental fillings, e) bioaccumulated MeHg in marine organisms animals, e.g., fish, sharks and whales, and f) Hg as a water contaminant (Zhang et al., 2017). Therefore, all sources of human Hg exposure that can affect children, adolescents, adults and also the elderly, need to be identified, eliminated or minimized (e.g., by restricting the intake of foods containing elevated levels of Hg, like tuna and whale and by actively reducing the level of Hg in the water used for drinking and bathing (Oskarsson et al., 1996; Palmer et al., 2006; Chaste and Leboyer, 2012; Mortazavi et al., 2016).

3.2. Mercury and autism spectrum disorder

Exposures to toxic Hg compounds have been suggested as one of the potential causals or contributing factors (Bernard et al., 2001) in children diagnosed with ASD by many researchers (Table 1). In this section, we discuss the possible association between Hg levels in different samples (blood, hair, teeth, urine, erythrocytes, etc.) focusing on the many ASD cases by reviewing the current literature in the field. A review analysis of 91 studies that examined the potential link between Hg exposures and the subsequent risk of ASD diagnosis, published from 1999 through February of 2016, revealed that the majority (74%) of the studies reported Hg exposure as an important risk factor, with direct and indirect effects on the subsequent ASD diagnosis (Kern et al., 2016; Qin et al., 2018). Furthermore, Kern et al. (2017) reported possible biases regarding the association between Hg and ASD due to a potential conflict of research interests, where 86% of the reports with public health/industrial affiliation found no relation between Hg and ASD, whilst only 21% of those without industry affiliation found no relation. Similarly, in another review, it was claimed that major environmental toxicants such as Hg, Pb and persistent organic pollutants (POPs) could represent a risk factor for ASD. However, the real scale of the impact on humans is still to be established (Ye et al., 2017). Adams and Romdalvik (2007) found a significantly higher level of Hg (2.1-fold) in the teeth samples of ASD children (n = 15) compared with typically developing children (n = 11). They also reported that higher usage of oral antibiotics might have a negative role in the excretion of Hg from the body (Adams and Romdalvik, 2007). A study on 45 ASD children and the same number of neurotypical children from Upper Egypt reported that the Hg concentrations in hair and blood were significantly higher in the ASD children compared with neurotypical children (Yassa, 2014). Furthermore, a remarkably higher concentration of Hg was reported in the hair sample of ASD children as 3.35 mg/kg compared with their neurotypical counterparts (0.5 mg/kg) (Blaurock-Busch et al., 2012). Ryu et al. (2017) conducted a longitudinal cohort study of 458 mother child-pairs to assess the Hg levels in different stages of pregnancy and after birth (2–3 years old). They reported a positive association between blood-Hg concentrations in late pregnancy and children, aged five years exhibiting more autistic behaviors. The interaction of Hg in the endocrine, thyroid and sex hormones homeostasis and the effect, particularly on fetal testosterone may play an important role in fetal neurodevelopment and the etiology of ASD (Ryu et al., 2017). A recent meta-analysis reviewed the possible association between Hg and ASD by analyzing 44 published articles by Jafari et al. (2017). They found a significantly elevated level of Hg in whole blood, red blood cells and brain samples and lower Hg-levels in hair samples of ASD patients compared with neurotypical cases (Jafari et al., 2017). They proposed that detoxification mechanisms by glutathione-S-transferase (GST) are impaired in ASD patients, and these patients have a lower concentration of GSH, which leads to the retention of toxins such as Hg in the body. Also, some concentrations of Hg are stored in the nerve cells and showed a restricted effect on detoxification or sequestration of Hg in ASD patients compared with neurotypical individuals. A cross-sectional cohort study reported that there is no causal relationship between Hg exposure and ASD by measuring blood and hair Hg-concentration in 82 ASD children compared with 55 neurotypical children (Ip et al., 2004). They found no significant differences between blood and hair Hg-levels in ASD and children and non-ASD children (Ip et al., 2004). Mostafa and Refai (2007) reported that 40 ASD children compared with their non-ASD child counterparts had significantly higher serum positivity to anti-neuronal antibodies. The higher anti-neuronal antibodies were further correlated with the higher Hg-levels in the blood samples of the ASD children (Mostafa and Refai, 2007).

