

## Pathogenesis of Brain: Autism Spectrum Disorders

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### Editorial

Autism spectrum disorders (ASDs) affect as many as 1 in 45 children and are characterized by deficits in sociability and communication, as well as stereotypic movements. Many children also show severe anxiety. The lack of distinct pathogenesis and reliable biomarkers hampers the development of effective treatments. As a result, most children with ASD are prescribed psychopharmacologic agents that do not address the core symptoms of ASD. Autoantibodies against brain epitopes in mothers of children with ASD and many such children strongly correlate with allergic symptoms and indicate an aberrant immune response, as well as disruption of the blood–brain barrier (BBB). Recent epidemiological studies have shown a strong statistical correlation between risk for ASD and either maternal or infantile atopic diseases, such as asthma, eczema, food allergies and food intolerance, all of which involve activation of mast cells (MCs). These unique tissue immune cells are located perivascularly in all tissues, including the thalamus and hypothalamus, which regulate emotions. MC-derived inflammatory and vasoactive mediators increase BBB permeability. Expression of the inflammatory molecules interleukin (IL-1 $\beta$ ), IL-6, IL-17 and tumor necrosis factor (TNF) is increased in the brain, cerebrospinal fluid and serum of some patients with ASD, while NF- $\kappa$ B is activated in brain samples and stimulated peripheral blood immune cells of other patients; however, these molecules are not specific. Instead the peptide neurotensin is uniquely elevated in the serum of children with ASD, as is corticotropin-releasing hormone, secreted from the hypothalamus under stress. Both peptides trigger MC to release IL-6 and TNF, which in turn, stimulate microglia proliferation and activation, leading to disruption of neuronal connectivity. MC-derived IL-6 and TGF $\beta$  induce maturation of Th17 cells and MCs also secrete IL-17, which is increased in ASD. Serum IL-6 and TNF may define an ASD subgroup that benefits most from treatment with the natural flavonoid luteolin. Atopic diseases may create a phenotype susceptible to ASD and formulations targeting focal inflammation of the brain could have great promise in the treatment of ASD.

Recent studies have shown strong associations between allergies, asthma, autoimmune diseases and psoriasis in the mother with increased risk for ASD in their children. Moreover, mothers with mastocytosis or MC activation syndrome were much more likely to have children who developed ASD.

Allergies and auto-immune diseases have been increasing significantly. Early reports indicated more frequent allergies in ASD children, with food allergies being the most prevalent complaint, often in the absence of elevated serum IgE or positive skin tests. A large epidemiological study of noninstitutionalized children ( $n=92\,642$ ; 0–17 years old) showed that eczema was strongly associated with ASD and attention deficit hyperactivity disorder. Another study of atopic subjects ( $n=14\,812$ ; 3 years old) and non-atopic subjects ( $n=6944$ ) also showed a strong association between atopy and risk of both ASD and attention deficit hyperactivity disorder.

A case control study of children and young patients with ASD ( $n=5565$ ) and controls ( $n=27\,825$ ) matched to birth year (1980–2003) and sex reported that allergies, asthma and autoimmune disorders were diagnosed more frequently, with psoriasis occurring more than twice as often, in ASD patients than controls. An experimental study actually reported neurochemical changes and autistic-like behavior in a mouse model of food allergy.

MCs can be activated by fungi, such as *Aspergillus fumigatus* which triggers IgE-independent MC degranulation and fungal zymosan induces leukotriene production from human MCs. Moreover, MCs can be stimulated by aluminum and mercury.

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