Environmental Pollution 227 (2017) 234–242

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

The association of environmental toxicants and autism spectrum disorders in children☆

Bi Su Ye [a], Anna Oi Wah Leung [b], Ming Hung Wong [a, c, d, *]

[a] Consortium on Health, Environment, Education and Research (CHEER) and Department of Science and Environmental Studies, The Education University of Hong Kong, Tai Po, Hong Kong, China
[b] Department of Biology, and Croucher Institute for Environmental Sciences, Hong Kong Baptist University, Kowloon Tong, Hong Kong
[c] School of Environment, Jinan University, Guangzhou, China
[d] Key Laboratory for Heavy Metal Pollution Control and Reutilization, School of Environment and Energy, Peking University – Shenzhen Graduate School, Shenzhen, China

ARTICLE INFO

Article history:
Received 23 December 2016
Received in revised form
17 March 2017
Accepted 17 April 2017

Keywords:
Mercury
Lead
PBDEs
PCBs
BPA
Phthalates

ABSTRACT

Autism spectrum disorders (ASDs) is a set of complex neurodevelopment disorders that is prevalent in children and is increasing at a steady rate in recent years. However, the etiology of autism is still poorly understood. Humans are at higher risk of chemical exposure than in the past as a result of the increasing usage of chemicals in various fields, including food preservation, agriculture, industrial production, etc. A number of environmental agents have been suggested as contributing factors to ASD pathogenesis, which includes heavy metals (Hg and Pb), persistent organic pollutants (DDT, PBDEs and PCBs) and emerging chemicals of concern (phthalates and BPA). These three main categories of toxicants could be the cause of ASD in children. Recent research into the causes of ASD that have been linked to environment factors are reviewed in this paper. There are evidence supporting the etiological link between exposure to environmental toxicants and the development of ASD. Children exposed to these toxicants in the environment exhibit signature traits of ASD and have been reported with high body burdens of these chemicals and/or their metabolites, which may provide an explanation for the observed relation, yet comprehensive evidence in humans is limited, highlighting the need for further research.

1. Introduction

Autism spectrum disorders (ASDs) is a set of complicated disorders related to neurodevelopmental that affects normal functioning of the brain and may consequently lead to lifelong disabilities (Hallmayer et al., 2011). Autism is characterized by well-documented biochemical imbalances such as redox imbalance, oxidative stress, and associated mitochondrial dysfunction (Kaur et al., 2014). ASD is typically diagnosed during childhood since children and infants are high-risk population groups and are more susceptible to neurological disorders than adults (Liew et al., 2015). Furthermore, symptoms of ASD manifest during the first three years of life as social deficits, communication difficulties, and cognitive delays (Hallmayer et al., 2011). Autistic individuals exhibit repetitive and stereotyped behaviors as well as restricted interests (Nevison, 2014). People with Asperger syndrome (considered as high-functioning autism) do not exhibit significant delays or difficulties in language or cognitive development, but may have difficulties with social skills, sensory input and require rigid routines whereby their environment is predictable and familiar (Austism Speaks Inc, 2016).

The prevalence of ASD has increased dramatically in the US from 1 in 2500 children in the early 1970s to a currently reported rate of 1 in 68, as estimated by the Centers for Disease Control and Prevention Center (CDC) (2014). Similar increasing trends have also been recorded in Europe and Asia. For instance, the current estimate of prevalence in the UK has reached as high as 157 per 10,000, whereas the incidence rate was only 4.4 per 10,000 between 1966 and 1991 and 12.7 per 10,000 between 1992 and 2001 (Quaak et al., 2013). In comparison to Western countries, recent epidemiology studies have estimated ASD prevalence as 14.8 per 10,000 in Asia (Sun et al., 2013). In China and Hong Kong, for

☆ This paper has been recommended for acceptance by Dr. Chen Da.

* Corresponding author. Consortium on Health, Environment, Education and Research (CHEER) and Department of Science and Environmental Studies, The Education University of Hong Kong, Tai Po, Hong Kong, China.
E-mail address: minghwong@eduhk.hk (M.H. Wong).

http://dx.doi.org/10.1016/j.envpol.2017.04.039
0269-7491/

example, it is estimated that 10.3 and 5.49 in every 10,000 children are diagnosed with autism (Sun et al., 2013; Wong and Hui, 2008). In general, there is a paucity of data regarding the prevalence of ASD in China. According to statistical data compiled by CDC (2016) from various studies that were undertaken between the period from 1964 to 2014, an average of about 1–2% of the population in Asia (Japan, Hong Kong, Taiwan, South Korea), Europe, and North America has been diagnosed with autism. The incidence of autism in boys has also been found to be significantly higher than in girls (NINDS, 2016). The continuously rising prevalence of ASD appears to be more notable in recent decades worldwide. This has aroused a much wider public concern, and substantial research efforts have been undertaken to elucidate the reasons behind this observed shift in prevalence. Various factors have been proposed, including broader diagnostic criteria, improvement in case ascertainment and increased awareness and recognition of ASD (Sun et al., 2013). However, these factors could only partly account for 1/3 of the increase in autism prevalence; the remaining portion of the increase could be attributable to actual incidence of autism (Hertz-Picciotto et al., 2006). There may also be many different factors that could cause ASD in a child, such as genetic, biologic and environmental factors which act alone or together. Therefore, the challenging question remains unanswered of what causes ASD, highlighting that more in-depth research and understanding into the complex causes of autism are needed.