Epidemiological studies of the Hg-based compound named Thimerosal (49.55% Hg by weight) used as a preservative in vaccines and other serum-based biopharmaceuticals indicate relationships between the level of Hg exposure from Thimerosal and a subsequent atypical autism diagnosis (Geier et al., 2017a, 2017b). Also, the risk of neurodevelopmental disorders following Thimerosal-containing Hib vaccine was revealed compared with Thimerosal-free Hib vaccine applied from 1995 to 1999 in the United States (Geier et al., 2018). Conversely, there are some studies that evaluated Hg concentrations in the urine, blood, and stool of infants who received Thimerosal-containing vaccines and revealed that vaccination above safe limits could not raise the blood concentration of Hg, and indicated that EtHg was very quickly eradicated through the stools (Pichichero et al., 2002; Gadad et al., 2015). A study by Uno et al. (2015) found no convincing evidence that there is a connection between vaccination against measles, mumps, and rubella (MMR), increased Thimerosal dose and increased ASD risk. In addition, studies examining chelation therapy report on a significant decline in the blood levels of Pb and Hg with the use of DMSA (Sandborgh Englund et al., 1994; Geier et al., 2008; Arnold and Morgan, 2015; Davis et al., 2013; Bjørklund et al., 2017c), and also report a decrease in the severity of the symptoms associated with ASD (Yassa, 2014). Another study proposed a protective role of Se in the prevention of neurotoxicity induced by Pb and Hg (El-Ansary et al., 2017a, 2017b). However, a cohort study was conducted on 56 ASD children, their siblings (n = 42) and neurotypical children (n = 121) to examine the association of urine Hg-levels and ASD by Wright et al. (2012). They reported that considering age, sex, amalgam status, and creatinine corrections there was no significant association between urinary Hg-levels and ASD (Wright et al., 2012). Similarly, a study on ASD children (n = 84), developmentally delayed children (n = 49) and neurotypical children (n = 159) showed that total Hg-levels in the serum drawn from mothers and newborn blood spots (heel prick tests) were not significantly correlated with the risk of ASD. Although the ASD children showed Hg levels about 50% higher than for neurotypical children, the difference was not statistically significant due to the large standard deviations (Yau et al., 2014). In another study conducted by Bradstreet et al. (2003) the authors found a higher urinary Hg-level compared with neurotypical children regardless of the sources of Hg, in the urine of ASD children (Bradstreet et al., 2003). However, elevated Hg levels have been found in blood samples (Daniels, 2006; Palmer et al., 2006; Geier et al., 2008; Yassa, 2014; Mostafa and Al-Ayadhi, 2015), tooth specimens (Adams and Romdalvik, 2007) and also in hair samples of children who were diagnosed with ASD (Hodgson et al., 2014; Mohamed et al., 2015). In a study of ASD children (n = 77) in Saudi Arabia, a significantly higher level of hair Hg-concentration compared to neurotypical children was reported (Al-Ayadhi, 2005). Adams et al. (2008) reported lower Hg-levels in the hair of ASD children. The children with lower levels were 2.5-fold more likely to ASD incidence than those with higher Hg hair concentrations. In a recent study, the Hg-level in the hair of ASD children (n = 74) was not found to be significantly different from neurotypical children (n = 74) (Skalny et al., 2017a). Similarly, Skalny et al. (2017b) did not find a significant difference between Hg-levels in the hair of ASD children (n = 33) when compared with neurotypical children (n = 33). The finding that mothers with amalgam fillings transfer Hg to the fetus is of utmost concern since amalgam dental fillings remain in the organism for many years (Bose-O'Reilly et al., 2010). Transfer through breast milk occurs to a lesser extent since the infant's digestive system produces Hg-sequestering metallothioneins (Aschner et al., 2006). The ASD children's hair Hg-level also correlated with oral antibiotics given in the first 18 months of life (2.5 fold higher incidence) and the number of maternal dental amalgams (Adams et al., 2008).

Elevated urinary coproporphyrin excretion, which is an indicator of Hg toxicity, has been reported in 83% of children diagnosed with ASD (Geier and Geier, 2006, 2007). As a potential biomarker of ASD in association with Hg, porphyrins have been evaluated in 100 children in Egypt following three groups: 40 ASD children, 20 healthy siblings of ASD children and 40 neurotypical children by Khaled et al. (2016). Significantly, higher levels of Hg, Pb, along with the porphyrins

pentacarboxyporphyrin, coproporphyrin, precoproporphyrin, uroporphyrins, and hexacarboxyporphyrin were reported in ASD children compared with neurotypical children and with healthy siblings of the ASD children (Khaled et al., 2016). Higher Hg in ASD children may be attributed to the increased Hg exposure as well as the declined Hg excretion and both lead to the high Hg body burden, where coproporphyrin and precoproporhyrin may be considered as suitable biomarkers for Hg exposure and severity of autism (Khaled et al., 2016). This elevation can cause immune, sensory, neurological, and motor dysfunctions (Geier et al., 2008; Kern et al., 2011). Also, it has been hypothesized that use of some oral antibiotics in the children with a subsequent diagnosis of ASD may have decreased their capability to excrete Hg, resulting in a higher level of Hg in, for example, their baby teeth (Adams and Romdalvik, 2007). Moreover, in a study performed according to population-based cohort research, consisting of 96,736 children aged 8–14 years, the authors revealed that the use of antibiotics during pregnancy was a critical risk factor for ASD (Atladóttir et al., 2012). For example, it has been reported that the use of sulfonamides as an antagonist for folate, and impaired status of folate have been implicated as a risk factor in the ASD patients (Main et al., 2010). However, the relationship between ASD and antibiotics is a new finding, which needs further investigation.

Several studies have evaluated the effects of trace elements on the development of the nervous system (Kuntz et al., 1982; Drasch et al., 1994; Skalny et al., 2018). Lewis et al. (1992) studied the risk related to metal exposure including Hg, chromium (Cr), Pb, cobalt (Co), silver (Ag), nickel (Ni) and cadmium (Cd) in amniotic fluid at 16–18 weeks' gestation in 92 women. Their children were examined when they were three years old; results indicated correlations between total metal exposure and the number of infectious diseases the children had acquired, as well as with reduced cognitive function in the same children. El-Baz et al. (2010) studied 32 patients with ASD and found a highly significant elevated level of hair Hg-concentration than in neurotypical children. They also reported a higher level of Hg in ASD children who had routine vaccinations, however not statistically significant, but higher, Hg levels correlated with ASD children with a maternal history of dental amalgam fillings and higher fish consumptions during pregnancy (El-Baz et al., 2010). However, a toxicokinetic model study reported that there is no significant association between MeHg exposures through Hg contained fish ingestion and ASD (McKean et al., 2015). Recently, Li et al. (2018) reported a higher level of Hg in the blood of ASD children (n = 180) compared with neurotypical children (n = 184).

