

## **Autism Spectrum Disorders and the Immune System**

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The exact cause of autism spectrum disorders (ASD) is not well understood. ASD is likely to involve a combination of genetic, immunological and environmental factors, and may encompass several diseases with distinct origins. Currently there are no biological markers for ASD, and diagnosis is based solely on behavioral criteria.

A recent, dramatic rise in the incidence of ASD has sparked an intense effort toward a greater understanding of the disease. Several studies have linked immune system abnormalities to autism. Aberrant immune activity during critical periods in development potentially could enhance neurological disorders. The following is a brief summary of the current research correlating ASD and immune dysfunction.

### **Cytokines**

Cytokines are proteins made by immune cells that regulate the nature, intensity and length of an immune response. Additionally, cytokines are important in the development and health of the central nervous system (CNS). Thus, abnormal cytokine production during critical windows of brain development could have long-term effects on the health of the nervous system.

Increased levels of proinflammatory cytokines such as TNF-alpha, and decreased levels of anti-inflammatory cytokines such as IL-10 have been observed in children with ASD. Imbalanced levels of these cytokines can augment inflammation and cause excess damage to tissues.

Cytokines secreted by T cells can be categorized into two major subsets termed T<sub>H</sub>1 (associated with a cell response and inflammation) and T<sub>H</sub>2 (associated with allergies and asthma). One study found elevated proportions of T<sub>H</sub>2-producing lymphocytes in subjects with ASD when compared with controls.

However, another study demonstrated a T<sub>H</sub>1-skewed cytokine profile. A third study found increased levels of both T<sub>H</sub>1 and T<sub>H</sub>2 cytokines without a compensatory increase of the regulatory cytokine IL-10 in a small group of ASD children. These contrasting findings may represent different categories of ASD, a theory that may be explored by taking behavioral characteristics into account.

The CNS contains different cell types that have a role both in brain function and the CNS immune response. A study in 2005 of brains from people with ASD showed inflammation characterized by activation of these specialized brain cells. Additionally, altered cytokine patterns were observed in the brains and cerebrospinal fluid of subjects with autism compared to controls. Abnormal immune responses in these brain cells in people with ASD may influence neural function and development, and could indicate an attempt by the activated cells to repair CNS damage.

### **Autoimmunity**

Autoimmunity is a condition where a person's immune system is unable to differentiate "self" from "nonself" components. In such cases, the immune system develops "self-reactive" antibodies and/or

cells that lead an attack against the body's own tissues as if they were foreign invaders. Autoimmunity is well defined in diseases such as rheumatoid arthritis and systemic lupus. However, autoimmune reactions to brain tissues also may be involved in a subset of autism cases. The presence of antibodies to brain tissues is abnormal and can be detrimental to CNS development and function.

Several studies have demonstrated the presence of autoantibodies specific to various CNS tissues in subjects with autism and animal models, including myelin basic protein, neuronal and glial filament proteins, and several other unidentified brain antigens. These studies show that autoimmune activity can be associated with autism in some (but not all) cases. It is difficult to determine whether these autoantibodies contribute to the development of the disorder or if they are a consequence of the disease.

### **Gastrointestinal Immunity**

Gastrointestinal (GI) symptoms, including abdominal pain, bloating, diarrhea and constipation have been reported in a subset of subjects with ASD. Those with GI symptoms have been found to have inflammatory cytokine profiles in mucosal immune cells and peripheral blood compared to controls. The exact relationship between GI symptoms and ASD is unclear. The GI tract is the site of extensive and specific immune activity, and it has been proposed that immune-mediated GI pathology may lead to systemic immune activation and inflammation in the brain. However, there is yet to be concrete data to support this claim.

### **Conclusion**

There appears to be a strong correlation between immune dysfunction and autism, though the extent to which aberrant immune activity is involved in the pathogenesis of autism is unknown. ASD must be recognized as a spectrum of diseases, each of which may have a distinct cause and disease process. Future research should focus on finding biological markers for ASD and its variations. This breakthrough would open the door for early testing and intervention during the first few years of life, a time that is critical for brain and neural development.

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