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Environmental influence on neurodevelopmental disorders; potential association of heavy metal exposure and autism

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Abstract

Environmental factors have been severally established to play major roles in the pathogenesis of neurodevelopmental disorders including autism spectrum disorder (ASD). ASD is a neurodevelopmental disorder that is associated with symptoms that reduce the quality of life of affected individuals such as social interaction deficit, cognitive impairment, intellectual disabilities, restricted and repetitive behavioural patterns. ASD pathogenesis has been associated with environmental and genetic factors that alter physiologic processes during development. Here, we review literatures highlighting the environmental impact on neurodevelopmental disorders, and mechanisms by which environmental toxins may influence neurodevelopment. Furthermore, this review discusses reports highlighting neurotoxic metals (specifically, lead, mercury, cadmium, nickel and manganese) as environmental risk factors in the aetiology of ASD. This work, thus suggests that improving the environment could be vital in the management of ASD.

Keywords

autism; neurodevelopmental disorders; neurotoxicity; metals; environment

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The authors declare no conflict of interest.

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1. Autism Spectrum Disorder as a Neurodevelopmental Disorder

Neurodevelopmental disorder (NDD) is an umbrella word for different conditions resulting from aberrant brain development. This abnormal neurodevelopment is mostly due to foetal exposure to harmful substances. Its symptoms include deficit in behaviour, cognition, communication and periodically motor skills. Autism spectrum disorder (ASD), amongst other neurodevelopmental conditions, such as attention deficit/hyperactivity disorder (ADHD), intellectual disability, falls in this category (Bromley et al., 2013; Mullin et al., 2013). ASD manifests during the first three years of life and is known to affect the brain regions responsible for social interaction, communication and other patterned behaviour. ASD prevalence approximates 0.6% of the global population and is prevalent in the male gender (Xiao et al., 2014). The recorded increase in ASD rate is associated with increased awareness and introduction of new diagnostic benchmarks (Lundström et al., 2015). In its latest report, the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network noted increased rate of ASD between 2014 and 2016 (Baio et al., 2018).

Specific brain regions have been linked with the symptoms of ASD, such as basal ganglia, temporal lobe, frontal lobe, amygdala, limbic structures, and cerebellar region (Xiao et al., 2014). Histological studies show elevated dendritic spines density in Golgi-infiltrated pyramidal neural cells of layer II in the frontal, parietal and temporal lobes and layer V of the temporal lobe in ASD patients indicating distorted cortical synaptic action (Hutsler and Zhang, 2010). Genetic, in-utero imaging, histologic and functional data all indicate that altered sequence of neural connectivity is the biological basis for intellectual and behavioural anomaly characterized with many neurodevelopmental disorders (Lein, 2015).

2. Environmental Impact on Neurodevelopmental Disorders

The environment has been established to be a strong determinant of juvenile health with higher risk of disruption to neurodevelopment. Grandjean and Landrigen pointed to over a dozen industrial chemicals categorized as neurodevelopmental toxicant and emphasized the presence of other neurotoxicants which have not been tested on humans (Grandjean and Landrigan, 2014). The drastic rise in the prevalence of neurodevelopmental disorders supports the idea that environmental factors may play a major role in these disorders (Landrigan et al., 2012). Animal studies have established exposure to environmental neurotoxicants at a low dosage, which would normally have little or no damaging effect to the nervous system, may lead to a lasting alteration in the physiologic development/ maturation activities (Rauh and Margolis, 2016). The behavioural damages associated with early life vulnerability to environmental toxicants carry a huge cost to individuals, their families and society at large (Gould, 2009); hence the need for more studies to better understand the association between environmental toxicity and neurodevelopmental consequences. Early evidence of environmental influence on neurodevelopmental disorders has been associated to the increased rate of autism are linked to congenital rubella (Lein, 2015). Other studies linked foetal infections to other neurodevelopmental disorders aside ASD (Lee et al., 2015; Ohkawara et al., 2015) and also included other non-genetic risk factors such as paternal age (Idring et al., 2014), metabolic rate, hormones and maternal nutrition (Lein, 2015) however, another study found no link between certain risk factors and

possibility of having a child with neurodevelopmental disorder. These risk factors include: maternal/paternal age, sea food consumption during gestation, smoking during gestation, method of childbirth, dental amalgam and exposure to pesticides (Yassa, 2014).

