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Epidemiologic Approaches to Autism and the Environment

By Craig J. Newschaffer, Ph.D.

The science of epidemiology often is critical to discovering links between environmental exposures and particular diseases. Epidemiologists study how health outcomes are distributed across populations and, by making comparisons across population subgroups, they learn what factors are likely to increase risk of disease.

The two most common approaches used to establish that environmental factors play a role in causing a disease are to contrast disease rates in a single population at different points in time and to compare disease rates at the same point in time across different populations. If disease rates change markedly within a population over time, it is a strong sign that some environmental factors are at play since changes in disease risk due to genetic predisposition evolve over the course of generations, not decades.

If rates at a single point in time are markedly different across distinct populations (e.g., in different countries), this also suggests environmental causes, especially if the rates correlate with factors influencing the nature of environmental exposures in the populations compared (for example, degree of industrialization, or dietary preferences).

These basic epidemiologic approaches work best for diseases that are diagnosed quickly, definitively and inexpensively. When this is the case, epidemiologists are confidant that the variation in disease rates seen when they make comparisons are not by-products of differences in the manner in which the condition is diagnosed.

Autism by the Numbers

Because there is no medical test for autism, with diagnosis based on complex behavioral criteria, the diagnostic process, is time-consuming, involves periods of uncertainty, and can be quite expensive. This is horribly frustrating to parents searching for help for their child and also is challenging for epidemiologists seeking to understand patterns of disease in groups.

Over the last two decades there has been a tremendous increase in the number of children in the United States diagnosed with autism spectrum disorders—that is unquestioned—and the numbers demonstrate conclusively that autism is a major public health problem. Being certain that these trends represent true changes in risk also would provide strong support for the notion that environmental factors are involved in causing autism. Unfortunately, there are considerable challenges to either proving that the trend represents real risk or to disproving that the trend is caused by shifting diagnostic practice over time.

It is nearly impossible to substantiate that a time trend in disease rates reflects real risk when the mechanisms or risk factors underlying that disease are unknown. Although recent strides have been made in understanding the biology underlying autism, we don't yet know what fundamental process or processes go awry in the brain leading to autism.

On the other hand, to disprove that a trend is due to diagnostic changes, good data must be available to show how diagnostic practice has or has not changed. Unfortunately, there is a dearth of real data on this for autism. We know that there have been considerable changes in the understanding and awareness of autism in the medical and educational communities, but when it comes to quantifying the extent of these changes and determining how they impact the prevalence of autism, there is a great deal of anecdote and speculation and very little data.

For a disease like melanoma, a deadly form of skin cancer where there also has been a large increase in rates over recent years, epidemiologists have good data available on relevant diagnostic practice, namely the rate at which screening biopsies are used. With these data, screening-biopsy rates in a community can correlate to that community's melanoma rates. If high rates of screening biopsy are associated with high rates of melanoma, this suggests that melanoma rate trends are related to diagnostic approach.

Further, melanoma rates by disease stage (early- vs. late-stage disease) can be examined separately. If communities with high biopsy rates tend to have higher rates of early as opposed to late-stage melanoma, this adds evidence that the increasing rates are due to changes in the way the cancer is diagnosed, not real risk, because early-stage melanoma is much more likely to be detected through the screening biopsy approach.

For autism, shifts in diagnostic approach do not involve something easily trackable like biopsy rates. Even changes we can track, such as rephrasing the guidelines that describe behavior indicative of autism, likely capture only a small portion of the evolving understanding of this complex condition. The informal shifts in interpretation of criteria are more likely to have impact, and quantifying the magnitude of these changes and their impact on rates of diagnosis is extremely difficult.

Even though the most common approaches used to establish connections between environmental exposures and disease face fundamental challenges when applied to autism, epidemiology still offers support for continued research of a link between autism and the environment. Although much of this evidence is indirect, it is still compelling.

Genetics and the Environment

In the late 1970s, studies of twins indicated conclusively that genes strongly influence the risk of autism. These twin studies were landmark research with tremendous impact for families, establishing the biologic basis for autism and scuttling the long-standing conventional wisdom that it was parents' interactions with their children caused autism. So it is not surprising that the initial interpretation of this work emphasized the large influence genes appeared to play. In fact, based on these studies, it often is said that autism is "highly heritable."

