

# A Review on the Role of Inflammation in Attention-Deficit/Hyperactivity Disorder

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## Keywords

Attention-deficit/hyperactivity disorder · Inflammation · Neuronal damage · Biomarkers

## Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition that impairs quality of life in social, academic, and occupational contexts for both children and adults. Although a strong neurobiological basis has been demonstrated, the pathophysiology of ADHD is still poorly understood. Among the proposed mechanisms are glial activation, neuronal damage and degeneration, increased oxidative stress, reduced neurotrophic support, altered neurotransmitter metabolism, and blood-brain barrier disruption. In this way, a potential role of inflammation has been increasingly researched. However, evidence for the involvement of inflammation in ADHD is still scarce and comes mainly from (1) observational studies showing a strong comorbidity of ADHD with inflammatory and autoimmune disorders; (2) studies evaluating serum inflammatory markers; and (3) genetic studies. A co-occurrence of ADHD with inflammatory disorders has been demonstrated in a large number of subjects, suggesting a range of underlying mech-

anisms such as an altered immune response, common genetics, and environmental links. The evaluation of serum inflammatory markers has provided mixed results, likely due to the small sample sizes and high heterogeneity between biomarkers. However, there is evidence that increased inflammation during the early development may be a risk factor for ADHD symptoms. Although genetic studies have demonstrated a potential role for inflammation in this disorder, there is no clear evidence. To sum up, inflammation may be an important mechanism in ADHD pathophysiology, but more studies are still needed for a more precise conclusion.

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## Epidemiology

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by the impairing symptoms of inattention and/or hyperactivity/impulsivity [1]. A meta-analysis published in 2007 has demonstrated that the worldwide prevalence of ADHD in

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children and adolescents is of 5.3% (95% CI: 5.01–5.56) [2]. In adults, ADHD has been shown to persist in about 50–70% of the cases depending on methodological issues in the studies [3, 4]. Accordingly, a meta-analysis has shown a prevalence of about 2.4% in adulthood [5]. Concurring with those results, a recent study conducted by the World Health Organization has found a prevalence of 2.5% in adults in the 30 countries evaluated [6].

## Impairments

ADHD impairs the quality of life and well-being in social, academic, and occupational contexts for both children and adults. The pathology is correlated with a wide range of psychiatry comorbidities, psychological dysfunctions, and risk behaviors. Observational studies conducted in large populations have demonstrated that an ADHD diagnosis is a risk factor for substance use disorder [7], criminal behavior [8], and greater susceptibility to physical injuries [9]. A cohort study that followed 1,92 million people, 32,061 of whom having a diagnosis of ADHD, found a significant increase in the mortality rate in this population. The increase in mortality was mainly related to death caused by unnatural factors, especially accidents [10]. Adverse outcomes in adolescence and adulthood include academic and vocational underachievement [11], obesity [12], unemployment, low economic status [13], emotional dysregulation [14], and pregnancy in adolescence [15]. It has been shown that ADHD patients present higher suicide attempts when compared to the general population [16]. To sum up, ADHD has an important impact in the quality of life of those affected, comparable to other severe psychiatry disorders [17].

## Diagnosis

The diagnosis of ADHD is based on the assessment of inattentive or hyperactive-impulsive symptoms. According to the Diagnostic and Statistical Manual of Mental Disorders, ed 5 (DSM-5), the diagnosis of ADHD should be performed when there is clear evidence that the symptoms impair the quality of life in social, academic, or occupational performance [1]. In addition, the symptoms should be present in 2 or more different settings, and their onset should be prior to 12 years of age. The diagnosis relies on the reporting of patients or other informants (relatives, teachers), and the clinical interview remains the gold standard.

The diagnosis of ADHD involves cultural and ethnical differences related to the attitudes towards the disease. For instance, it has been reported that African American youths have more ADHD symptoms when compared to Caucasians, but the latter were diagnosed two-thirds as often [18]. This difference could be explained by parents' beliefs about ADHD and the lack of access to treatment [18]. Currently, there is no biomarker for the diagnosis of ADHD, and the reliance only on a clinical interview may be an important factor predisposing negative cultural views on the disorder and uncertainty concerning the validity of the diagnosis [19].

## Neurobiological Basis

The neurobiological basis of ADHD has been confirmed through genetic and neuroimaging studies [5]. Twin studies have shown that ADHD has a strong heritability of 70–80% in both children and adults [20]. According to genome-wide association studies, approximately 40% of the heritability is associated to common genetic variants [21]. In addition, candidate gene studies have mainly shown the influence of genes involved in the monoamine neurotransmitter system [22]. A recent genome-wide association meta-analysis conducted with 20,183 ADHD patients and 35,191 controls identified 12 independent loci exceeding genome-wide significance [Demontis, pers. commun.]. The biological role of the identified loci appears to be related to neural development and plasticity, neuronal wiring, dopamine levels in the synapses, intellectual disability, and the development of speech and learning [Demontis, pers. commun.]. In relation to environmental factors, severe early maternal deprivation appears to have a causal role [22]. However, other environmental factors such as maternal smoking and alcohol use, low birth weight, premature birth, and exposure to environmental toxins have also been associated with ADHD symptoms [23, 24].