3.3. Mercury and neurotoxicity

The CNS is considered the primary target for Hg toxicity. The neurotoxic effects of Hg exposure involve numerous interrelated mechanisms ultimately leading to cell damage. It has been demonstrated that Hg induces dysfunctions in multiple organelles, including mitochondria, endoplasmic reticulum, and acidic compartments (Vergilio et al., 2015). Furthermore, recent studies have suggested that polymorphism of several genes may mediate changes in Hg metabolism and sensitivity (Custodio et al., 2005; Echeverria et al., 2006; Wang et al., 2012a).

The neuroinflammatory response may be mediated by Hg-induced differential modulation of NF-kB DNA binding activities in brain regions (Dong et al., 2001). It has been shown that Hg significantly reduced neuronal migration in cultures, presumably due to modulation of cytokine production (IL-6, TNF-α) (Sass et al., 2001). Hence, it is proposed that Hg-induced TNF-alpha production in the brain may have a significant impact on ASD development (Curtis et al., 2011). Perinatal Hg exposure also results in the induction of brain autoimmune response, which is characterized by infiltration of CD4 + T cells and accumulation of brain-reactive IgG (Zhang et al., 2010). Moreover, it has been demonstrated that Hg exposure correlates with antigen presentation system gene expression in autistic children (Stamova et al., 2011). Finally, Hg can activate the vascular endothelial growth factor (VEGF) and IL-6 release from human mast cell, which may significantly contribute to the disruption of blood-brain barrier and brain inflammation (Kempuraj et al., 2010).

One of the targets of Hg neuro-toxicity and neuroinflammation is microglia (Bjørklund et al., 2017d). Microglia may exert some control over the immune system in the brain and stimulate the various types of chemokines, proteases, cytokines, eicosanoids, complement and excitotoxins (Blaylock, 2004a, 2004b). For instance, microglial immune cytokines can be stimulated by Hg (El-Ansary and Al-Ayadhi, 2014). Moreover, it has been reported that MeHg exposure up-regulates glial IL-6 production that may be considered as the glial mediator of MeHg neuro-toxicity (Chang, 2007). The activation of the innate neuroimmune system and neuroglia were revealed in the brain tissue and cerebrospinal fluid of ASD patients, indicating that neuroimmune disorders could present in the brain of autistic patients and may contribute to the various, diverse autistic phenotypes (Pardo et al., 2005).

Oxidative stress is one of the key mechanisms mediating Hg neurotoxicity (Farina et al., 2011). The primary target of Hg pro-oxidant action is anti-oxidant selenoproteins due to the high affinity of Hg to selenol (-SeH) groups (Farina et al., 2013). In particular, the affinity of Hg to selenol groups is significantly higher than that for thiol groups (Bjørklund, 2015; Bjørklund et al., 2017b). Correspondingly, MeHg was shown to inhibit GPX and TRX activity (Branco et al., 2012). The existing data also demonstrate an inhibitory effect of Hg exposure on SOD activity (Kumagai et al., 1997). Due to the high affinity to thiol groups, Hg was also shown to deplete the intracellular pool of reducing agents, predominantly GSH (Bjørklund et al., 2017b). In turn, neuronal GSH depletion significantly increases MeHg accumulation and the predisposition of the neuronal tissue to oxidative stress (Kaur et al., 2006). Thimerosal exposure was also associated with GSH depletion (James et al., 2005). However, the pro-oxidant effect of Hg exposure is related not only to inhibition of the anti-oxidant system. It has been demonstrated that Hg both directly and indirectly increases ROS production. In particular, Hg-induced activation of NADPH-oxidase may at least partially mediate the increase in ROS production (Aguado et al., 2013; Rizzetti et al., 2013). Moreover, certain Hg complexes may directly produce superoxide (Aliaga et al., 2010). Also, Hg is also capable of alteration of mitochondrial electron transport chain (Carratù and Signorile, 2015), ultimately leading to impaired energy homeostasis and ROS overproduction (Belyaeva et al., 2012). In general, Hg-induced oxidative stress results in oxidative damage to biomolecules in both cortical neurons and Purkinje cells (Syversen and Kaur, 2012). Superoxide anion radical, peroxynitrite, as well as hydrogen peroxide were shown to be overproduced in Hg-exposed astrocytes (Shanker et al., 2004). Increased ROS production and oxidative stress may at least partially mediate the neurotoxic effects of Hg. In particular, some authors reported that ROS-induced activation of ERK1/2 and p38 is associated with mitochondrial-dependent apoptosis in neuronal cells exposed to MeHg (Lu et al., 2011). Prooxidant activity of Hg was also shown to mediate the inhibitory effect of MeHg on Jak-STAT signaling, which is crucial for the developing brain (Monroe and Halvorsen, 2006). It has also been demonstrated that MeHg-induced ROS production down-regulates glutamine synthetase activity, thus affecting glutamate utilization (Xu et al., 2012). Taken together with reduced uptake of glutamate by astrocytes (Aschner et al., 2007); such changes may result in excessive glutamate accumulation and excitotoxicity (Juarez et al., 2002). Altered glycine and γ-aminobutyric acid play a significant role in Hg-induced excitotoxicity (Fitsanakis and Aschner, 2005).