3. Mechanisms Involved in Environmental Influence on Neurodevelopment

There are postulated mechanisms that act as an intermediate between environmental agents and genetic risk factors that alter developing neural connectivity. It should be noted that the mechanisms discussed here are by no means exhaustive. They include;

1. Epigenetic/ genetic mechanism.
2. Immune dysregulation/ neuroinflammation
3. Oxidative stress and mitochondrial malfunction.
4. Endocrine alteration
5. Neurotransmitter alterations and aberrations in signalling pathways

3.1. Epigenetic/ Genetic Mechanism

Epigenetic mechanism refers to modulations in the DNA that affects gene expression but do not alter genetic sequence (Modabbernia et al., 2017). There is compelling evidence from experimental and clinical investigations that epigenetic mechanisms are crucial in controlling physiologic development of the nervous system, intellectual ability and changes in synapses. Epigenetic changes in the nervous system has also been linked to neurodevelopmental disorders, however, very few information has directly linked environmental agents to neurodevelopmental disorders through epigenetic mechanism. Lesiak et al demonstrated that the non-dioxin-like (NDL) polychlorinated biphenyls (PCB), PCB 95 elevated synapse formation through increased expression of miR132 (Lesiak et al., 2014). Yao et al linked miR132 to the suppression of methyl-CpG binding protein-2 (MeCP2) (Yao et al., 2017). Furthermore, there could be anomalies in genes that code for specific proteins that are responsible for the breakdown of foreign substances and endogenous toxicants. An example involves paraoxonase 1 (PON 1), an enzyme needed for hydrolysis of organophosphate (OP) pesticides, and which have been implicated in elevated risk of autism.

3.2. Immune Dysregulation / Neuroinflammation

Interaction between the immune system and neural cells is essential for neurodevelopment (Patterson, 2011). There are disparate cytokines synthesized in the brain where they play important function in neurodevelopment such as synaptogenesis, anatomic plasticity and neuronal differentiation (Garay and McAllister, 2010). Neuropoietic cytokines such as interleukin-6 (IL-6) and the type II interferon gamma (IFNɣ) have distinct roles in neurodevelopment (Masi et al., 2015). IFNɣ functions to regulate growth of dendrites through effects on transcription and signal transducers and mitogen-activated protein kinase (MAPK) signalling. Neuropoietic cytokines also communicate with different neurons *ex-vivo* to regulate dendritic growth and synaptogenesis and *in-utero* to regulate synapse removal in the developing murine brain (Lein, 2015). Cultured hippocampal neural cells

show that increased IFNɣ alters the balance of inhibitory to excitatory signalling. While reduced IFNɣ leads to decreased density of presynaptic terminals in the spinal cord of adult Mice. There is evidence of increased level of neuropoietic cytokines such as IL-6 in ASD patients (Masi et al., 2015). The effect of maternal inflammatory intermediaries and antibodies on prenatal neurodevelopment is also an established mechanism for ASD occurrence (Modabbernia et al., 2017). Additional research has also alluded to a possible role of neuroinflammation and prostaglandin E_2 (PGE2) pathway in the onset of ASD, advocating for the use of prostaglandin E_2, Cyclooxygenase-2 (COX-2) and Microsomal prostaglandin E synthase-1 (mPGES-1) as a biomarker for autism progression (Qasem et al., 2018).

3.3. Oxidative Stress/Mitochondrial Dysfunction

Environmental factors such as mercury, lead, and many persistent organic pollutants (POPs), could lead to an imbalance between free radicals and antioxidants which results in neurodevelopmental aberration. Oxidative stress is also a proposed mechanism by which mitochondrial dysfunction occurs. Exposure to certain chemicals may lead to mitochondrial toxicity and consequently an imbalance in ATP level in neural cells. This has been reportedly linked to ASD (El-Ansary, 2016; Jafari et al., 2017; Rossignol and Frye, 2012).