ADHD is characterized by structural and functional dysfunctions in a wide range of cortical and subcortical regions. A recent mega-analysis performed in a sample of 1,713 patients with ADHD and 1,529 controls has demonstrated a volume reduction in the nucleus accumbens, amygdala, caudate, hippocampus, and putamen in patients with the disorder [25]. A meta-analysis of functional magnetic studies including approximately 200 ADHD patients and 200 controls has demonstrated a reduction in the activity of distinct cortical regions during tests requiring attention and impulsivity control [26]. Although

a wide literature has repeatedly shown that ADHD has a strong neurobiological basis, its pathophysiology is still poorly understood. It is believed that several factors, including genetic and environmental factors, interact during development, giving rise to ADHD symptomatology.

### **The Role of Inflammation**

Among the neuropathological mechanisms believed to be involved in ADHD, there has been a growing interest in the immune system. Over the last years, an increasing body of evidence has supported the role of inflammation in neuropsychiatric disorders. A strong association between altered inflammatory mechanisms and neuropsychiatric disorders has been provided for depression [27], schizophrenia [28], bipolar disorder [29], and post-traumatic stress disorder [30] through systematic reviews and meta-analyses. It has been hypothesized that inflammatory mechanisms are related to the pathophysiology of neuropsychiatric disorders through several mechanisms. Among them are glial activation [31], neuronal damage and degeneration [32], increased oxidative stress [33], reduced neurotrophic support [34], altered neurotransmitter metabolism [35], and blood-brain barrier disruption [36]. For ADHD, evidence supporting a role of inflammatory mechanisms comes from 3 main lines: comorbidity with inflammatory and autoimmune disorders, biochemical markers, and genetic studies. In this sense, the aim of this review is to present a summary of the existing literature regarding the role of inflammation in the pathophysiology of ADHD.

### **Comorbidity with Inflammatory and Autoimmune Disorders**

Observational data from a large number of subjects show a strong association between ADHD and inflammatory and autoimmune disorders. Miyazaki et al. [37] performed a systematic review and meta-analysis with more than 61,000 children (about 8,000 ADHD patients) to evaluate an association between ADHD and allergies. They found that ADHD patients were more likely to have asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis in comparison to the non-ADHD subjects from the population. Similar results were found by Schans et al. [38], performing a systematic review and meta-analysis examining the co-occurrence of atopy and ADHD. They found a higher presence of asthma, eczema, and rhi-

nitis in ADHD patients when compared to a control population. A prospective cohort study performed with more than 23,000 patients demonstrated that a personal and a maternal history of autoimmune disease were also associated with an increased risk of ADHD [39]. Among the autoimmune diseases there were thyrotoxicosis, type 1 diabetes, autoimmune hepatitis, psoriasis, and ankylosing spondylitis. Cross-sectional studies have also identified a higher prevalence of psoriasis in ADHD patients [40].

The higher co-occurrence of ADHD with inflammatory and autoimmune disorders may suggest a range of underlying mechanisms, including an altered immune response, common genetics, and environmental links. It has also been suggested that increased cytokine release due to an inflammatory process may affect the prefrontal cortex functioning [41]. In addition, ADHD abnormalities may be the result of an exaggerated central nervous system inflammatory response in the fetus caused by maternal inflammation, such as in allergy or autoimmune diseases. The prevalent comorbidity between ADHD and inflammatory disorders may also explain the association found between ADHD diagnosis and the use of acetaminophen during pregnancy [42]. To sum up, although observational data support the co-occurrence of ADHD and inflammatory and autoimmune disorders, the studies conducted so far have not identified which factors may have a causal role in this comorbidity. For that, well-designed prospective studies are still needed.

### **Biochemical Markers**

Studies searching for inflammatory biomarkers in ADHD patients have not provided conclusive findings, likely due to small sample sizes and a high heterogeneity among biomarkers. Inflammatory markers tested in this population include specific antibodies, cytokines, and neurotrophic factors. Passarelli et al. [43] evaluated the role of antibodies against Purkinje cells as a possible marker of an immune response in ADHD patients. These specific antibodies were chosen since a role of the cerebellum in the pathophysiology of ADHD has been previously proposed [5]. The authors found a significantly higher immunoreactivity against anti-Purkinje cell antibodies in ADHD patients when compared to controls, suggesting an involvement of the autoimmune system in the disorder. These results have been replicated in a following study [44], and the authors also demonstrated that ADHD patients had increased serum levels of interleukin

6 (IL-6) and IL-10. Increased levels of antibasal ganglia antibodies [45] and antibodies against the dopamine transporter [46] have also been detected in ADHD, supporting the role of the immune system in the disorder.