In general, scientists agree that genetics is one risk factor that can cause the development of ASD, however, epigenetics, transcriptomics, immune system disruption and environmental factors may also play a role. The complex interactions between genes and environmental factors may occur before, during, and after pregnancy. Exposure to environmental toxicants such as mercury, lead, bisphenol A, phthalates, and nutrition deficiency such as folic acid, vitamin D, or fatty acid may be associated with an increased risk of ASD. Other factors such as mature maternal or paternal age, preterm delivery, low birthweight, maternal infection, maternal exposure to environmental pollutants, obstetric complications, use of certain medications during pregnancy, and maternal diabetes or obesity are also factors (Lampi et al., 2012; Xu et al., 2014). In a study of infertility treatments, there were no evidence to link the treatment with the risk of ASD among singleton births, and the data for multiple births were found to be inconclusive in a study of 77,403 children born in 1995–1998 (Grether et al., 2013).

The major purpose of the present article is to review whether there is a possible association between some environmental toxicants (namely heavy metals, persistent organic pollutants, and emerging chemicals of concern) and ASD in children, with the support of different types of studies. The associations between the most representative chemicals in each of the above categories, including mercury (Hg), lead (Pb), dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), bisphenol A (BPA), and phthalates will be discussed.

1.1. Hereditary components related to causation of autism

It is widely accepted that a strong hereditary component is implicated in ASD (Buxbaum and Hof, 2011; Johnson et al., 2013). Approximately 30–40% of all neurodevelopment disorders are caused by genetic factors alone (Landrigan et al., 2012). Fragile X and Rett syndrome have been identified as genetic causes. The genetic causation is supported further by twin, family and linkage studies. A substantial number of candidate autism susceptible genes at multiple loci have been identified by linkage; association and cytogenetic studies, suggesting polygenic factors contribute etiologically to autism (Hertz-Picciotto et al., 2006). It has also been demonstrated that concordance rates among monozygotic twins and recurrence risk in siblings can reach up to 70–90% and 2–14%, respectively, whereas the concordance rates in dizygotic twins (0–10%) appear to be no higher and even lower than the rates among siblings (Hallmayer et al., 2011; Hertz-Picciotto et al., 2006; Mitchell et al., 2012). However, a comprehensive study of autistic twins born between 1987 and 2004 reported a 60% concordance rate in monozygotic twins and 27% concordance in dizygotic twins, indicating environmental components shared by twins are linked with autism (Hallmayer et al., 2011).

A study involving the genetic testing of chromosomal abnormalities in 218 children in the US diagnosed with ASD born from 1983 to 2009 found that approximately 80% had negative genetic test results (NGTRs). About 20% had positive genetic test results (PGTRs), of which ~7% were probable de novo mutations. Of the 80% with NGTRs, the subjects examined did not possess any identifiable genetic findings from high-resolution blood chromosome or blood-chromosome microarray testing (Geier et al., 2016). Therefore, environmental factors seems to play an increasing role in ASD etiology. The findings also suggest that sociability scores of the children with NGTRs significantly worsened with age which seems to further indicate that an environmental component is a contributing factor to the development of ASD. On the contrary, sociability scores did not worsen with age for children with overall PGTRs. The results of another study on a cohort of 933 subjects (aged 13 months to 22 years old) provide support of chromosomal microarray analysis as part of the initial diagnostic evaluations of patients with ASD (Shen et al., 2010).

1.2. Environmental factors related to causation of ASD

Despite the significance of genetic roles in pathogenesis of autism, explorations on the association between environmental factors and autism have increased recently. US National Research Council (2000) estimated that exposure to environmental toxicants contribute to 3% of neurodevelopment disabilities directly. Moreover, a growing body of studies have shown that the developing brain of the fetus is exquisitely vulnerable to environmental toxicants. Therefore, prenatal exposure (especially during the first trimester of pregnancy) have greatest impact on the brain ranging from subclinical dysfunction at low levels of exposure up to overt toxicity, leading to a spectrum of neurodevelopment disorders (Landrigan, 2010). Furthermore, various environmental contaminants such as heavy metals and POPs have been a long-term concern of autism advocate due to their toxic and endocrine-disruptive nature (De Cock et al., 2012; Ko et al., 2013; Nowack et al., 2015).

The etiological factors implicated in autism development still remain elusive and controversial, however, it is commonly agreed that causes of ASD are heterogeneous and are attributed to complicated interactions between genetic factors and environmental pollutants interacting synergistically or in parallel with each other (Quaak et al., 2013; Rossignol et al., 2014).

2. Environmental toxicants

2.1. Heavy metals and autism

Heavy metals are naturally occurring elements with a relatively high density (>5.0 g/cm^3) or high atomic weight (Fergusson, 1990). Exposure to highly toxic heavy metals such as Hg and Pb can cause damage to brain cells, which lead to neurological defects, development delays, socio-behavioral disabilities and intellectual impairment (Gorini et al., 2014). Exposure during infancy and early childhood will lead to lifelong neurobehavioral changes in children, due to their weaker immune system and poorer detoxifying ability