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Review article

Risk factors in autism: Thinking outside the brain

Lauren Matelski [a, b, c], Judy Van de Water [a, b, c, *]

[a] Division of Rheumatology, Allergy, and Clinical Immunology, Department of Internal Medicine, University of California, Davis, 451 E Health Sciences Drive, Suite 6510 GBSF, Davis, CA 95616, USA
[b] NIEHS Center for Children's Environmental Health, University of California, Davis, USA
[c] The M.I.N.D. Institute, University of California, Davis, USA

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ABSTRACT

Autism spectrum disorders (ASD) are complex neurodevelopmental conditions that have been rising markedly in prevalence for the past 30 years, now thought to affect 1 in 68 in the United States. This has prompted the search for possible explanations, and has even resulted in some controversy regarding the "true" prevalence of autism. ASD are influenced by a variety of genetic, environmental, and possibly immunological factors that act during critical periods to alter key developmental processes. This can affect multiple systems and manifests as the social and behavioral deficits that define these disorders. The interaction of environmental exposures in the context of an individual's genetic susceptibilities manifests differently in each case, leading to heterogeneous phenotypes and varied comorbid symptoms within the disorder. This has also made it very difficult to elucidate underlying genes and exposure profiles, but progress is being made in this area. Some pharmaceutical drugs, toxicants, and metabolic and nutritional factors have been identified in epidemiological studies as increasing autism risk, especially during the prenatal period. Immunologic risk factors, including maternal infection during pregnancy, autoantibodies to fetal brain proteins, and familial autoimmune disease, have consistently been observed across multiple studies, as have immune abnormalities in individuals with ASD. Mechanistic research using animal models and patient-derived stem cells will help researchers to understand the complex etiology of these neurodevelopmental disorders, which will lead to more effective therapies and preventative strategies. Proposed therapies that need more investigation include special diets, probiotics, immune modulation, oxytocin, and personalized pharmacogenomic targets. The ongoing search for biomarkers and better treatments will result in earlier identification of ASD and provide much needed help and relief for afflicted families.

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* Corresponding author. Division of Rheumatology, Allergy, and Clinical Immunology, Department of Internal Medicine,University of California, Davis, 451 E Health Sciences Drive, Suite 6510 GBSF, Davis, CA 95616, USA.
E-mail address: javandewater@ucdavis.edu (J. Van de Water).

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1. Introduction

Autism is a spectrum of neurodevelopmental disorders that manifest in early childhood. The core features of autism spectrum disorders (ASD) include persistent difficulties in verbal and nonverbal communication, along with restricted, repetitive patterns of behavior, interests, or activities [1]. There has been much debate and inquiry surrounding the nature of the increase in prevalence of ASD, and recent reports certainly paint a picture of concern. In the United States (US), these heterogeneous neurodevelopmental disorders are currently estimated to affect 1 in 68 (or 147 in 10,000, reported in 2010 for birth year 2002), which is 30% higher than the previous (2008) estimate of 1 in 88 [2]. This is but a glimpse into the overall trend that has been ongoing for over 20 years in the US, which appears to extend globally. Available reports from other countries show variable rates of autism prevalence with definite increases over time, but these estimates are mostly limited to high-income countries [3]. Other countries reporting high rates of autistic disorder (AD) include Sweden (72.6 cases per 10,000 in 1999) and South Korea (94 cases per 10,000 in 2011), and high rates of pervasive developmental disorders (PDD) have also been reported in South Korea (189 cases per 10,000 in 2011) as well as the United Kingdom (116.1 cases per 10,000 in 2006) and Japan (181.1 cases per 10,000 in 2008) [3]. *But is this observed rise in prevalence real (due to increasing cases/incidence), or is it due to heightened awareness and changes in diagnostic criteria (reviewed in Ref. [4])?* There is evidence to support both positions.

