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Review article

Environmental factors in the development of autism spectrum disorders

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ABSTRACT

Autism spectrum disorders (ASD) are highly heterogeneous developmental conditions characterized by deficits in social interaction, verbal and nonverbal communication, and obsessive/stereotyped patterns of behavior and repetitive movements. Social interaction impairments are the most characteristic deficits in ASD. There is also evidence of impoverished language and empathy, a profound inability to use standard nonverbal behaviors (eye contact, affective expression) to regulate social interactions with others, difficulties in showing empathy, failure to share enjoyment, interests and achievements with others, and a lack of social and emotional reciprocity. In developed countries, it is now reported that 1%–1.5% of children have ASD, and in the US 2015 CDC reports that approximately one in 45 children suffer from ASD. Despite the intense research focus on ASD in the last decade, the underlying etiology remains unknown. Genetic research involving twins and family studies strongly supports a significant contribution of environmental factors in addition to genetic factors in ASD etiology. A comprehensive literature search has implicated several environmental factors associated with the development of ASD. These include pesticides, phthalates, polychlorinated biphenyls, solvents, air pollutants, fragrances, glyphosate and heavy metals, especially aluminum used in vaccines as adjuvant. Importantly, the majority of these toxicants are some of the most common ingredients in cosmetics and herbicides to which almost all of us are regularly exposed to in the form of fragrances, face makeup, cologne, air fresheners, food flavors, detergents, insecticides and herbicides. In this review we describe various scientific data to show the role of environmental factors in ASD.

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1. Introduction

Autistic individuals typically have restricted capacity for communication, a compromised ability to interact with others, and unusually repetitive (stereotypic) behaviors that often make social interactions challenging, hurt job potential, and make numerous other problems more likely. The American Psychiatric Association categorizes autism spectrum disorder (ASD) among many other neurodevelopmental disorders, which include Tourette's Disorder, Tic Disorder, and Social Communication Disorder (Neurodevelopmental Disorders. DSM-5 Development (Geschwind, 2009; Lichtenstein et al., 2010). In developed countries, it is now reported that 1% to 1.5% of the children have autism (Geschwind, 2009; Lichtenstein et al., 2010; Zablotsky et al., 2015). Genetic predisposition may explain around 10% of cases. There are genetic diseases, for example Angelman syndrome, Rett syndrome, fragile X syndrome, Cohen syndrome, and Down's syndrome, which greatly increase the probability of developing autism (Fombonne, 2003; Geschwind, 2009; Lichtenstein et al., 2010; Zablotsky et al., 2015). Monozygotic twin concordance has been discovered as reaching 70%–90% for just autistic behavioral traits and it is generally assumed that ASD is due to inherited genetic defects (Geschwind, 2009). However, this conclusion is based on misinterpretations of existing data and bias reporting (see below) and this concordance could be due to exposure to environmental agents that are neurotoxic to the developing twins' brains (Chamak, 2010). Of note, a significant percent of monozygotic twins (MZ) are discordant (Hallmayer et al., 2011). In dizygotic twins, it has not been proven to be higher than in their isolated brothers (Chamak, 2010; Hallmayer et al., 2011) and there is strong evidence that environmental factors play as much of a role in development of autism as the genetic factors (Hallmayer et al., 2011). The number of children who have ASD has increased considerably since the early 1980s (Tammimies et al., 2015). ASD varies significantly in presentation among those affected (Geschwind, 2009; Lichtenstein et al., 2010). It is, therefore, not surprising that the etiology of ASD is thought to be similarly heterogeneous and multifaceted in nature. The broad spectrum in the definition of ASD suggests that the disease may result from exposure to certain environmental agents instead of primarily a genetic disorder (Landrigan, 2010; Ortega García et al., 2007; Tammimies et al., 2015). This rather controversial view is explained in detail in this review.