Oxidative stress and glutamate excitotoxicity may significantly contribute to Hg-induced cytoskeletal alterations (Pierozan et al., 2017). In particular, it has been reported that Hg binds both kinesin and tubulin molecules thus preventing tubulin polymerization and kinesin-mediated microtubule activity (Stoiber et al., 2004). Mercury possesses

a higher affinity to sulfhydryl groups of cytoskeletal proteins than to those in chelators like EDTA (Stoiber et al., 2004). Finally, 21 studies revealed that Hg might induce higher anti-neuronal antibodies as well as immune, sensory, neurological, and motor dysfunctions in ASD patients, although four studies reported no significant increased level of Hg in ASD children (Table 1).

4. Aluminum

4.1. Aluminum and the environment

Aluminum is the third most abundant metal in the Earth's crust and is one of the most durable, light, strong and corrosion resistant elements in the periodic table. It is naturally found in silicates, cryolite, and bauxite-containing rock (Krewski et al., 2007). Its slightly soluble salts are neurotoxic compounds with known adverse health effects in a variety of living organisms, including microbes, plants, fish, and mammals (Rahbar et al., 2016). Aluminum has a constant presence in our daily lives, including cookware and cans, boats, housing, aluminum foil materials, airplanes, components of electrical devices and cars (Blaylock, 2012). Routes of human exposure to toxic Al species include food (Krewski et al., 2007) and Al-containing water through the digestive tract, skin absorption, occupational inhalation of particles containing Al and/or Al compounds and the use of cookware and food packaging materials made from elemental Al and Al-containing alloys (Shaw et al., 2014; Weidenhamer et al., 2014). Further, consumer products such as antacids (aluminum hydroxide), astringents, food additives (aluminum oxides), antiperspirants, fuel additives, explosives, propellants, building materials, components of electrical devices, airplanes, boats, cars and cosmetics raise their users' exposure to toxic Al species, which are excreted from the human body in feces and urine (Krewski et al., 2007; Shaw and Tomljenovic, 2013; Rahbar et al., 2016). Hydroxylated salts of Al are most frequently used as vaccine adjuvants (Tomljenovic et al., 2014). According to some authors, Al adjuvants rupture and damage the phagolysosomes, produce reactive oxygen species, and stimulate potassium efflux from several cell types (Aimanianda et al., 2009). Also, Al is a highly reactive metal and oxidizes very easily, forming a stable aluminum oxide on its surface. Aluminum has only existed as a metal in the last 150 years, due to human production of Al from its very stable oxide ore. Therefore, humans have not evolved in the presence of metallic Al. Aluminum oxide is extremely stable and probably has a low bio-reactivity, and comprises a high fraction of the earth's crust.

4.2. Aluminum and autism spectrum disorder

It has been proposed that Al exposure may contribute as an environmental factor to cause ASD when taken in its elemental or salt form via oral ingestion and/or as adjuvant (Morris et al., 2017). Numerous studies highlight the relevance of Al exposure and development of ASD (Table 1). For example, Shaw and Tomljenovic (2013) have reported the potential involvement of Al adjuvants in the development of ASD. They found the prevalence of ASD in areas where exposure to vaccine-derived Al is high. Indeed there are controversies between the relationship of Al adjuvant and development of ASD regarding the consideration of ASD as a single entity or in a combined term of heterogeneous syndromes like Pervasive developmental disorder (PDD), Attention deficit hyperactivity disorder (ADHD), attention deficit disorder (ADD), and ASD. However, recently the increasing frequency of ASD occurrences may have been attributed to the passive relationship between the Al adjuvant and ASD (Morris et al., 2017). A recent study by Mold et al. (2018) demonstrated that patients with ASD have abnormally high brain levels of Al. Long-term exposures to both Al and fluoride (F) have several adverse health effects, which have a marked resemblance to the symptoms used to diagnose ASD (Sealey et al., 2016). The synergistic interaction of Al and fluoride induce several side effects with a striking resemblance to ASD (Strunecka et al., 2016). It interplays with numerous glycolytic enzymes, inducing suppression of cellular energy synthesis and elevating the potential neurotoxic effects in children (Strunecka et al., 2016). A study recently conducted on 100 ASD children in Egypt to examine the potential relationship between ASD and environmental factors by Mohamed et al. (2015) found mean hair levels of Al in ASD children were higher, compared with 100 neurotypical children. Al-Farsi et al. (2013) reported a similar increased level of Al concentration in the hair of ASD children versus neurotypical children in Oman. However, there is also evidence that the Al concentration levels in ASD children vary greatly (Dickerson et al., 2017). Conversely, several studies reported higher Al concentration in the hair samples of neurotypical children than ASD children (Albizzati et al., 2012; Adams et al., 2006). In a study, a remarkably higher concentration of Al was reported in the hair sample of ASD children at 15.21 mg/kg compared with neurotypical children (8 mg/kg) (Blaurock-Busch et al., 2012). Rossignol et al. (2014) summarized, in a review that out of 11 case-control studies, three showed an elevated level of Al in ASD children. In blood, the Al concentration was almost similar to neurotypical children, but in hair and urine, the concentration was mostly similar but was elevated in some cases. Also, the mean levels of Al in the hair of the ASD patients were notably higher than in neurotypical individuals (Mohamed et al., 2015).