Several cytokines have been researched as possible neurochemical markers of ADHD. As previously mentioned, there is a high heterogeneity among the biomarkers tested, which makes the interpretations of the findings more challenging. Evaluation of pro- and anti-inflammatory cytokines and the cytokine-related neurotrophin S100B have been performed by Oades et al. [47] in the serum of ADHD patients. There was no major imbalance in the levels of inflammatory markers between ADHD patients and controls, and there were no differences in the levels of S100B. In a second study, however, the total serum S100B levels were positively associated with reduced symptoms in patients [48]. Serum IL-6 and tumor necrosis factor alpha were evaluated in a different study, and no significant results were found [49].

Although the previously mentioned studies did not show significant main findings related to inflammatory markers, a cohort study performed with more than 1,500 premature and low-birth-weight newborns measured 25 inflammation-related proteins in the serum and found that children who had elevated concentrations of inflammation-related proteins during the first 2 postnatal weeks were more likely to have attention problems at 24 months [50]. In addition, neonatal infections, which are associated with inflammatory responses, and systemic inflammation during the first postnatal month increased the risk of ADHD [51, 52]. To sum up, the evaluation of serum levels of inflammatory markers in ADHD patients has provided mixed results, likely due to small sample sizes and a high heterogeneity between biomarkers. However, there is evidence that increased inflammation during the early development may be a risk factor for ADHD symptoms.

## Genetic Studies

There has been evidence from genetic studies that polymorphisms in genes related to inflammatory pathways play a role in ADHD. Smith et al. [53] performed a study evaluating a set of 164 single-nucleotide polymorphisms (SNPs) from 31 candidate genes in a total of 398 subjects. They found that 2 SNPs in a cytokine-related gene, the ciliary neurotrophic factor receptor (*CNTFR*), were associated with ADHD inattentive symptom severity. A population-based association study performed in 546 ADHD patients and 546 controls has also identified

an association between the *CNTFR* and ADHD in both adults and children. An association of ADHD with genes of the major histocompatibility complex has been reported [54], supporting the role of inflammation and autoimmunity in the disorder. However, those findings were not replicated in a recent genome-wide association meta-analysis [Demontis, pers. commun.].

A genome-wide association study performed by Zayats et al. [55] in 478 ADHD patients and 880 controls found no SNPs at the significance threshold. However, a pathway analysis found an association with SNPs involved in the regulation of gene expression, cell adhesion, and inflammation. A study performed by de Jong et al. [56] investigated a genomic overlap between ADHD and other psychiatric disorders in 318 individuals, 93 of whom with a diagnosis of ADHD. They found a similar genetic signature between ADHD and depression in genes related to inflammation. Segman et al. [57] investigated the role of the IL-1 receptor antagonist gene variable number tandem repeat polymorphism in the risk of ADHD. The IL-1 was chosen since it has been shown to modulate catecholaminergic transmission in mice [58]. They evaluated a sample of 86 children with ADHD and found an association between the 4-repeat allele and an increased risk for ADHD, and an association between the 2-repeat allele and a decreased risk. However, the same results were not replicated in a larger sample [59].

Although a good number of genetic studies provide evidence on the role of inflammation in ADHD, it is important to consider that there is a high variation between the methodologies performed. In addition, there is no consensus about which inflammatory-related genes predispose to ADHD. A possible explanation for that is the fact that ADHD is a disorder with a highly heterogeneous genetic makeup and clinical presentation. Therefore, studies focusing on a more homogeneous population may be more likely to be conclusive.

## Conclusions

There has been a growing interest in inflammation as a predisposing mechanism in psychiatric disorders. In ADHD, evidence from comorbidity with inflammatory and autoimmune disorders, serum biomarkers, and genetic studies can be found. The high co-occurrence between ADHD and inflammatory disorders suggests a range of underlying mechanisms, including altered immune response and common genetic and environmental links. Biomarkers measured in ADHD patients have pro-



vided unclear results. However, increased inflammation during the early development appears to be related to an ADHD phenotype. ADHD is a highly hereditary disorder; therefore, it might be expected that polymorphisms in inflammatory-related genes are present in patients. Although some studies have found this association, there is no consensus about which genes are affected. To sum up, there have been indications for a role of the immune system in the pathophysiology of ADHD. However, well-designed studies are still needed to confirm this hypothesis.

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