3.4. Endocrine Disruption

The need for thyroid and several other hormones for physiologic brain development has linked hormonal imbalance to ASD. It has severally been reported that males are more susceptible to ASD. Also, the genetic and physiologic manifestation in ASD patients are different in males and females. Environmental factors that result in hormonal imbalance (specifically testosterone in foetus) may be partly responsible for the onset of ASD. For example, brominated flame retardants are linked to elevated testosterone level leaving foetus more vulnerable to ASD (Braun et al., 2014). Aside testosterone, alterations in estrogen receptors have been shown to be associated with a high incidence of ASD (Crider and Pillai, 2017)

3.5. Neurotransmitter Changes and Aberrations in Signalling Pathways

Alterations in neurotransmission, including serotonin, glutamate and gamma-aminobutyric acid (GABA) has been shown to be associated with ASD (Modabbernia et al., 2017). There may be a direct interplay between some environmental agents and the neurotransmitter pathways. An example is the direct effect of lead on N-methyl-D-aspartate (NMDA) receptors (Neal and Guilarte, 2010). Many environmental agents have also been linked to abnormal glutamate level in umbilical cord blood (Palou-Serra et al., 2014). Additionally, exposure to PCB and polybrominated diphenyl ethers (PBDE) seems to disrupt calcium-linked signalling pathway which results in abnormal dendritic growth and a consequent anomaly in neural connectivity which is a characteristic of ASD (Palou-Serra et al., 2014).

4. Metal Exposure in ASD

Excessive metal exposure has detrimental effect on the nervous system. The developing nervous system is particularly vulnerable to heavy metal toxicity compared to adults (Jafari

et al., 2017), hence metals which are one of the main environmental toxicants have been linked to abnormal neurodevelopment. Such metals include: lead (Pb), mercury (Hg), arsenic (As), cadmium (Cd), aluminium (Al), manganese (Mn), nickel (Ni), amongst others. Environmental toxicants disrupt the process of neurodevelopment either in combination with inherited vulnerability or by epigenetics (Bjørklund et al., 2018; Homs et al., 2016).

A close link exists between the level of environmental toxicants and the increased number of ASD diagnoses (Dickerson et al., 2015). A previous report showed that exposure to diesel, mercury, lead, methylene chloride, manganese and a wide-ranging assessment of metals during perinatal period is closely linked with ASD (Roberts et al., 2013). In addition, research carried out in Saudi Arabia found an increased blood level of mercury and lead and a notable decline in selenium in kids diagnosed with ASD when compared to healthy children (El-Ansary et al., 2017). Furthermore, low level of glutathione (GSH) has been recorded in ASD patients as a major basis of this disorder (Kern et al., 2011). Several neurotoxic metals have been reported to alter GSH production. GSH is an antioxidant in the brain and acts as the major defence system against free radicals produced by toxic metals (Ijomone, Omamuyovwi Meashack et al., 2018; Nair et al., 2015).

Children are more susceptible to the harmful effects of xenobiotics because they continually undergo rapid growth and development (Hassanien and El Shahawy, 2011) Prenatal life to early childhood is a period of increased endangerment to developmental process as a result of ongoing post-partum brain development (Rodier, 1995). The developing brain of the foetus is extremely vulnerable to environmental toxicants as the placenta does not adequately provide protection against environmental toxicants hence the ability to cross the placenta barrier. Also, the blood-brain barrier is not formed until 6 months after birth (Gorini et al., 2014), therefore prenatal exposure to toxicants causes the greatest damage on the brain ranging from subclinical dysfunction to a spectrum of neurodevelopment disorders depending on the level of exposure (Landrigan, 2010).

The role of heavy metals in the onset of autism have been a cause for worry as a result of certain attributes like toxicity and endocrine disruption (De Cock et al., 2012; Ko et al., 2012). Neurons and glia in the developing brain are vulnerable to damage by metals such as lead and mercury which may result in permanent neurodevelopmental damage (Rice and Barone Jr, 2000) This occurrence can be due to the minimal restorative ability of the developing nervous system to anatomical damage during the early post-natal years (Hassanien and El Shahawy, 2011). Also, children possess immature and ineffective sequence of metabolism and detoxification, with poorer immune system especially during infancy. So, they are more susceptible to hazardous effects than adults (Henn et al., 2014) because they cannot effectively eliminate these toxicants. In the sections below, we highlight several metals reported as potential environmental risk factor in ASD pathogenesis.