On the other hand, some studies reported no relevance between Al contents of hair (Fido and Al-Saad, 2005; Al-Ayadhi, 2005) and Al contents of urine and blood of ASD children (Albizzati et al., 2012). For example, Adams et al. (2006) reported an increased Al concentration in urine of ASD children compared with their neurotypical siblings. However, Albizzati et al. (2012) and Rahbar et al. (2016) found a higher concentration of blood Al level in neurotypical children compared with ASD children. A study by Blaurock-Busch et al. (2011), found higher hair Al concentrations, but lower Al urine concentrations in ASD children compared to neurotypical children (Blaurock-Busch et al., 2011). Skalny et al. (2017a) and De Palma et al. (2012) have reported no significant difference in hair Al concentration between the ASD and neurotypical children. Moreover, we have observed a significant decrease in serum Al levels only in children with atypical autism, but not childhood autism (ICD-10 criteria) (Skalny et al., 2017c). The interactive effects of ASD and polymorphisms in the GST genes regarding blood levels of Al revealed the association between GSTP1 rs1695 and blood levels of Al among Jamaican children (Rahbar et al., 2016).

However, it has been shown that the association between blood Al contents and GSTP1 rs1695 may vary according to the autism severity.

There are also indications that the Al adjuvants in vaccines could be causally associated with the symptoms used to diagnose ASD (Tomljenovic and Shaw, 2011; Shaw and Tomljenovic, 2013; Miller, 2016). Thus, a recent study reported a positive correlation between the levels of the toxic metals including Al and the severity of the ASD symptoms as assessed by using the Childhood Autism Rating Scale (CARS) (Metwally et al., 2015). According to numerous studies, the interaction of Al in ASD patients was attributed to suppression of cellular energy synthesis and elevation of the potential neurotoxic activities in ASD children. Only two studies did not find relevance between Al levels/exposure in ASD children (Table 1).

4.3. Aluminum and neurotoxicity

Considerable research, over the past two decades, has focused on Al neuro-toxicity in more central pathophysiological pathways, which could induce much of the toxicity of Al and aluminofluoride compositions on the brain (Shaw and Tomljenovic, 2013). These pathways could activate the brain's innate immune system with the release of pro-inflammatory cytokines, chemokines, neurotoxic concentrations of excitotoxins and immune mediators in the microglia.

Al-induced reactive gliosis was associated with decreased

antioxidant enzyme levels, as well as up-regulation of glial fibrillary acidic protein (GFAP) and ionized calcium-binding adapter molecule 1, TNF-α, IL-1-β, and iNOS (Prakash et al., 2013). Moreover, it has been noted that Al-induced increase in NF-kB and IL-1α levels in murine brains was not mirrored in the liver serum of treated animals, this proinflammatory effect of Al may be selective to the brain (Campbell et al., 2004). Al exposure resulted in glial activation with a significant increase in NF-kB and TNF-α expression, as well as HSP70 induction. It is notable that curcumin inhibited these responses and is indicative of the potential role of oxidative stress in pro-inflammatory response (Sood et al., 2012). Similarly, the protective effect of another antioxidant, mangiferin, was demonstrated with respect to Al-induced oxidative and nitrosative stress, inflammation, and decreased BDNF levels (Kasbe et al., 2015). It has also been demonstrated that Al-induced oxidative stress is associated with mitochondrial dysfunction and altered energy homeostasis in the brain (Kumar, Gill, 2014). Oxidative stress-induced glial activation in metal-exposed animals is also associated with B-cell infiltration of the prefrontal cortex (Akinrinade et al., 2015). Aluminum was also shown to induce oxidative DNA damage and is associated with increased p53 expression and cell cycle disruption due to increased cyclin D expression in different brain regions (Kumar et al., 2009).

Exposure to aluminum lactate (10–100 μM) resulted in a significant dose-dependent increase in brain TNF-α and IL-1-α levels (Becaria et al., 2006). NF-kB activation is involved in the induction of TNF-α, IL-6, and iNOS expression in Al exposed rats (Zaky et al., 2013). It is proposed that Al-induced activation of NF-kB and HIF-1 in human brain cells is, at least partially responsible, for apoptotic signaling (Lukiw et al., 2005). These data are in agreement with the observation of increased neuronal apoptosis in Al exposed animals and a compensatory up-regulation of Bcl-2 expression (Niu et al., 2007). It is also notable that various aluminum citrates possess different toxicity profiles affecting either neurons or glia in hippocampal cultures (Platt et al., 2007).

Primary brain cultures exposed to Al are characterized by a significant impairment of nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) expression in parallel with increased proinflammatory cytokine production (MIP-1α, TNF-α) (Johnson and Sharma, 2003). The majority of Al neurotoxic effects are supposed to be associated with direct binding of the $Al3+$ ion by oxygen-based ligands (Exley, House, 2011). It is also notable the direct interaction of $Al3+$ with superoxide anion may result in the formation of the aluminum superoxide semi-reduced radical ion ($AlO_2(aq)2+$) (Exley, 2004). Interference with essential metals like $Mg2+$ and $Ca2+$ (Exley and House, 2011) via direct interaction of $Al3+$ ion with ATP (Exley, 2012) may also play a significant role in Al neuro-toxicity and excitotoxicity (Blaylock, 2004b, 2012).

Either by oral ingestion as salt or as an adjuvant, Al exposure may induce the dysfunction or activation of glial cells that are important in maintaining the homeostasis of the CNS and in neurodevelopment (Morris et al., 2017). Furthermore, Al can induce the activation of microglia to produce TNF-α, IL-6, iNOS, NOS-2, neuroinflammatory PICs and ROS (Zaky et al., 2013). The microglia may govern the regulation of neurogenesis and neurodevelopmental factors and interfere with synaptic pruning and with the proliferation of neurons, which in turn, may lead to the development of ASD (Kettenmann et al., 2013; Edmonson et al., 2016; Hoeijmakers et al., 2016).

