Autism: Peer-Reviewed Analysis

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Autism: Do Environmental Factors Play a Role in Causation?

Ted Schettler MD, MPH, Science Director
Science and Environmental Health Network

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What Is Autism?

Autism is a pervasive developmental disorder that involves social, language, sensory, and motor deficits, behavioral abnormalities, and may also be associated with mental retardation. Kanner coined the term "autism" in 1943 to characterize a group of children in whom he identified a complex set of characteristics that clustered together, including abnormalities in social development, verbal and non-verbal communication, and symbolic thinking. In 1944 Asperger described a similar set of characteristics, except that his patients did not have language delays as described by Kanner.

Autism usually becomes apparent by the age of three or four, though the timing of diagnosis depends on the severity of symptoms. Autistic children display varying degrees of impairment of social skills, limitations in the use of language, echolalia (repetition of a word or sentence just spoken by another person), deficiencies in symbolic thinking, stereotypic/repetitive behavior, self-injury behavior, seizures, and mental retardation (Rapin 1997).

The diagnostic criteria for autism have evolved over the years. According to current criteria found in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSMIV), the diagnosis of autism depends on combinations of symptoms and signs from the realms of social interaction, communication, and behavior. Other pervasive developmental disorders (PDDs) include PDD-not-otherwise-specified (PDD-NOS) and Asperger syndrome. PDD-NOS includes individuals who do not fulfill the autism criteria in one of the three categories, or did not do so early enough in life. Rett's syndrome, generally thought to be seen only in females, and childhood disintegrative disorder are two relatively unusual additional severe developmental disorders that share some features of autism but are unlikely to have the same causes.

Children with pervasive developmental disorders are not always easy to diagnose and classify. Considerable effort has been invested in developing the Autism Diagnostic Interview (ADI) and the Autism Diagnostic Observation Schedule (ADOS) (LeCouteur et al. 1989, DiLavore et al.

1995) as reliable diagnostic instruments These tools have made it possible to combine samples of people with autism for study purposes, but their use is time-consuming, and they are not the standard of care in clinical practice. As a result, clinicians vary considerably in their use of diagnostic labels.

In recent years, autism has increasingly been considered a spectrum of conditions (autism spectrum disorders—ASD), but the value of using such a continuum is a matter of debate because of considerable variability in manifestations of altered social interaction, communication, and behavior. Yet, it is generally agreed that ASDs are likely to share at least some risk factors and causal mechanisms, such as overlapping genetic predisposition and gene expression, although these may be involved in different ways at varying times during development.

Autism Prevalence and Trends

The prevalence of autism and trends over time is the topic of considerable debate and disagreement. Uncertainties arise from two main sources. First, record keeping has been relatively sparse and inconsistent since Kanner first coined the term "autism". Second, inconsistencies in the use of diagnostic terminology over time or from place to place make it difficult to achieve consensus.

Prevalence surveys in the 1960s and 1970s dealt with a narrow definition of autism as defined by Kanner, and did not account for people who were not also mentally retarded. Autism prevalence from studies published before 1985 are 4-5 per 10,000 for the broader spectrum of conditions and about 2 per 10,000 for Kanner's more narrowly defined classic autism (Wing 1993).

In the 1990s, pervasive developmental disorder—not otherwise specified (PDD-NOS) and Asperger syndrome were added to the DSMIV. Clinicians often use these diagnostic categories for milder or less formulaic manifestations of developmental abnormalities. As a result, prevalence surveys in recent years often, but not always, include individuals with conditions that would not have been included in earlier surveys.

In 1999, a 210% increase in the number of children with autism reported to the Department of Developmental Services in California from 1987 to 1998 suggested that the incidence of autism was rapidly increasing (California HHS 1999). Considerable debate since then has focused on whether or not the reported increase is a result of changing diagnostic patterns and changing terminology—for example, substituting "autism" for "pervasive development disorder"—or whether the increase can be explained by "diagnostic substitution" of patients who would previously been diagnosed as mentally retarded (Croen and Grether 2003, Fombonne 2003).

Reanalysis of the original California data indicates that the increase cannot be explained entirely by diagnostic substitution (Blaxill et al. 2003, Croen and Grether 2003). In that reanalysis, over the period of 1987-1994, the probability of becoming a Department of Developmental Services

client for mental retardation by age 4 remained relatively constant while the probability of becoming a client for autism increased steadily from about 2/10,000 births in 1987 to 10/10,000 births in 1994. The discussion surrounding the validity of the California data emphasizes the importance of accounting for case ascertainment bias, distinguishing between incidence (rate of new cases of autism) and prevalence (point estimate of total cases, new and old, at any time in a given population), and considering the prevalence of autism in annual birth cohorts independently as they age. Considering these factors, Blaxill et al. conclude that the increase is real.