4.1. Lead

Lead (Pb) is classified as a non-essential metal and is abundant in the surrounding. It has no known physiologic role in the body but has several industrial and domestic function. It is used as 1) and antiknock agents in planes 2) the yellow pigment in paints 3) a composition of tin toy 4) a projectile in small calibre ammunition (Fuentes-Albero et al., 2015). However,

excessive Pb exposure has been linked to damage in the nervous system particularly in children however, the mechanism by which is yet to be fully unravelled (Akinyemi et al., 2019). Blood lead level at 10μg/dL was initially set as the benchmark at which alterations to neurodevelopment occur. However, there is convincing proof that negative effect on neurodevelopment occurs following Pb exposure even at blood Pb level less than 10μg/dL (Kim et al., 2013).

Pb exposure in early life has been established to be detrimental to brain health. It impairs normal neurodevelopment and causes cognitive deficits in adult life (Kim et al., 2013). It has also been reported to increase the individual's chances of violent/criminal behaviour (Cecil et al., 2008). Pb exposure has been named as one of the causes of ASD. This was corroborated in a study by Kim et al establishing that exposure to Pb even at 7–8 years of age can result in ASD development (Kim et al., 2016). As earlier stated, the primary cause of ASD could be the low level of antioxidants like GSH. This is supported by a study that showed a high level of blood Pb and Hg and low level of antioxidants (GSH and vitamin E) in ASD patients in contrast to neurotypical kids (Fuentes-Albero et al., 2015). in addition, Qin et al. (2018) recorded increased Pb blood levels in ASD affected children in contrast to children without the disorder (Qin et al., 2018). Another study which supports the high level of Pb in children with neurodevelopmental disorder was by Gump et al. They investigated the level of Pb and Hg in 9–10 years old children with the aid of physiological functioning and neurodevelopmental assessments. Elevated Pb level was linked with abnormal behaviour, communication deficits and imbalanced emotions (Gump et al., 2017).

A recent report showed that Pb induced dopaminergic dysfunction in developing nervous system. Pb resulted in structural damage to developing neurons in head of *Caenorhabditis elegans* (C. *elegans*). This was accompanied by functional consequences revealed by alterations in behaviour controlled by dopamine signalling. The study also shows perturbation of dopamine transporter and reduced dopamine levels that was associated with inhibition of monoamine oxidase (Akinyemi et al., 2019). Interestingly, dopaminergic dysfunction has been associated with autistic-like behaviour. Dysfunction in two major midbrain dopaminergic neuronal signalling – mesolimbic and nigrostriatal circuits – have been reported in autistic subjects (Pavăl, 2017).

4.2. Mercury

Mercury (Hg) is found innate in the environment and has become even more abundant by human activities such as mining leading to a 1.5 percent increase in atmospheric Hg. There are functions it performs that increases its availability in the atmosphere such as use in Hg extraction, used in certain products (electronic device, paint) and industrial use as a catalyst (Pirrone et al., 2010; Rice et al., 2014). Hg is mostly transferred into the biological system via contaminated food like plants or fishes (Rice et al., 2014). Hg exists in both organic and inorganic forms. The most available form of organic Hg is methylmercury (MeHg) while inorganic Hg is available in either mercuric or mercurous form with a mean half-life of forty days (Magos and Clarkson, 2006).

Following overexposure to Hg, the metal crosses the blood brain barrier (BBB) and builds up particularly in the cerebellum, visual cortex and the spinal cord (Jafari et al., 2017).