However, these twin studies also indicated unequivocally that genetic influences *did not completely* explain autism risk. The numerous genetic epidemiology studies that followed have brought us closer to identifying specific genes that influence autism risk. But they also consistently have indicated that the genetic mechanisms underlying autism are extremely complicated.

Complexity in genetic inheritance can come from a number of different sources, one of which is interaction between genes and environmental exposures. Gene-environment interaction in autism means that genes passed on to a child may contribute to that child's autism, not because the genes directly influence the developing nervous system, but because they affect that child's biologic response to an environmental exposure that, in turn, dysregulates the developing brain.

We know that hundreds of chemicals have the potential to disturb basic brain development processes; for instance, the way growing brain cells move and connect. What we don't know is how harmful these chemicals can be at low levels of exposure, and which specific genes might make some children more vulnerable to low-dose exposure than others. However, if genetic susceptibility and environmental exposures interact, many of the epidemiologic studies done to date that have characterized only genes, but have not measured environmental exposures, have had little choice but to "count" autism caused by the interaction between genes and environmental exposures as being caused by genes.

So the argument that says, "because genetic epidemiology has shown autism to be highly heritable, there is little room for environmental influences" should be viewed with skepticism. Moreover, we are just now learning about entirely new sets of biologic mechanisms, referred to as "epigenetics," that influence the expression of genes—whether genes are "turned on" or "turned off." Early indications are that epigenetic processes are highly influenced by environmental exposures.

To date, there have been few epidemiologic studies completed that have directly linked environmental exposures and autism. Some studies have suggested that during pregnancy, both viral infection and the use of certain medications known to cause birth defects elevate autism risk. More recent research has reported associations of certain air pollutant exposures, most notably airborne mercury, cadmium, nickel, and chlorinated and diesel particulates with autism. But caution should be used when interpreting this work due to limitations in the way air pollution exposure was measured and the way autism cases were counted.

There are other chemicals with direct neurotoxic effects or with the potential to alter neurodevelopment by acting on the endocrine or immune system that could warrant consideration in autism research. These include polychlorinated biphenyls (PCBs); complex mixtures of persistent contaminants stored in lipid; brominated fire retardants (BFRs); chemicals that are structurally similar to PCBs and found in increasing concentrations in people and the environment; phthalates, substances used in making plastics and certain pesticides. Epidemiologic study of these chemicals as risk factors for autism is only the beginning.

The Challenges of Studying Autism and the Environment

As work continues in the area of environmental exposures and autism, it is critical to remember that, just as gene environment interaction creates complexity for genetic research, it also will complicate studies focused on environmental exposures. When the samples used in epidemiologic studies include mixes of children with differing degrees of genetic susceptibility to environmental exposures, the overall estimated effect on autism risk can appear very small, but may in fact be very large in a subgroup of children who are most highly genetically susceptible.

For example, mercury has well-known adverse neurotoxic effects, and for several years there has been mounting concern over thimerosal, a mercury-containing preservative used in multidose vials of vaccines. Childhood vaccine-related thimerosal exposure now has been investigated in several epidemiologic studies, and the findings have been quite consistent in indicating that thimerosal exposure is not responsible for the dramatic increases in autism cases witnessed over the past few decades.

However, although there is no discernible effect in the population overall, there still may be an effect in a subgroup of the population especially susceptible to mercury. There is a continuing need for research on susceptibility to low-dose mercury exposure via thimerosal, as well as via other routes. Autism epidemiologists wait for these findings, as well as for findings on markers of susceptibility to other neurotoxicants.

Although the debate continues over whether the increase in autism is attributable to changes in risk versus changes in diagnostic tendencies, resolution of this debate is not a precondition for moving forward with epidemiologic research on autism and the environment. The complex picture emerging from work on the genetic epidemiology of autism, coupled with what is known from animal and human research on the neurodevelopmental effects of a variety of environmental exposures, and the limited existing epidemiologic data on environmental factors and autism is sufficient to motivate more work in this area.

The next generation of autism epidemiology studies is moving ahead by capturing information on a range of different exposures while simultaneously collecting DNA samples to allow genetic characterization. This will allow investigation of select hypotheses right now and will ensure that these data can be returned to as findings on markers of susceptibility become available.

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