Another recent survey in Atlanta, GA found autism prevalence of 1.9 per 1000 in 3-year-old children to 4.7 per 1000 in 8-year-olds (Yeargin-Allsopp et al. 2003). In this survey, the term "autism" included autistic disorder, Asperger syndrome, and PDD-NOS. A recent study in the United Kingdom reported a prevalence of 1.7 per 1000 children for autistic disorder and 6.3 per 1000 for the entire autism spectrum.

The debate over autism prevalence and trends has important practical consequences for two major reasons. First, an increasing prevalence of ASD buttresses arguments for additional research into their causes and identification of opportunities for prevention, as well as additional resources for clinical and educational services. Second, if the prevalence of autism is increasing, as recent surveys suggest, an important contributing role for environmental factors becomes more plausible.

In all studies, males are about 3-4 times more likely to be affected with ASD than females. In the Atlanta study, among the children with autism, 20% had mild mental retardation (MR), 11% moderate MR, 7% severe MR, and 3% profound MR. Eight percent of the children with autism also had epilepsy and 5% had cerebral palsy.

Autism: A Singular Disorder of Brain Development or Multisystem Disease?

In the past two decades autism and ASD came to be considered to be primarily disorders of brain development. This formulation was an advance over prior psychoanalytic formulations associated with Bruno Bettelheim, who attributed autism to the social reticence of "refrigerator mothers", even though it was later shown that social reticence was more likely in fathers (Eisenberg 1957). A significant contributor to this shift was the discovery of abnormalities in postmortem brain tissue, particularly in the limbic system and cerebellum (Bauman and Kemper 1985). The nature of these abnormalities suggested to some people a prenatal origin for autism, probably before 30 weeks gestation. This finding, in conjunction with the high concordance in monozygotic twins, led to a formulation that autism was a genetically programmed disorder that begins in utero.

While postmortem brain tissue of young autistic subjects is hard to obtain, it has been easier to study brain abnormalities using various types of neuroimaging. After years of poorly replicated

findings, the single most common observation has been that head circumference, brain volume and brain weight are all greater in children with autism than in children who are developing typically. Moreover, retrospective head circumference studies in children diagnosed with autism show that the brain volume increase occurs postnatally, as autistic children are usually born with normal or even slightly small head circumferences, but have an unusually rapid brain growth trajectory in the first few years of life (Lainhart et al. 1997, Woodhouse et al. 1996, Courchesne et al. 2001). While this post-natal brain volume increase could result from abnormalities in brain development that are set in motion in utero, it also raises the possibility that post-natal influences are having an impact on autistic brain development. In either case, environmental factors could play a role.

Along with evidence that brain development may be altered postnatally and not just in utero, other findings suggest that not just the central nervous system but other organ systems as well may be affected in autism. Associated gastrointestinal, immunologic, and metabolic abnormalities that co-occur with neurologic signs and symptoms in many people with autism suggest that autism may actually be a multi-system disorder with a variety of manifestations (Gillberg and Billstedt 2000). Consequently, some clinicians, research scientists, and advocates have begun to think about autism as associated with a number of potential co-morbidities, which may, in some instances, be causally related to the entire symptom complex.

Intestinal abnormalities: Gastrointestinal abnormalities reported in children with autism include gastritis, reflux esophagitis, non-specific colitis, constipation, and altered intestinal absorption (Horvath et al. 1999, D'Eufemia et al. 1996, Accardo and Bostwick 1999, Wakefield et al. 1998, Afzal et al. 2003). These conditions can cause bloating, abnormal bowel movements, abdominal pain, and irritability, which in turn, can trigger behavioral abnormalities and abnormal sleep patterns. Pathological examination of intestinal biopsies has revealed abnormal immunological markers (Torrente et al. 2004, Ashwood et al. 2003). It appears that some dietary interventions may help improve these symptoms in autistic children. Whether or not these gastrointestinal abnormalities are in any way related to the cause of neurological manifestations of autism is a matter of conjecture. One hypothesis that has not been well studied, for example, theorizes that abnormal intestinal absorption of dietary components or toxic chemicals facilitates toxic impacts on brain development.