Although some researches have linked Hg to the aetiology of ASD however, there are reports that contradict these findings. Some studies compared the amount of blood Hg in pregnant women and found no autistic related behaviour in offspring after birth (Golding et al., 2018). Jafari et al carried out a study to measure the blood Hg level and discovered a notable increase in the brain and blood of ASD patients when compared to neurotypical individuals (Jafari et al., 2017). There are mechanisms responsible for eliminating toxicants such as Hg, to prevent the body organs from damage. One mechanism is via Gluthathione-S-transferase (GST) activity. GST eliminates foreign substances and drugs hence preventing build-up of toxins in the biological system (Alabdali et al., 2014). Another mechanism involves attachment of Hg to GSH for excretion through the bile. Reports have shown that these mechanisms are dysfunctional in ASD patients hence the increased level of Hg in the tissues. The build-up of Hg kick-starts oxidative stress and inflammatory reactions in the brain and also elevated amount of auto anti-bodies which are necessary for the on-set of autism and other neurodevelopmental disorders (Jafari et al., 2017). Another affirmation that Hg exposure is linked to ASD is by a study which reported a positive relationship between maternal exposure to mercury fillings and autistic offsprings (Geier et al., 2012). Furthermore, Yassa and colleagues, assessed blood and hair samples of 45 ASD children (3–10 years) and linked foetal and post-natal exposure to Hg and/or Pb to autistic characteristics. Interestingly, the study also disclosed that the use of anti-heavy metal treatment alleviated the autistic symptoms recognized in the patients (Yassa, 2014). Contrastingly, other findings have not shown any association between Hg and ASD. The results proposed no negative effect of blood Hg level with regards to autism (Golding et al., 2018; Yau et al., 2014). Another report that supports this finding found no effect of foetal exposure to MeHg on physical autistic characteristics (van Wijngaarden et al., 2013). Furthermore, a study by Mckean et al measured the bloodspot Hg levels in newborns and reported no known correlation between MeHg exposure and increased risk of autism (McKean et al., 2015). Nevertheless, mercury poisoning and autism present with like symptoms (mentally and physically) (Bernard et al., 2001; Geier et al., 2008). There are several identical occurrences in the brain following Hg poisoning compared to the brain of an ASD victim. They include neuronal necrosis, dendritic overgrowth, gliosis, mitochondrial dysfunction, neuroinflammation, brain immune response, an imbalance between free radicals and antioxidants, lipid peroxidation and axonal demyelination (Geier et al., 2010; Kern et al., 2012).

4.3. Cadmium

Cadmium effect on cells may result in either a direct or indirect alteration in brain developmental process. It interferes with cell cycle progression, proliferation, differentiation, as well as induction of apoptosis (Dong et al., 2001; Yang et al., 2004). When compared to Pb and methylmercury, its effect on neuronal development is still debatable (Kim et al., 2013). There is little information about the possible relationship between Cd exposure and the elevated risk of autism. Studies recorded significantly decreased Cd level in hair of autism affected children in contrast to children of same age living without autism (Kern et al., 2007; Shearer et al., 1982). Concurrently, in comparison with control children, there was decreased Cd hair level in children with autistic characteristics categorized as childhood-

onset pervasive disorder (Wecker, 1985). However, some reports contradict the above findings (Al-Ayadhi, 2005; Al-Farsi et al., 2013; Blaurock-Busch et al., 2011).

Yorbik and his colleagues also reported decreased Cd urine concentration in children which is consistent with the reported decreased hair Cd level (Yorbik et al., 2010). The decrease in urinary Cd elimination affirms that children with autism may have altered metal-breakdown mechanisms which may lead to an elevated body burden of heavy metals (Blaurock-Busch et al., 2011; Yorbik et al., 2010). Metallomics evaluation in human scalp hair in 1,967 autistic children of age 0–15 years reported that 8.5 % patients are plagued with increased Cd concentration. Specifically, the highest Cd concentration (12.1%) was found in toddlers aged 0–3years concurrent with the report on Pb. These findings collectively imply that there is increased vulnerability to environmental toxicant poisoning during early life which may result in epigenetic changes and neurodevelopmental disorders (Yasuda and Tsutsui, 2013; Yasuda et al., 2013). Yasuda et al also reported in a previous write of the preferential accumulation of these metals in females, thus a probable higher rate of susceptibility during pregnancy (Yasuda et al., 2012).

4.4. Nickel

Nickel (Ni) is one of the metals established to be a poised threat to health (Ijomone, Omamuyovwi M et al., 2018; McDermott et al., 2015). Ni most commonly finds its way into the biological system via food, water, skin contact, air usually during its industrial use where it has negative consequence on organs such as kidney, lungs, liver and brain (*reviewed in* (Das et al., 2008; Song et al., 2017)). Presence of Ni in the body can lead to production of free radicals (which results in oxidative stress), disruption of protein action, a resultant imbalance in antioxidant level (Chen et al., 2017; Ijomone, Omamuyovwi Measshack et al., 2018) and indirect alteration of DNA repair process (Chen et al., 2010). Oxidative stress is an established mechanism for metal neurotoxicity and Ni is not exempted (Ijomone, Omamuyovwi Measshack et al., 2018). Developmental alterations of various neurotransmitter systems including cholinergic, dopaminergic and GABAergic, as well as behavioural deficits in later life following early life exposures to Ni was demonstrated in a C. *elegans* model (Ijomone et al., 2020).