2. Autism: overestimation of the inherited genetic origins

For over a century, the belief is held that autism is a genetic and heritable disease (Chamak, 2010; Hallmayer et al., 2011; Landrigan, 2010; Tammimies et al., 2015). A thorough inspection of outcomes and claims that support a strong genetic source of autism demonstrates incorrect interpretations, methodological biases, and flawed approximations, not to mention overstated media reports. Recently, Hallmayer et al. (2011) carried one of the largest twin-pair studies. They completed 192 twin-pair studies and reported that a large degree of risk for ASD in MZ was due to environmental factors and a smaller risk was due to heritability or genetic. Of note, they have not considered the *de novo* mutations and single copy number variations (CNV) as we describe below.

3. More than 1000 genetic and genomic disorders and still counting

ASD is considered a highly heritable disorder; yet genome-wide association studies, copy number variation, and candidate gene association have found no single genetic factor accounting for over 90% of ASD cases. Interestingly, trio (the parents and the affected children) exome sequencing analyses, where exons or the expressed genes are sequences, have revealed genes with recurrent *de novo* loss-of-function variants in the infants, where such mutations are not found in the parents (Tammimies et al., 2015). There more than 1000 genes that are predicted to play a role in ASD. In an attempt to collate all genes and recurrent genomic imbalances that have been implicated in the etiology of ASD, the recent exhaustive review of the clinical genetics and research genetics literature has shown that there may be 103 disease genes and 44 genomic loci reported in subjects with ASD or autistic behavior (Betancur, 2011; Tammimies et al., 2015). These genes and loci have all been causally implicated in intellectual disability, indicating that these two neurodevelopmental disorders share common genetic bases.

Prenatal exposure to harmful chemicals, or occurrence of an infection during the primary gestation period of a maturing fetus, can detrimentally affect the development of the immune system (Landrigan, 2010). The occurrence and exposure to harmful chemicals or infection can increase the incidence of autoimmune deficiencies in young children. Thus, research has linked autoimmune deficiencies as one of the many trademarks of autism spectrum disorder. There are various examples of autoimmune abnormalities observed in autistic children, such as a higher influx in pro-inflammatory cytokines, a decrease in plasma IL-23, and an elevated count of plasma leptin levels (Hertz-Picciotto et al., 2008). This strong correlation of exemplifying irregular immune system devolvement in autism demonstrates that damaging events are possibly occurring during certain stages of the gestation period. During specific stages of the gestation period, critical stages of the immune system development take place. In theory, if certain parts of the immune system development are altered, adverse life lasting effects may persist. There is assumption that during prenatal and initial postnatal stages of fetal development that neurodevelopment and immune system developments have an association to one another. Research suggests that during development of the fetus there is an influx of the TH1 response, which aids in pro-inflammatory response (Hertz-Picciotto et al., 2008). Thus the association of the occurrence of an infection can induce certain immunological changes, such as an inflammatory response (Hertz-Picciotto et al., 2008).

Nevertheless, research has shown that postnatal inflammation that occurs during the primary stages of fetal development can result in irreversible effects in the cerebral and peripheral regions of the Central Nervous System (Hertz-Picciotto et al., 2008). This occurrence of brief inflammation and influx of cytokine release can promote predisposition to seizures in adult life (Hertz-Picciotto et al., 2008). For example, a study to investigate if exposing certain harmful endotoxins during critical developmental stages can induce seizures. This study was done with male Sprague Dawley rats where bacterial endotoxin lipopolysaccharide LPS were injected into the rats at a certain developmental stage at Postnatal day (P) 7 to P14. The end results at six to eight weeks post infection showed that there was, indeed, an increase in predisposition to seizures and also an increase in cytokine release and heightened activity in the hippocampus, such as neuronal degradation (Galic et al., 2009; Hertz-Picciotto et al., 2008). In addition, the results also showed that exposing the LPS only at certain stages induce seizures, and when exposing rats to the LPS before P1 and after P20 there was no significant predisposition to seizure occurrence (Hertz-Picciotto et al., 2008). In conclusion both studies conclude that exposure to harmful chemicals and induced endotoxins such as LPS, to a developing fetus during vital