Earlier this year, a population-based study of a large Danish cohort found that 60% of the increase in documented autism prevalence could be attributed to changes in reporting practices, including changes in diagnostic criteria [5]. Similarly, a recent report from Sweden concluded that autism symptom phenotype prevalence was actually stable during the study period, and administrative changes were responsible for the apparent increase in official registered prevalence [6]. A slightly older report using data from the US suggests that greater than 70% of the tracked rise in autism since the late 1980s represents a true increase in the disorder rather than a constant-prevalence condition that was underdiagnosed in the past [7]. In 2009, another investigation concluded that while several factors, including changes in diagnostic criteria, an earlier age of diagnosis, and the inclusion of milder cases, did contribute to the observed rise in autism, these could not account for the full extent of the increase [8]. This is clearly a complex and difficult metric to capture, and despite great efforts to standardize diagnostic criteria across regions and countries, we may never know the actual prevalence of ASD. However, the majority of reports and findings from the US seem to support the frequency of ASD being on the rise.

But what makes it so difficult to accept these statistics, and why do we keep searching for alternate explanations? Is it too alarming or frightening to consider that autism rates could really be increasing this quickly? Are the data not compelling enough in either direction? Whether or not the increase is “real” does not change the fact that a large proportion of individuals with ASD are severely impaired, and a report from California earlier this year indicates that the number of substantially disabled cases is also increasing dramatically [9]. The majority of individuals with ASD also suffer from one or more serious medical comorbidities such as gastrointestinal (GI) distress, immune system dysfunction, seizures, sleep disorders, and psychiatric problems, in addition to the core social and behavioral features that define this disorder [10]. On the more extreme end, patients with autism can be completely nonverbal, exhibit aggressive or self-injurious behavior, intellectual disability, a personality disorder, or some combination. Those individuals that fall on the more drastically impaired end of the spectrum will require lifelong care, which can have negative psychological consequences for caregivers, usually immediate family members, in addition to creating substantial economic costs and demand for services [11].

Researchers and the scientific community recognize the need to continue their focus on deciphering the etiology of ASD in order to identify risk factors, prevent adverse outcomes, provide early identification, and better treat patients. Great progress has already been made in this area, with increasing evidence for and recognition of the important roles the environment and immune system play in ASD, and how this information can be used to improve lives.

2. More than genetics: environmental factors

Although ASD has been shown to be highly heritable, there is more to the story than can be solely explained by genetics. Several genetic syndromes are known to have significant associations with autism (for review, see Ref. [12]), but these account for a minority of cases. And while the exact ranges from different studies vary, monozygotic twin concordance rates of autism and associated conditions consistently amount to less than 100%, which strongly suggests a role for environmental factors [13]. Indeed, epidemiological studies have identified numerous correlations between non-genetic influences and ASD, opening the doors for further studies to investigate mechanisms, establish causation, and in some instances promote regulatory actions [14].

Maternal treatment with pharmaceutical drugs such as the valproic acid, thalidomide, and antidepressants (specifically selective serotonin reuptake inhibitors), especially during the first trimester of pregnancy, has been associated with an increased risk of ASD in the child [15,16]. However, it can be difficult to decipher medication-related effects from those of the mother's underlying condition that may also influence autism risk [17]. Exposure to various toxicants including pesticides, polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs), can have detrimental consequences on developmental processes, particularly for genetically susceptible individuals. Not only do PCBs and PBDEs have endocrine-disrupting and neurotoxic effects, but both also persist in the environment and bioaccumulate up the food chain [18]. In addition, many neurotoxic compounds are suspected to interfere with neurotransmitter systems also implicated in ASD [19]. Maternal residential proximity to agricultural applications of pesticides during pregnancy has been associated with an increased risk of ASD, but this scenario may represent abnormally high exposure levels [20]. These chemicals have the additional potential to cause immunotoxicity, which may lead to altered cytokine production frequently observed in ASD [21].

Although advanced maternal and paternal age are well established risk factors for autism, a recent, large international study

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