5. Arsenic

5.1. Arsenic and the environment

Arsenic is released into the environment via both geochemical and anthropogenic processes. As-based compounds are considered to pose one of the most significant potential threats to human health as judged by their frequent occurrence, toxicity, and by the number of humans exposed (Rosen and Liu, 2009). Worldwide, As poisoning through As-contaminated groundwater is one of the most threatening public health problems (Tyler and Allan, 2014; Bjørklund et al., 2017e). Recent studies reported that more than 140 million people are exposed to chronic As pollution in drinking water at levels exceeding the World Health Organization's (WHO) recommended a limit of 10 μg/L (WHO, 2011). The majority of heavily exposed people reside in developing countries, like Argentina, Bangladesh, India, China and so on (Rahman et al., 2011, 2016; Lopez et al., 2016). Because of its worldwide occurrence and its toxicity, As is seen as a critical toxicant. However, small amounts of elemental As (As^0) exist in the Earth's crust, As is mainly found in minerals such as realgar (As_4S_4), orpiment (As_2S_3) and arsenolite (As_2O_3).

In developing and developed societies, As exists mainly in inorganic forms (iAs), in the + 5 and + 3 oxidation states in arsenate and arsenite salts, as well as in generally less toxic organometallic arsenicals, like arsanilic acid ($C_6H_8AsNO_3$) and arsenicin A ($C_3H_6As_4O_3$), and the more toxic industrial reagent arsine H_3As. In 2000, the total industrial-age production of As was estimated at 4.53 million tons (Han et al., 2003). More than 200 million people worldwide are exposed to As through drinking water (Kabay et al., 2010). The total costs of 1 kg of As emissions into the environment are $3742 (in 2010 USD), and nearly 20% of these costs are related to IQ loss and other psychiatric disorders (Nedellec and Rabl, 2016). In particular, the increase of As levels in various substrates was associated with IQ loss (Hamadani et al., 2011; Nahar et al., 2014; Wasserman et al., 2014). Therefore, the brain may be considered as one of the key targets for As toxicity.

5.2. Arsenic and autism spectrum disorder

Several studies suggest environmental As exposure in children is related to the risk of subsequent ASD diagnoses but the findings vary greatly from one case report to another (Table 1) (Lonsdale et al., 2011; Yasuda et al., 2013; Dickerson et al., 2016, 2017; Skalny et al., 2017a). Li et al. (2017) reported significantly elevated levels of As in blood of children with ASD diagnosis compared with the levels found in neurotypical children. Two other studies reported a relationship between As exposure and ASD (Al-Ayadhi, 2005; Dickerson et al., 2015). Obrenovich et al. (2011) conducted a study among 26 ASD and 39 neurotypical children to assess the status of metal contents in hair samples. In their study, it was found that the As levels of hair in ASD children is significantly higher compared with neurotypical children. Similar results were reported in Saudi ASD subjects with elevated hair As concentrations found to be higher when compared with their counterparts (Al-Ayadhi, 2005). Skalny et al. (2017a) reported an opposite result after conducting a study on 74 ASD and the same number of neurotypical children. They reported in the 2–4 years age group 73% ASD children showed lower As concentration than neurotypical children in terms of their hair metal contents. Kern et al. (2007) also reported significantly lower hair As concentration in ASD children than in their neurotypical siblings. However, other studies reported there are no significant changes among ASD and neurotypical children regarding the hair concentration level of As (Fido and Al-Saad, 2005; De Palma et al., 2012). Blaurock-Busch et al. (2011) studied 25 ASD children in Jeddah city and examined their hair and urine trace metal contents. They reported a significantly higher concentration of As in hair in ASD children at 2.94 mg/kg compared with neurotypical children (0.7 mg/kg), whereas there were no significant differences in the urine As content between the ASD and neurotypical children. A study conducted by Adams et al. (2013) also reported that in terms of blood As and urine As levels there was no significant difference between ASD and neurotypical children, with very slightly elevated levels in the neurotypical children. Conversely, Li et al. (2017) demonstrated a higher level of As concentration in blood of ASD children compared with their neurotypical counterparts. However, Rahbar et al. (2012) reported significantly lower blood As concentration in the ASD children compared with

neurotypical siblings in Jamaica, in agreement with our observations in children with atypical autism (Skalny et al., 2017c). Recently, Dickerson et al. (2016) reported a lower ASD prevalence in areas with high ambient concentrations of Pb, Hg, and As. They conducted the study on 4486 ASD children living in 2489 census tracts in five sites of the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network. It is not possible to draw any meaningful conclusions regarding the interactions of As and the development of ASD. However, as a potential environmental risk factor for the etiology of ASD, it should be considered as a matter of scientific interest to design further studies. The diverse neurotoxic effects that may be induced by As warrants further examination of As as a causal factor for the development of ASD in children. In summary, there are mixed results about the interaction of As in ASD children that summarized in Table 1.

5.3. Arsenic and neurotoxicity

Arsenic exposure significantly was seen to affect brain morphology, resulting in gliosis and neuronal degeneration, as well as blood-brain barrier disruption (Selim et al., 2012). In particular, both inorganic As and dimethylarsinic acid induce neuronal apoptosis via activation of JNK and p38 signaling and caspase activation (Namgung and Xia, 2001). Also, the apoptotic reaction was associated with up-regulation of Bax and Bak expression, as well as depression of Mcl-1 in the cerebral cortex of As-exposed mice. Moreover, As-induced apoptosis was shown to be related to oxidative stress, such as depletion of GSH, and increased levels of lipid peroxidation, indicated by its inhibition with N-acetylcysteine (Yen et al., 2011; Rahman et al., 2018). Correspondingly, oxidative stress was shown to mediate neurotoxic effects of As exposure (Liu et al., 2013b). Furthermore, it can be seen that chronic exposure to As could stimulate cognitive impairments and hippocampal neuronal apoptosis through overexpression of BMP2/Smad-dependent declined BDNF/TrkB signaling pathway in rats (Pandey et al., 2017). Oxidative stress was shown to mediate neurotoxic effects of As exposure (Liu et al., 2013b).

