Opinion

Not so many years ago, the development of infant and childhood vaccines was heralded as a monumental milestone in conquering childhood infectious disease. One needs only to look back a generation or two to recall images of children in iron lungs and wheelchairs due to summer outbreaks of polio and to the collective joy when the March of Dimes initiative culminated in the long-awaited development of the Salk polio vaccine in the early 1950s. In those early days, parents and children would line up and wait for hours at local clinics to receive an injection of this precious liquid that would protect infants and children from the ravages of this deadly disease. Fast forward to the 21st century and a generation of parents who themselves were protected from polio and other deadly infant diseases [measles, mumps and rubella-MMR] is wary of having their own children vaccinated to protect them against the very diseases that have so profoundly improved infant mortality statistics and many other public health parameters.

What happened? Autism. Its incidence has risen dramatically over the past half century, seemingly inexplicably, causing parents and clinicians alike to search frantically to identify the cause of this frightening statistic. Autism, first described by Kanner in the 1940s, is actually categorized as a spectrum of disorders linked to impairments of socialization often linked to cognitive impairment. Some cases seem to result from an apparent failure of an infant to achieve critical milestones of development, such as the acquisition of language. In other cases, young children have been observed to regress suddenly to lose some of their social and/or cognitive abilities. That this developmental regression has been observed on occasion to occur shortly after routine vaccination has prompted many questions as to the potential role of vaccines in the genesis of this disorder. Media coverage has served to ‘spread the news’ that has alarmed many parents and resulted in a decline in the number of children who are receiving infant and childhood vaccinations, a serious threat to public health. Scientific studies from prestigious pediatric organizations demonstrating no statistical link between the use of infant and childhood vaccines as a cause of ASD have, in some cases, done little to convince an anxious public of their safety.

So, what is going on here? Is this fear of childhood vaccinations merely a hysterical reaction to an unexplained epidemic of autism, or is there some rational basis to this concern about the effect of vaccines that has not yet been identified by current research? The answer, in my opinion, is a qualified ‘yes’ to both. Parental fears have been exacerbated by the extensive coverage of the suggested ‘vaccine’ link to Autism Spectrum Disorder (ASD). Likewise, the feverish search on the part of the scientific community to either prove or disprove the vaccine hypothesis has left us bereft of real answers.

In my view, ASD is an example of a classic genetic multifactorial threshold disorder in which multiple factors in combination and degree determine whether a threshold of neurodevelopmental impairment is reached that is clinically defined as autism. This model, called the Quantitative Threshold Exposure (QTE) hypothesis, proposes that ASD is triggered by the cumulative effects of exposure to immune stimulatory factors that act as antigens to impair normal immune system (IS) and associated central nervous system (CNS) functions during critical developmental stages [1]. The model rejects the concept that a single genetic or environmental agent is the cause of most cases of ASD. This explains why no direct link between autism and vaccines has been identified in exhaustive epidemiological studies.

The QTE model is supported by the fact that, to date, NO specific genetic or environmental risk factor has been identified as THE cause of autism. Rather, the QTE hypothesis proposes that it is the quantitative exposure level to any number or combination of genetic and environmental risk factors at critical developmental stages that determines whether the threshold exposure level is sufficient to cause ASD. Moreover, the level of exposure necessary to trigger an impairment of CNS development may vary significantly with the timing of exposure to determine threshold impact and the severity of ASD.
So, what is this collection of risk factors for autism? A critical issue confronting parents and clinicians alike is our current inability to define which fetuses/infants and young children may be at enhanced risk for developing ASD. Despite important advances in our understanding of the physiological basis for ASD, it is currently impossible to predict which children will develop this disorder. To identify at risk infants, it is essential to identify genetic and environmental factors that may be linked to autism risk. Risk factors impinging on normal brain development may result from pre-natal or early post-natal exposure to agents and/or abnormal gene products that may disrupt the normal process of brain development that begins in utero and extends several years postnatally. Specific genetic profiles and epigenetic factors, such as maternal prenatal immune system dysregulation/activation, have shown a correlated increased risk for the development of autism. Direct evidence of a link between abnormal brain maturation and dysregulated immune system function has been shown by research studies that have identified differences in the immunologic composition of the cerebral spinal fluid microglia and macrophages in autistic individuals. With increased research, it may be possible in the future to calculate the weighted significance of risk factors with documented causal connections to ASD and generate a combined risk factor assessment profile for predictive and preventive clinical evaluations.

