Attention-deficit/hyperactivity disorder

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EDITORIAL

Attention-deficit/hyperactivity disorder: is there a connection with the immune system?

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Most major psychiatric disorders have been linked in some way to the immune system, including schizophrenia, bipolar disorder, and depression (e.g., [2]. Although perhaps less well known, attention-deficit/hyperactivity disorder (ADHD) has also been associated with immune alterations. In the current issue of *European Child and Adolescent Psychiatry* Verlaet and colleagues [12] investigated a range of immune markers in a group of children with ADHD compared to healthy controls. They found some indication of increased levels of oxidative damage markers in children with ADHD. The authors argue that chronically increased oxidative stress might lead to immune dysfunction resulting in increased IgE levels which might explain the link between ADHD and allergies. There is indeed strong evidence that ADHD is associated with allergy; individuals with atopic disease having a 30–50% greater chance of developing ADHD [10].

What have been the most compelling recent findings connecting ADHD with immune alterations? In a nationwide register-based cohort study in Denmark, occurrence of infections requiring hospitalizations were convincingly associated with subsequent increased risk of having a diagnosis of ADHD, by a hazard rate ratio of more than 2 [5]. One of the possible explanations that the authors propose is a direct impact of the infection on the brain, as a result of crossing of infective agents through the blood–brain barrier. There may be involvement of microglial activation, pro-inflammatory cytokines, molecular mimicry, anti-neuronal autoantibodies, and/or self-reactive T cells [8], an area certainly worthy of further investigation in relation to ADHD.

Another likely explanation for the link between infections and ADHD is the involvement of immune-related genes in the etiology of ADHD. Such a genetic connection was recently confirmed in a study [11] that used summary-level data from available genome-wide association studies, with the aim of determining if common genetic polymorphisms of psychiatric disorder are shared with those associated with medical conditions characterized by involvement of immune and inflammatory processes (including allergic conditions, classic autoimmune diseases, other inflammatory diseases, and vulnerability to infectious disease). ADHD genetic risk was specifically associated with genetic risk of serum C-reactive protein (a general marker of immune activation), childhood ear infection, psoriasis, rheumatoid arthritis, and tuberculosis susceptibility.

Studies have also pointed to a relation between ADHD and autoimmune diseases and/or a history of maternal autoimmune disease. In a Danish National Hospital Register study [7], the association of ADHD with autoimmune disease in the individual was most notable with regard to arthritis juvenilis, type 1 diabetes, and autoimmune thyroiditis; maternal autoimmune conditions associated with ADHD in the offspring included type 1 diabetes and ankylosing spondylitis. Another study using Norwegian national registries, based on a cohort of 2,500,118 individuals pointed to partially sex-specific associations between presence of ADHD and an autoimmune disease: while there was a clear link between ADHD and psoriasis in both sexes, this relation was much stronger in females than in males; Crohn's disease and ulcerative colitis were linked to ADHD exclusively in females [3]. The authors speculate about the possible etiology for the sex-specific effects by pointing to findings that glial cells, apart from their immunomodulatory properties and involvement in inflammation, may also modulate sex-determined neurodevelopmental processes.

Another Norwegian registry-based study [4] found that maternal multiple sclerosis and rheumatoid arthritis were associated with 80% and 70% higher odds of ADHD in their offspring, and maternal asthma with 50% higher odds. There were also associations of maternal hypothyroidism and type 1 diabetes and offspring ADHD. The authors discuss three

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possible mechanisms: through involvement of common genetic factors, involvement of environmental factors including maternal medication use during pregnancy, or through central nervous system inflammatory response in the fetus.

Direct involvement of autoimmunity in the etiology of ADHD has been suggested by the finding of auto-antibodies against dopamine transporter correlating with ADHD symptom severity in a genetically based subgroup of children with ADHD [1]. The authors provide the hypothesis that these autoantibodies may be associated with dysregulation of neuro-immune systems given that dopamine can mediate the cross-talk between the immune and nervous systems.

The potential role for neuro-immune components in ADHD may also have therapeutic implications. One option worthy of further investigation is to increase levels of vitamin D, which has protective effects against inflammation and oxidative stress and levels of which are on average lower in children with ADHD than in healthy children [9]. Another possibility would be to eliminate food components that may trigger adverse physical, allergic reactions [6].

Further study of the etiological mechanisms explaining the link between ADHD and the immune system would be very welcomed and may focus on the interplay between altered immune responses, and common genetic and environmental risks.

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