Altered metabolic processes: Another hypothesis that has received some attention focuses on abnormal metabolic processes in some autistic people. This theory holds that at least some autistics have an impaired ability to properly metabolize toxic chemicals or metals to which they may be exposed through normal dietary intake or through exposure to contaminated food, water, or air. (Alberti et al. 1999, Waring 1997) Most reports that address this hypothesis are anecdotal or involve studies of relatively small numbers of children. This is also an area of profound uncertainty and debate. Larger well-designed and well-controlled studies will be necessary in order to draw any meaningful conclusions.

Immune system abnormalities: Cell-mediated immunity and antibody levels have been reported to be abnormal in some people with autism (Gupta 2000, Singh et al. 1991, Burger and Warren 1998, Jyonouchi et al. 2001). Autoimmune antibodies have also been described (Singh et al. 1988, Gupta 2000) and increased autoimmune disease has been documented in family members of autistic individuals (Comi et al. 1999). As a result, abnormalities of the immune system are the basis for additional hypotheses about the causes of autism. Genetically determined immune system abnormalities might theoretically help to explain an abnormal response to toxic chemicals or metals in autistic people as well. This, too, remains an area of conjecture and significant research interest.

Causes of Autism

Genetic factors: The causes of autism are unknown. A limited number of twin studies show that genetic factors undoubtedly play an important role but are not fully explanatory. In monozygotic twins ("identical twins"), if one twin is diagnosed with autism, the other twin has a 70-90% chance of having a similar diagnosis (Steffenburg et al. 1989, Folstein and Rosen-Sheidley 2001). The severity of the condition in identical twins, however, may differ considerably. (Bailey et al. 1995) In dizygotic (fraternal) twins, if one is diagnosed with autism, the chance of the other having a similar diagnosis is to 5-10%. Non-twin siblings of people with autism also have a 3-8% chance of having the same diagnosis, which is more than a 10-fold increase in risk compared to the general population. (Rutter et al. 1997)

These family studies of autism and related conditions help provide clues to both genetic and environmental causes. If, for example, dizygotic twins have a higher likelihood of a shared diagnosis than non-twin siblings, it suggests that a uterine environmental factor or something in the early postnatal shared environment may play a role. But dizygotic twin data are relatively sparse, making it difficult to draw firm conclusions. It is also important to note that differing levels of severity of characteristics of autism among twins and siblings with similar diagnoses raise the possibility that, while genes may play an important role in autism causation, these genetic factors may be influenced to a greater or lesser extent by exposure to environmental agents, whether chemical, biological, or nutritional.

Environmental agents: Many different environmental agents have been considered as possible contributors to the development of autism, in combination with a genetic predisposition. A number of problems complicate the design of research programs to explore these possibilities. Among them is the suspicion that the spectrum of disorders that are included in ASD may actually represent a very heterogeneous mix of conditions with disparate causes. Under these circumstances, no simple combination of genetic and environmental factors will ever be identified as contributing to the majority of cases of autism. Because of this, some researchers suggest a shift of research focus to identification of subtypes of autism that, while not purely homogeneous, will nevertheless have lower variability within the group being studied. A complementary shift in emphasis comes out of the argument that the autism is not a unitary

diagnosis but rather is a manifestation of a final common pathway that can result from multiple types of injuries to or abnormalities in the developing nervous system.

No clear picture has emerged from research into environmental contributors to autism, though there are tantalizing clues. In utero exposure to the rubella virus (the cause of "German measles") can impair brain development of the fetus leading to varying degrees and combinations of blindness, deafness, birth defects, mental retardation and autism (Desmond et al. 1967). Children with autism resulting from gestational exposure to rubella virus may improve, worsen, or remain about the same. Post-natal herpes simplex virus brain infections (encephalitis) may also result in an autism-like syndrome. (Ritvo et al. 1990).

Two pharmaceutical agents, thalidomide and valproic acid, are also implicated in the development of some cases of autism. The morning-sickness drug, thalidomide, is best known for the tragic and often severe limb defects that it caused in the offspring of some women who took it while pregnant. A 1994 Swedish study, however, reported that five out of a group of 100 children who had been exposed to the morning-sickness drug thalidomide in utero developed autism. The risk was particularly increased when the exposure to the drug occurred early in pregnancy—20-24 days after conception (Stromland et al. 1994).