Several studies have focused on the quantitative analysis of Ni concentration in the tissue of ASD patients. A study by Al-farsi et al measured the level of Ni in hair samples of children with ASD. There was a notable increase in hair Ni level in contrast to children without ASD (Al-Farsi et al., 2013). Another study carried out in USA showed that children born to parents who lived in areas with high atmospheric Ni were diagnosed with ASD. These finding thus suggests that perinatal exposure to Ni is a risk factor for ASD development (Roberts et al., 2013). However, there are reports that contradict these studies. A study by Blaurock-Busch et al. measured the level of Ni in the hair of ASD patients and found a mild increased Ni level in hair of children without ASD in contrast to affected children (Blaurock-Busch et al., 2011). Skalny et al. also found no notable difference for hair Ni in children with ASD when compared to control (Skalny et al., 2017).

4.5. Manganese

Manganese as an essential metal, has several physiologic functions which include: balancing internal milieu, protein, lipid and carbohydrate breakdown, healthy brain activity, cofactor for several enzymes to name a few (Ijomone et al., 2019)). However, excess Mn exposure has severally been reported to induce neurotoxicity and could also be an environmental risk factor for neurodegenerative disease (Chen et al., 2015; Martins et al., 2019). Studies have associated excessive exposure to Mn with negative academic performance and cognitive impairment, short term memory loss and attention deficits (Langley et al., 2015). Developmental neurotoxicity following Mn exposure has been reported. Infant exposure to Mn can be through household dust, contamination via vehicle emissions, industrial wastes and tap water (Gunier et al., 2013). Zota et al investigated the level of certain metals Mn inclusive in the tap water, household dust, ambient soil and found a high level of Mn. This establishes that early exposure to Mn is usually from domestic environment as infants are usually indoors (Zota et al., 2016). Developmental neurotoxicity induced by Mn has negative effects on motor skills (Oulhote et al., 2014), academic achievement (Khan et al., 2012), cognitive ability (Rink et al., 2014).

Multiple researches have investigated the interplay of Mn in the aetiology of ASD using the quantitative analysis of Mn level in the hair, blood, urine, tooth enamel and atmospheric prevalence and have reported varying results. A study by Henn et al documented an inverse relationship between blood Mn level and concomitant mental development grades (Henn et al., 2010). Arora and colleagues, also supported an inverse association between Mn and autistic features (Arora et al., 2017). Another study by Abdullah et al compared the level on Mn in the tooth enamel of age and gender balanced children and found a significant lower concentration in the enamel of ASD patients when compared to neurotypical children (Abdullah et al., 2012). Contrastingly, it was documented by De Palma et al that there is no disparity in hair Mn concentration in contrast to the control group (De Palma et al., 2012). Furthermore, another investigation reported no linkage between post-natal blood Mn level and ASD using Jamaican children between ages 2–8years as their case study (Rahbar et al., 2014).

Mn overexposure results in an imbalance between reactive oxygen species and antioxidants. As reported in a previous study, variations in glutathione-S-transferase (GST) genes plays a part in the aetiology of ASD (Schmidt et al., 2011). GST genes are responsible for coding of enzymes involved in regulating the level of free radicals. For example, glutathione S-transferase mu 1 (GSTM1), glutathione S-transferase theta 1 (GSTT1) and glutathione S-transferase pi (GSTP1). This is coherent with a study that postulated the possible combined effect of GSTP1 and blood Mn level in the aetiology of ASD. This suggests that an alteration to the GSTP1 gene may increase the occurrence of mitochondrial dysfunction and oxidative stress which have been reported as mechanisms for ASD (Rahbar et al., 2015). Additionally, Mn has been severally associated in dopaminergic dysfunction. Mn is known to result in structural, functional and neurochemical alterations of the dopaminergic system (Chen et al., 2014; Ijomone et al., 2019; Ijomone et al., 2016; Peres et al., 2018; Peres et al., 2016). Considering that dopaminergic dysfunction has been linked to autistic behaviour

(Pavăl, 2017), further establishes the potential of Mn overexposure as a risk factor in ASD pathogenesis.

