Maternal autoimmunity is a risk factor for common neurologic diseases of childhood

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When a child presents with epilepsy, particularly infantile epilepsy, genetic etiologies are often considered. The discoveries of copy number variants and monogenic epilepsy disorders have changed diagnostic considerations in pediatric epilepsy. Despite diagnostic advancements, many epilepsy patients do not receive an etiologic answer. Environmental factors clearly play a role in seizure expression in children, as best illustrated by cases of fever-provoked seizures. Recent descriptions of pathogenic autoantibodies associated with autoimmune encephalitis have been fundamental in establishing immune-mediated mechanisms as a cause of acquired epilepsy.[1] In the ongoing iterations of epilepsy classifications, the International League Against Epilepsy now includes infection and immunity as etiologic causes of seizures in children.[2]

The study by Rom et al.[3] in this issue of *Neurology*® is provocative, as it compels us to consider the influence of fetal environmental factors upon risk of future epilepsy in childhood. The study, performed in Denmark between 1977 and 2008, uses birth and disease registries and data linkage (n = 1,927,343 births). The study's aim was to determine if parental (maternal or paternal) rheumatoid arthritis (RA) was associated with subsequent diagnosis of epilepsy in the participants' children. In an attempt to reduce confounding data with birth-related insults that commonly result in seizures (e.g., hypoxic ischemic encephalopathy), neonatal seizures were excluded. Important variables such as maternal age, maternal history of epilepsy, and neonatal Apgar scores were adjusted for, and did not affect the results.

During the study period, 1,909,859 children who survived the perinatal period were included. Of these, 13,511 children were exposed to maternal RA and 31,491 children were subsequently diagnosed with epilepsy after a mean follow-up of 16 years. The main findings were that maternal RA increased the risk of childhood epilepsy, whereas paternal RA did not. The authors found that maternal RA increased the risk of early childhood (up to 4 years) and late childhood epilepsy (5–15 years), but not adolescent (>15 years) onset of epilepsy. Furthermore, the mother having clinical RA at the time of pregnancy generated a higher risk of childhood epilepsy compared to preclinical RA, although both were associated with a higher risk of childhood epilepsy. The authors concluded that maternal clinical RA increased the risk of childhood epilepsy by up to 90%. The authors acknowledged expected limitations of population-based data linkage. In addition, specific epilepsy syndromes were not explored in this population-based approach, which would have been of high interest. Though RA was the only autoimmune disease assessed in this linkage, it can be hypothesized that other maternal autoimmune diseases could render similar vulnerabilities.

The authors discuss the hypothesis that maternally derived immunologic factors may affect the fetus and increase seizure vulnerability. The fact that paternal RA did not influence the risk of childhood epilepsy makes it more likely that there is a fetal environmental exposure resulting in an increased risk of epilepsy, rather than a heritable factor (although mitochondrial or X-linked inheritance remains a theoretical possibility). While therapies to treat maternal RA could conceivably be an alternative exposure factor that increases epilepsy risk, the fact that mothers with preclinical RA (presumably not taking immune-modulating medications) had offspring with an increased risk of epilepsy makes this less plausible. It is still conceivable that genetic factors are involved; however, these genetic vulnerabilities may be immunologic rather than neurologic.

This study adds to the growing literature that maternal autoimmune diseases influence the development of the fetal brain and increase the risk of childhood neurologic disease. Maternal autoimmune disease increases the chance of Tourette syndrome in offspring.[4] A recent meta-analysis found an increased risk of autism in children of mothers with autoimmune disease.[5] Mothers of autistic children also have a higher incidence of brain-reactive autoantibodies than controls, and these autoantibodies are more common in mothers with clinical autoimmune

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disease, particularly RA and systemic lupus erythematosus.[6] Animal studies have shown that infection and immunologic activation in mothers increase the risk of altered behavior in offspring, reminiscent of autism.[7]

Rom et al.'s population study provides insight into associations, but does not help us appreciate the precise pathophysiologic mechanisms. Assuming the mechanism is immunologic, there are a number of different possibilities to explain the increased risk of neurologic disease in the offspring of mothers with autoimmune disease. In general, the fetus is more vulnerable to immune-mediated brain disease as the fetal blood–brain barrier, though functionally effective, is more vulnerable to environmental factors.[8] One possibility is that a specific autoimmune process (e.g., CNS-specific autoantibodies or autoreactive activated lymphocytes) is transferred to the fetus. An alternative mechanism could be a nonspecific upregulation of the inflammasome, as manifested by cytokine and chemokine dysregulation. Finally, it is plausible that a maternally derived immune activation may represent a secondary hit contributing to the expression of seizures (i.e., increase expression of genetically derived vulnerabilities).

Regardless of mechanism, there are a number of unanswered questions: Does an inflammatory insult on the fetal brain result in permanent alteration of neuronal development? Or could this fetal exposure result in a persistent immune activation of the CNS that is potentially exacerbated after birth by environmental triggers? These biological uncertainties raise the question as to whether this fetal immune priming could be modified using immune suppression or modulation ex utero. The article by Rom et al. adds to the evidence that maternal-fetal neuroimmunology may represent a substantial environmental contributor to future risk of common childhood neurologic diseases.

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