That said, there are certain risk factors with significant causal associations with ASD that current research suggests may have greater prognostic value than others. Research shows that maternal autoimmune disorders contribute to increased risk of giving birth to a child with autism. A research study conducted in Denmark of 700,000 births over a period of 10 years produced data showing that maternal rheumatoid arthritis was associated with an 80% increased risk for having a child with autism [2]. This and similar studies suggest that maternal antibodies associated with inflammatory responses linked to autoimmune disorders or infectious disease may bind to the developing fetal brain to impair normal growth. Immune cells in the brain called microglia may comprise a critical connection between maternal immune activation (MIA) and the dysregulated CNS development associated with autism. Research studies have shown that increased levels of microglial activation are associated with both schizophrenia and autism. The incidence rates for each of several common autoimmune disorders: Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA) and obesity/type 2-diabetes is significant in women of child-bearing age; their demonstrated link to development brain disorders in utero provides a powerful rationale for expert clinical management of these disorders during pregnancy. Moreover, biomarker testing for these disorders is necessitated by the fact that early stages may be asymptomatic and only identifiable by biomarker screening.

Long-term data from a 20 year research study in Denmark has provided significant evidence for the notion that maternal infection may trigger inflammatory responses that disrupt neural signal pathways critical to central nervous system (CNS) maturation [2]. The researchers found that hospitalization during the first trimester of pregnancy due to viral infection such as influenza increased the likelihood of having a child who developed autism spectrum disorder (ASD) by 3-fold. Moreover, bacterial infections in the second trimester correlated with a 40% increased risk of having a child with autism.

A clinical study based at Boston Medical Center between 1998-2014 correlated gestational obesity/diabetes with ASD occurrence in offspring [3]. Of 2734 mother/child pairs enrolled in this study, 102 children were diagnosed with ASD. The clinical data showed that chronic obesity and gestational or pre-gestational diabetes was associated with a four-fold increased risk of bearing a child with ASD. The individual associations of maternal obesity versus diabetes did not show this pattern of increased risk for ASD, suggesting that it is the combined association of obesity and insulin resistant diabetes that is most clearly linked to autism. Significantly, the combined obesity/diabetes clinical status in pregnant women also was associated with increased risk of other intellectual disability disorders, but not with other developmental disorders. More research needs to be done to develop a genetic profile that may be more quantitatively predictive of ASD risk. In addition, it is important to assess more carefully the impact of potential environmental mutagens in increasing the incidence of maternal and paternal mutation rates in reproductive cells that may increase the genetic predisposition for ASD.

The controversial category of infant vaccines such as measles, mumps and rubella (MMR) falls into this category as well. However, the absence of significant epidemiological data suggesting that vaccines per se are linked to any increase in ASD incidence rates requires the placement of this potential risk factor in the category of lesser impact multifactorial risk factors. It should be noted, however, that the chronic nature of inflammatory processes may impose risk for brain deterioration in children once neurodevelopment is largely completed. Hence, there is a need for follow-up in children born to high-risk mothers to prevent the long-term effects of chronic inflammation on brain function. Vaccines by their very nature directly impact immune system processes and may impose risk for brain deterioration in children once neurodevelopment is largely completed. Hence, there is a need for follow-up in children born to high-risk mothers to prevent the long-term effects of chronic inflammation on brain function. Vaccines by their very nature directly impact immune system function; combined with exposure to additional risk factors linked to ASD, infant and early childhood vaccines may have an additive effect on the threshold for ASD development (Figure 1).

Figure 1: Children wait in line to receive polio vaccine, 1956
(Courtesy of the Mississippi Department of Archives and History).
References


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