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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