Arsenic exposure also resulted in impaired neurite growth due to suppression of AMPK kinase activation (Wang et al., 2010). These data are in agreement of impaired neurogenesis in response to As exposure in mice (Liu et al., 2012b; Tyler and Allan, 2013). In particular, it has been demonstrated that As induced inhibition of Wnt/β-catenin signaling pathway and the related decrease in neuron-specific transcription factors, Pax3, neurogenin 1 and 2, and NeuroD (Hong and Bain, 2012)

Monomethylarsonous acid exposure in sub-toxic doses caused a significant increase in IL-1β, IL-6, TNF-α, COX-2, and MIF-1 expression in astrocytes (Escudero-Lourdes et al., 2016). It is notable that As-induced alteration of the arachidonic acid metabolic pathway may at least partially mediate inflammatory response and neuronal damage in exposed animals (Anwar-Mohamed et al., 2014).

Arsenic exposure significantly affects the glial component of the CNS. In particular, the expression of a pro-inflammatory cytokine such as IL-6 and NF-κB by arsenic trioxide could be regulated by overexpression of p-Akt in HAPI microglia cell lines (Chen et al., 2016b). Another study reported that IL-1β secretion and activation of STAT3 stimulated through As can be regulated by an increase of P38/JNK MAPK in HAPI microglia cells, inducing neuronal toxicity (Mao et al., 2016). Increased glial fibrillary acidic protein expression in As-exposed mice was associated with impaired learning and memory abilities (Jiang and Sun, 2011). It is notable that microglia is differentially susceptible to As species, being more sensitive to As(III) toxicity compared with As(V) (Wu et al., 2010). It is also notable that As also induces endoplasmic reticulum stress as assessed by increased GRP78, GRP94, and CHOP expression (Yen et al., 2011; Lu et al., 2014).

Mitochondria were shown to be the major target of As neuro-toxicity (Prakash et al., 2016). In particular, it has been demonstrated that As exposure inhibits electron transport chain complexes I, II, and IV, ultimately leading to increased ROS production in mitochondria. These changes are accompanied by mitochondrial MnSOD inhibition (Prakash et al., 2015). Mitochondrial dysfunction may be in turn associated with apoptotic death in microglial cells (Kharroubi et al., 2017).

Arsenic neuro-toxicity affects both the central and the peripheral nervous systems (Frankel et al., 2009). An in vitro study showed that As exposure inhibited neurite generation and further growth, which was followed by the impaired development of newly differentiated PC12 cells even with low-to-moderate levels of As exposure (Frankel et al., 2009). Also, studies have reported that As exposure induces apoptosis via the Bcl2/Bax pathway in the hippocampus of mouse brains cells and via NB4 cells by inhibition of nuclear factor NFκB (Wang et al., 2015), and also in PC12 cells (Rahman et al., 2018).

Exposure to As was shown to interfere with neurotransmitter metabolism. In particular, As exposure disrupts glutamate-induced gliotransmitter release resulting in altered neuronal function (Wang et al., 2012b). It also impairs glutamate transport through modulation of EAAT1/GLAST activity in glial cells (Castro-Coronel et al., 2011). Arsenic exposure significantly influenced dopaminergic alterations in the brain through increased expression of DAR-D2 receptor gene and is also associated with hyperactivity (Chandravanshi et al., 2014a). Moreover, As and dopamine potentiate neurotoxic effects on dopaminergic neurons (Shavali and Sens, 2007). Arsenic-induced alteration of cholinergic signaling was also associated with impaired spatial memory and learning in rats (Chandravanshi et al., 2014b). It has also been demonstrated that As-induced alteration of cysteine/glutamate transporters in brain cortex and hippocampus, as well as suppression of NMDAR in hippocampal neurons, was associated with spatial memory impairment in rats (Ramos-Chávez et al., 2015).

Finally, epigenetic modifications through modulation of DNA methylation are also considered as one of the mechanisms of As toxicity (Bjørklund et al., 2017e). In particular, it has been demonstrated that As exposure affects methylation of various genes (Martínez et al., 2011), and induces histone modifications (Cronican et al., 2013) in the CNS. It has also been demonstrated that differentiation status might influence the epigenetic effect of As exposure (Kim et al., 2016b).

6. Overview of intervention for metal-(loids) toxicity

Toxic metal exposure exerts certain stresses on body's immune system (disrupting antioxidant defense) and can be viewed as a potential candidate for the environmental factor of ASD etiology (Table 1). Research has shown that immune dysregulation and inflammation can be crucial factors for ASD development and are key components of the diagnosis and treatment of ASD (Bjørklund et al., 2016). However, current toxic metal detoxifying procedures are still unable to provide complete remission from ASD. Reducing toxic metal exposure is, of course, the primary intervention option followed by reducing the effects of exposure, by boosting natural detoxification reactions such as enhancing the glutathione protection/metallothionein activation. However, in an acute exposure scenario, synthetic chelating agents are used to detoxify toxic metals. For instance, Bjørklund et al. (2017c) reviewed the possible role of different chelating agents such as DMPS, DMSA, CaEDTA and BAL to detoxify Hg, Pb and As thus reducing their neurotoxicity. They found that DMSA is an effective agent to reduce the blood level of Pb and Hg and proposed that a combination of BAL with DMPS can be more effective than when used separately (Bjørklund et al., 2017c). However, the effects of chelating agents are in some way associated with the route of administration, organ-specific distribution, and, sometimes the status of antioxidants, e.g., with vitamin E, acetylcysteine, or lipoate (Pande and Flora, 2002; Kalender et al., 2013). A possible benefit for ASD children may be by Al-chelating drugs, including nutritional fibers or by adding bran to children's food (Metwally et al., 2015). Moreover, some dietary supplements have also been shown to have detoxification potential for toxic metal exposures in vulnerable groups, including children with ASD. It has been reported in

