

Can Exposure to Environmental Toxicants Influence Autism Susceptibility?

By Isaac N. Pessah, Ph.D.

Parents of autistic children are asking difficult questions: “Did my child become autistic after being exposed to multiple vaccines containing mercury preservative and other potentially toxic substances?” “My 24-month-old was in the top five percent in the number of spoken words in her age group until she was exposed to pesticides used at a nearby golf course: Is there a connection?”

Researchers also are seeking answers to complex questions. Can one or more chemical exposures cause an otherwise normal infant to develop autism? Are children genetically at risk for developing autism especially susceptible to the adverse effects of toxic chemicals? Will concentrations of environmental chemicals that have virtually no measurable effects on the general population seal the fate of a developing child genetically at risk for developing autism? Will chemical exposures make some aspects of the disorder more profound, or perhaps less responsive to treatment?

These questions underscore the urgent need for innovative research aimed at understanding the complex web of factors contributing to autism risk. In particular, multidisciplinary research is needed to better understand the potential interplay between immunological and neurobiological disorders underlying autism, as such knowledge undoubtedly will accelerate the discovery of novel and effective intervention strategies.

The earlier an intervention begins for children showing a tendency for autistic behaviors, the greater the chances of improvement. Thus, an intervention that can be implemented before symptoms have fully manifested, for example, preventing a toxic exposure, should have the strongest impact in reducing severity and potentially even preventing some cases of autism. Therefore, new research strategies must identify genomic, biochemical and physiologic markers that confer heightened susceptibility to environmental insults (chemicals and physical stressors) and pharmacological exposures in children already diagnosed with autism, and those at risk.

Why Autism Likely Has Environmental Contributions

It generally is agreed that autism is a neurodevelopmental disorder with many causes that ultimately result in core deficits in social interaction and communication, and in restrictive/repetitive patterns of interest and behavior. In this regard, the number of ways a child may become autistic could rival the number of ways humans can contract cancer.

Generally accepted estimates of prevalence range from 1 in 750 for the narrowest diagnostic criteria, to 1 in 166 for autism spectrum disorder (ASD). The California Department of Developmental Services records an average of 700 to 750 autism diagnoses each quarter.

Although autism may be one of the most heritable complex disorders, the defective genes conferring autism risk do not segregate in a simple Mendelian manner, and the prevalence of autism is approximately four times higher in males than in females. Results from more than 10 genome-wide autism screens indicate that potential susceptibility genes are spread across the entire genome.

Estimates of the number of genes involved in autism range from three to 10 on the low end, to as many as 100. However, no single gene defect appears to be sufficient to cause the full clinical syndrome we diagnose as autism. Evaluation of a broader autistic condition that includes communication and social disorders increases heritability from 60 percent to around 90 percent in identical twins and from 0 percent to 10 percent in fraternal twins. Yet even identical twins diagnosed with autism can exhibit a very different cadre of symptoms.

Therefore, autism is likely to have several causes, including interactions among multiple defective genes, epigenetic contributions (factors that cause genes to “turn on” or “turn off” without changing their structure), and exposure to environmental modifiers. Collectively, multiple factors, including environmental exposures, are likely to contribute to the range of problems experienced by children with autism.

Understanding Gene-Environment Interactions in Autism Risk and Severity

Susceptibility to Neurotoxic Chemicals—Pesticides as an Example

A major hypothesis put forth to explain the core symptoms of autism and associated problems, such as a high incidence of seizures, is that they emerge from imbalances in the activities of excitatory and inhibitory circuits within the developing brain. Normal development of brain circuitry relies on highly regulated patterns of electrical activity. These patterns not only help promote the growth and exact shapes of useful connections within the brain, but they also curtail the growth of unneeded connections. Several widely used pesticides of current and historical importance are in fact neurotoxic because of their ability to promote imbalances in these electrical activity patterns within the nervous system. Could some children who are genetically at risk for autism be more susceptible to the adverse actions of such pesticides?

In fact, several autism candidate genes (specific genes that have been associated with autism risk) encode for proteins that regulate excitation/inhibition within the central nervous system. These include metabotropic glutamate receptors, gamma-aminobutyric acid receptors (GABR), nicotinic cholinergic receptors (nAChR) and certain types of ion channels and transporters. Several of these neurotransmitter systems are known to be direct or indirect targets of pesticides frequently measured in detectable levels in children.

An intriguing example related to environmental triggers is that 30-35 percent of the children with autism exhibit seizures of varying severity from subclinical to generalized tonic-clonic seizures. An altered GABAA receptor (GABR) system is found fairly frequently in people with autism, and this has been proposed as a major underlying cause of seizure susceptibility, and possibly a contributor to several aspects of autism.

Chlorinated hydrocarbon insecticides, including heptachlor, chlordane, dieldrin and toxaphene are all potent GABR blockers, and although their use was discontinued in the United States between 1987 and 1990, their persistence in the environment and human tissues remains a concern. Several uses of lindane, a potent GABR blocker, continue, including control of head lice and scabies. A newer class of noncompetitive GABR antagonists, the 4-alkyl-1-phenylpyrazols that include fipronil, is being used for both domestic and agricultural applications. This raises important questions as to whether heritable

GABR deficiencies known to occur in children with autism confer heightened susceptibility to adverse responses produced by environmental exposure to GABR blockers.

Immunological Susceptibility in Autism

Inherited immune-system dysfunctions may represent one of the core causes of autism. Identifying patterns of immunological dysfunction common to autism, or specific to subgroups, by using transcriptional profiling and immune phenotyping in the context of a case-control study of autism provides a powerful approach that is likely to identify early biomarkers of risk, yield a better understanding of environmental risk factors and identify rational intervention strategies to mitigate these risks.

Psychological stressors, exposure to chemical triggers and infectious agents may work in concert to adversely influence the immune system, and altered immunity, in turn, could enhance susceptibility to developmental neurotoxicants. In this regard, children at risk of autism may be particularly susceptible to chemical triggers that have biological targets shared by both the immune and nervous systems. It is well documented that heavy metals such as mercury are potent immunotoxicants and neurotoxicants. In addition to mercury, several environmental pollutants of particular concern to neurodevelopmental researchers, including lead, manganese and arsenic, are known to adversely promote inflammatory responses and/or autoimmunity. Persistent organic pollutants such as polyaromatic hydrocarbons and polychlorinated biphenyls (PCBs) also are potent modifiers of immune responses. Therefore, children at risk for developing autism may represent a subpopulation particularly susceptible to environmental triggers of improper immune responses that impact the developing nervous system.

Autism is likely to have several causes involving abnormal immune and nervous systems with origins that likely occur during embryonic, fetal and early postnatal development. The approaches with the greatest potential for advancing our understanding must reflect this complexity, requiring the collaborative efforts of investigators in multiple disciplines. Population-based human epidemiology studies are needed to specifically explore the relationships among environmental chemical insults, immunologic alterations, and the expression of key genes already linked to autism. The design of future studies must recognize that genetic defects already linked to autism may supply tinder for heightened susceptibility to environmental sparks.

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