5. Concluding remarks

The brain is more vulnerable to harm during development hence the focus to unravel the possible toxins that could impair normal development. Environmental and genetic factors have been implicated in several neurodevelopmental disorders including ASD. Most often an interplay between environmental and genetic factors is required for this disorder hence it is classified as a multifactorial disorder. Here, we have discussed the role of neurotoxic metals in the aetiology of ASD and the mechanisms involved. These mechanisms include oxidative stress, immune dysregulation, epigenetic changes, and genetic mutations. Most of these mechanisms alter neural connectivity as the end result which is a distinct feature of ASD. We have also highlighted several reports which have attempted to use metal levels in various tissues as novel biomarkers for ASD detection. However, small sample sizes and different sampling approach warrants caution, and further studies. Further research is needed for in vivo monitoring of the mechanism of these metals in disrupting the neurodevelopmental integrity. Nevertheless, these findings increase the awareness about the potential detrimental association of environmental toxins (such as metals) and neurodevelopmental disorders.

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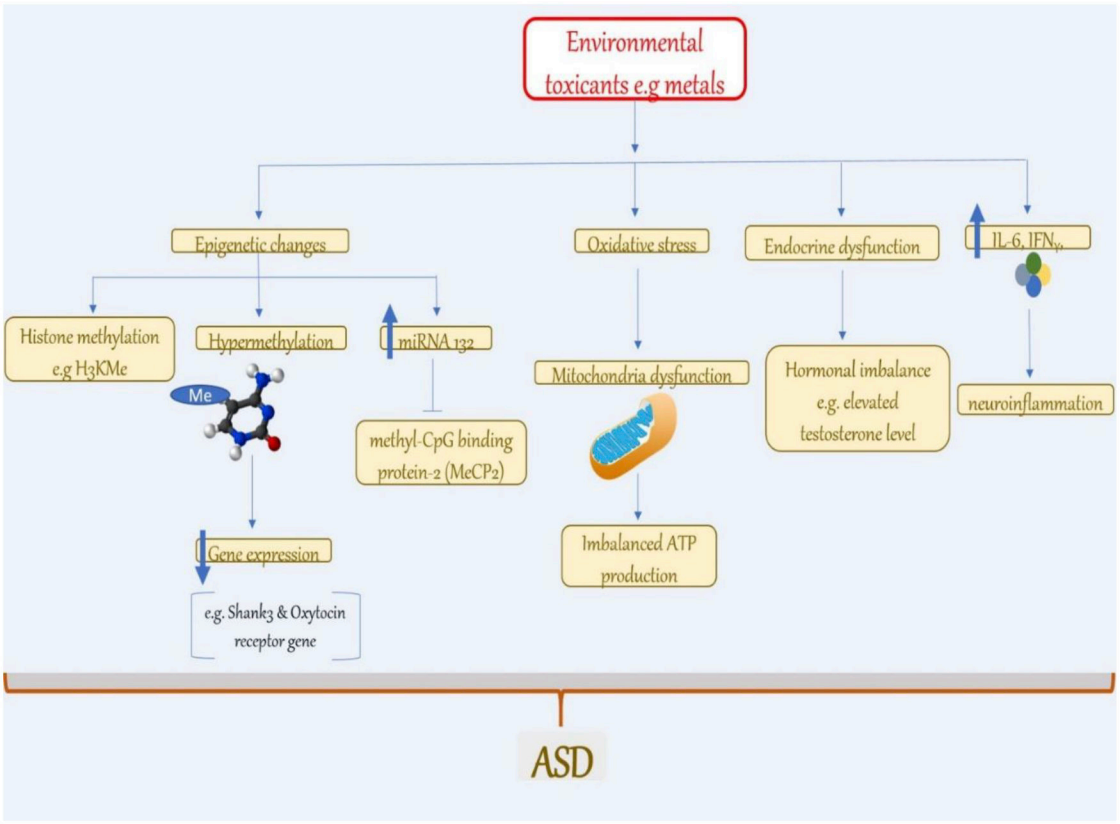

Figure 1: Potential mechanism of metal involvement in ASD pathogenesis.

A Schematic representation of mechanisms by which toxic environmental agents such as metals could be involved in ASD pathogenesis. These mechanisms have been implicated in the onset of ASD. Oxidative stress which is an imbalance between free radicals and antioxidants is one common mechanism by which metals exert their harmful effect in the brain. It results in a disproportionate energy production in neural cells. An interplay between these environmental agents and genes can also lead to alteration in the neurodevelopmental process. Aside the genes involved in neurodevelopment, certain hormones also have a role to play and an imbalance in the concentration of these have is implicated in the pathogenesis of ASD