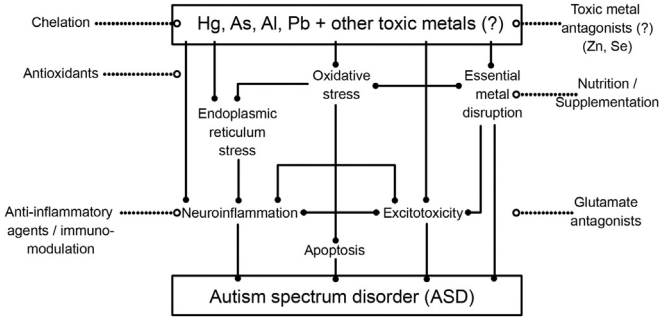

Fig. 1. The mechanisms of the pathogenetic role of toxic trace metals in autism spectrum disorder and the potential treatment strategies.

different studies that dietary components effectively/partly modulate the toxicity of metal-(loids) mainly through reducing their deleterious effects, by reduction of intestinal absorption, and subsequent bioaccumulation and/or direct counteracting their antioxidant and/or anti-inflammatory activity, among other factors (Jadán-Piedra et al., 2017). For example, animal model studies observed that high-Se lentil diets ameliorate As toxicity and reduce As-related atherosclerosis (Sah et al., 2013; Krohn et al., 2016). Additionally, Zn and Se supplementation could be beneficial against Pb, Cd, As induced toxicity as reported using in vitro model (Rahman et al., 2017; Hossain et al., 2018). Zn and Se supplementation boosted the GSH level as well as upregulated expression of GPx in the cells to ameliorate metal toxicity. Furthermore, it has been reported that supplementation with ascorbic acid, a-tocopherol, and L-methionine (100 mg/kg/day bodyweight) reduces Pb-induced oxidative stress in the kidney, liver, and brain of rats (1 mg/kg bodyweight, four weeks) with no significant decline in tissue burden (Patra et al., 2001). In most of the cases, the toxic metal-(loids) exert oxidative stress, which can be counteracted by using antioxidants from dietary sources for chronic exposure. However, acute exposure could be ameliorated through the clinical application of chelating agents. A recent study on 30 children with ASD and 30 neurotypical children showed that both impaired energy metabolism and oxidative stress are a potential predictive marker for ASD, which has great implications in both the diagnosis of and therapies for ASD (El-Ansary et al., 2017a, 2017b). Moreover, in another study on 47 ASD male children and 46 neurotypical children showed a positive correlation between different markers of neuroinflammation and ASD (Qasem et al., 2018). Also, ASD patients showed that serum Fe, Cu, Mn, Cd concentrations might be associated with neuroinflammation (Skalny et al., 2018). It was reported that metal exposures (e.g., As) could alter the arachidonic acid metabolic pathway which may mediate inflammatory response and neuronal damage (Anwar-Mohamed et al., 2014). Thus, regeneration of GSH/energy metabolism through the application of therapeutics could be promising preventive measures for metal toxicity in ASD patients.

7. Conclusion

The dramatic rise in the number of children diagnosed with ASD in the past two decades has actualized the need for safe and effective preventive measures. Over the last three decades, numerous studies have reported a possible relationship between ASD and Hg exposure. However, there are also some investigations that conclude that heavy metal exposure is not a risk factor for ASD. Therefore, an accurate evaluation of the relationship between ASD and heavy metals urgently needs more research. Although some of the existing data demonstrate that combined exposure and neuroinflammation may mediate neurotoxic effects of heavy metals and metalloids. In particular, mechanisms of metal neuro-toxicity that may initiate or accelerate the ASD pathogenesis include oxidative stress, endoplasmic reticulum stress, and essential metalloprotein disruption, all of which lead or contribute to neuroinflammation, excitotoxicity, and apoptosis. Also, numerous studies reported that ASD children are more susceptible to heavy metals than neurotypical children and this is reflected in biomarkers indicative of heavy metals, in the urine, brain, blood, hair, nails, and deciduous teeth. Therefore, the potential strategies for prevention and treatment of ASD may include a variety of methods targeting each of these mechanisms, including metal chelation or using heavy metal antagonists (Se, Zn), nutritional correction, antioxidant and anti-inflammatory therapy, and the possible use of glutamate antagonists (Fig. 1). Also, reducing exposure to heavy metals by a reduction in exposure to polluted water and heavy metal pollution. Additionally, increasing the body's natural detoxification ability, especially by increasing GSH (for Hg) and reducing exposure to oral antibiotics during pregnancy are the main advice to reduce potential prenatal exposure to toxic metals. With ongoing and increasing worldwide exposure to a broad spectrum of environmental pollutants, studies on their role in neurodevelopmental disorders and their epigenetic impact are of crucial importance.

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