Subsequently, in an autopsy examination of a person with autism, Rodier and colleagues found abnormalities in the brain stem and cranial nerves. (Rodier et al. 1996). This kind of abnormality is best explained by altered brain development during early gestation, similar to the time of increased risk in people exposed to thalidomide. Together these findings suggest that a critical period for autism induction may be very early in gestation. Valproic acid, an anti-seizure medication, has also been implicated as a cause of autism after gestational exposure (Christianson et al. 1994, Williams et al. 2001, Moore et al. 2000).

A recent review of the medical literature by the Agency for Toxic Substances and Disease Registry of the US Department of Human Services identified reports of chemical exposures that are potentially related to autism. (Allred and Wilbur 2002) Preconception parental occupational exposure to chemicals generally and maternal abuse of drugs have been linked to autism in offspring, but most of these studies have significant limitations. Studies of the potential role of anesthetics and labor-inducing drugs have mixed and inconclusive results. Maternal use of alcohol during pregnancy can result in fetal alcohol syndrome, a mixture of birth defects, intellectual and behavioral problems. Asperger syndrome and autism can coexist with other manifestations of fetal alcohol syndrome, suggesting that alcohol may, in some cases, be responsible for autism as a result of early gestational exposures (Aronson et al. 1997, Harris et al. 1995).

In recent years, other environmental factors have been suggested as playing a role in the development of autism. Interactions between genetic susceptibility and toxic exposures that may trigger those genetic factors are the subject of considerable research into the causes of autism.

For example, inter-individual variation in the absorption or excretion of heavy metals like mercury in susceptible individuals is under close scrutiny. Each hypothesis and the evidence that supports it, has attracted staunch, outspoken advocates, many of whom have organized in networks and organizations dedicated to further research, services for affected individuals, and treatment. (Defeat Autism Now, Autism Research Institute, Safe Minds, among others)

Autism and vaccines: Concerns about a potential relationship between vaccines and autism developed in the 1990s and intensified in 1998 after reports of a study of 12 children with regressive autism and gastrointestinal disease (Wakefield et al. 1998). The children referred for study had all been reported to be developing normally before losing acquired skills, including language, and all had developed diarrhea and abdominal pain. For 8 of the 12 children, parents or clinicians reported retrospectively that the onset of their behavioral symptoms began shortly after receiving MMR (measles, mumps, rubella) vaccine. On detailed examination, including biopsies and imaging studies, each of the children showed intestinal abnormalities, including inflammation. The study was noted to have limitations because it did not include any control patients and may have been influenced by retrospective ascertainment of vaccination timing and status, among other reasons. (Chen and DeStefano 1998) Nonetheless, although the authors clearly stated that the results did not show that MMR vaccine was responsible for the symptoms and findings, this study increased the concern of many about the safety of the MMR vaccine. The observations raised the possibility that MMR vaccine causes inflammation of the intestinal lining, facilitating increased intestinal permeability and excessive absorption of toxic compounds derived from certain foods.

In 2001, a committee of the Institute of Medicine at the National Academy of Sciences addressed the topic, reviewing published and unpublished literature addressing MMR vaccines and autism spectrum disorders, and interviewing research scientists who had investigated the matter (Institute of Medicine 2001a). The committee concluded "the evidence favors rejection of a causal relationship at the population level between MMR vaccine and autism spectrum disorders…. However, the committee notes that its conclusion does not exclude the possibility that MMR vaccine could contribute to autism spectrum disorders in a small number of children….." The committee noted "the proposed biological models linking MMR to vaccine to ASD, although far from established, are nevertheless not disproved." They also noted that vaccine protection from infectious disease is an extremely important public health measure and that the diseases that the vaccines prevent have significant associated morbidity and mortality.

Autism and mercury—vaccines and beyond: Another vaccine-related concern stems from the use of thimerosal as a preservative in vaccine preparations. Thimerosal is an organic mercury compound, metabolized to ethylmercury and thiosalicylate, and has been used in vaccines since the 1930s until it began to be phased out in the late 1990s. Concerns centered on the observation that organic mercury is a potent toxicant in the developing brain and that children receiving a full set of recommended vaccinations were often exposed to mercury at levels that exceed a "safe"

reference dose, established by the Environmental Protection Agency and affirmed by the National Academy of Sciences.

In 2001, a committee of the Institute of Medicine (IOM) examined the evidence that might help clarify any relationship or lack of relationship between thimerosal and autism (Institute of Medicine 2001b) That committee concluded that there was insufficient evidence to establish the link, but that the hypothesis is biologically plausible.

Since that IOM report, in a study of mercury levels in the blood of 40 children who had received vaccines containing thimerosal and 21 control children, the authors reported that no children in the treatment group had mercury blood levels that exceeded the "safe" level as estimated by the EPA. (Pichichero) The authors, however, determined that the half-life of ethylmercury is 5-7 days, and in some cases, blood samples were obtained well after peak blood levels would have occurred. As a result, and because only single blood samples were tested, the investigators were unable to determine what peak blood levels of mercury had actually been after vaccination. Moreover, no attempt was made to calculate the fluctuating mercury levels that will result over time as a child receives multiple vaccines beginning in infancy. Limitations of this study are discussed in some detail in correspondence (Colman 2003, Halsey and Goldman 2003, Westphal and Hallier 2003), and on the Safe Minds website www.safeminds.org.

A subsequent report in 2003 evaluated doses of mercury from thimerosal-containing vaccines and the incidence of neurodevelopmental disorders, including autism, using the Vaccine Adverse Events Reporting System, maintained by the Centers for Disease Control since 1990. (Geier and Geier 2003) Though the authors concluded that there was strong epidemiological evidence for a link between the thimerosal exposure and neurodevelopmental disorders, the study, as published, does not provide sufficient data to justify the conclusion. It is severely limited by its design and sources of data. It is an ecological study that examines vaccine use and adverse reactions reported in the entire population without being more precise about actual exposures to mercury in individual children who did, or did not, develop neurological disorders. Reporting bias is also likely to be a serious limitation. Moreover, the authors do not supply any of the detailed data, such as incidence of adverse effects and number of doses of vaccine administered, necessary to evaluate the significance of their conclusions. This study is uninterpretable and inadequate for drawing conclusions regarding a causal relationship between thimerosal and autism.

In 2004, Hornig et al. reported the results of a study of the impacts of thimerosal in autoimmune-sensitive mice. The investigation was prompted by reports of increased autoimmune disease in families of people with autism, which generated the hypothesis that, in some people with autism, autoimmunity might play a causal role. Mice were treated with thimerosal at levels intended to mimic the exposures of children given thimerosal-containing vaccines. Autoimmune-sensitive mice showed altered growth, reduced locomotion, exaggerated response to novelty, and changes in microscopic brain structure, including increased cell density in some brain regions, after exposure to thimerosal. Control mice resistant to autoimmunity did not show similar changes.

These results suggest an interaction of thimerosal with the immune system, causing neurobehavioral toxicity and structural brain changes, although it remains unclear if they are analogous with those seen in people with autism.

A final IOM report on vaccines and autism was released in 2004 after the committee reviewed the most current data and interviewed research scientists and authors. That report concludes, "the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism." (Institute of Medicine 2004) Commenting on the mice studies, the IOM committee said that the "connection with autism and these models is theoretical". An important unresolved issue is whether the immune system may play a contributory role in causing autism in some people or rather, that immune system abnormalities are another manifestation of the complex condition. This is likely to remain an important line of ongoing research.

Despite concerns about administering mercury-containing vaccines to pregnant women, infants, and children, thimerosal is not the source of largest mercury exposures in people. Methylmercury contamination of fish and dental amalgam fillings in teeth are other significant sources. Methylmercury easily crosses the placenta and is well known to impact normal fetal brain development. Cumulative mercury exposures from multiple sources, therefore, must be considered when assessing a potential link between autism and mercury.

Perhaps as well as any other example, the debate about the potential role of mercury in vaccines as a contributing cause of autism highlights the intense interest of parents, the general public, research scientists, and public health agencies in learning more about a possible causative role of environmental factors in autism. Fortunately, thimerosal-free vaccines are now available in the US, so parents are not faced with wondering about the safety of vaccines for this reason. Lifting this burden has been a relief, since vaccinations are extremely important public health interventions in the prevention of dangerous infectious diseases.

Summary

Autism is a complex disorder with social, language, sensory, and motor deficits, behavioral abnormalities, and may also be associated with mental retardation. These components may have widely varying expression in individuals. In recent years, associated co-morbidities, including gastrointestinal, metabolic, and immune system abnormalities, have raised new questions about the causes and manifestations of the full spectrum of autism-like disorders. Autism prevalence is generally thought to be increasing, though changing diagnostic criteria and increased reporting are likely to be contributing somewhat to that increase. Genetic factors are important in the causation of autism but are not fully explanatory. Various environmental factors, including infectious and chemical agents, are known, suspected, or theorized to play a role, as well.

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