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Psychopathology of attention deficit/hyperactivity disorder: from an inflammatory perspective

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Abstract

Background: Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattentiveness, hyperactivity and impulsivity, which may affect one's cognitive and psychosocial functioning. This review gives an overview of ADHD, particularly from an aetiological and clinical perspective. It also critically examines current evidence on the role of inflammation in ADHD and consolidates key findings in this area of research.

Results: The exact cause of ADHD remains unknown, and the aetiology of the disorder is believed to be multifactorial. Numerous genetic and environmental factors have been linked to the development of ADHD. Like many psychiatric disorders, ADHD has been associated with inflammation that occurs locally and peripherally. A growing body of evidence shows that maternal inflammatory status during pregnancy is associated with diagnosis of ADHD in the offspring, whereas oxidative stress, inflammatory biochemical markers and immune-mediated diseases have been observed in individuals with ADHD.

Conclusions: The underlying inflammatory processes and mechanisms in ADHD are not clearly understood. Therefore, further exploration is warranted in future research. This has clinical implications as inflammation may be a potential target in the treatment of ADHD.

Keywords: Attention deficit/hyperactivity disorder, Oxidative stress, Inflammation, Neuroinflammation, Immune-mediated diseases

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one the commonest neurodevelopmental disorders diagnosed during childhood. Some characteristic features of ADHD include inactivity, hyperactivity and inattentiveness, which may lead to psychosocial and functional impairments affecting one's daily life to a varying extent. Initially, it was believed that children with ADHD would gradually outgrow the symptoms of the condition. However, it is now clear that the disorder continues into adolescence and adulthood [1], which can significantly affect one's quality of life. ADHD incurs a high economic burden on the society. Research has shown that the estimated prevalence in children and adolescents is on the rise over the past few decades [2]. A systematic review of the global economic burden of ADHD reported per person total costs ranging from $US831.38 to 20,538 and national estimates ranging from $US356 million to 20.27 billion [3].

Like many other psychiatric diseases, it is difficult to pinpoint the exact cause of ADHD. However, research has linked ADHD with many genetic and environmental factors. Therefore, the aetiology of ADHD is likely to be multifactorial, and the associated genetic and environmental factors are likely to be interconnected. On the other hand, inflammation and immune dysregulation have been linked with many psychiatric disorders. About

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three decades ago, Smith proposed the "Macrophage Theory of Depression", which attributed excessive monokine secretion as a cause of depression [4]. Today, it is increasingly clear that immune dysregulation [5], local inflammation (or neuroinflammation) [6] and systemic inflammation [7] are implicated in psychiatric and neurodevelopmental disorders, including autism spectrum disorders (ASD) and ADHD.

Despite the conventional belief that the central nervous system (CNS) was immunologically inert and privileged, it is now evident that neuroimmune communications exist between the CNS and peripheral immune cells of the innate and adaptive immune system [8]. An understanding of the immune basis of neurological and psychiatric conditions leads to a better appreciation of the role of inflammation and immune system in the pathogenesis of these diseases. Therefore, this review gives an overview of ADHD, mainly from the aetiological and clinical perspectives and critically examines the current evidence on the role of inflammation in ADHD. This includes an in-depth review of the literature on various aspects of inflammation in ADHD, such as neuroinflammation and immune-associated conditions.

Main text

What is ADHD?

The earliest works of ADHD can be dated back to the eighteenth century. In 1755, the first documented description of symptoms resembling those of ADHD was found in a textbook titled "Der Philosophische Arzt" by a German physician, Melchior Adam Weikard. In the English translation by Barkley and Peters [9], many of the symptoms that belong to the inattentive dimension of ADHD were mentioned and coincide with some of our current understanding of ADHD. Some of these symptoms of an inattentive person include "studies matters superficially", make erroneous judgments, "misconceives the worth of things", "does not spend enough time and patience to search a matter", being reckless and often "considering imprudent projects" but are "most inconstant in execution". On the other hand, a Scottish physician named Sir Alexander Crichton mentioned a disorder which shared some similarities with ADHD in his work of three books "An inquiry into the nature and origin of mental derangement: comprehending a concise system of the physiology and pathology of the human mind and a history of the passions and their effects" in 1798 [10].

Many years later in 1902, a British paediatrician Sir George Frederic Still delivered his Goulstonian Lectures on "some abnormal psychical conditions in children" in London to the Royal College of Physicians, which were later published in Lancet [11]. In his lectures, Still described 43 children who were observed to have severe problems with attention and self-regulation. Still pointed out that "a notable feature in many of these cases of moral defect without general impairment of intellect is a quite abnormal incapacity for sustained attention". According to him, these kids were said to be defiant, aggressive, excessively emotional and were hard to discipline. However, they were intellectually normal. Many historians believe that Still's published lectures share some similarities to our current understanding of ADHD.

Interestingly, ADHD was not captured in the first edition of Diagnostic and Statistical Manual of Mental Disorders (DSM) [12], and the terminology for ADHD has undergone several changes and revisions before ADHD first appear in DSM-III-R [13]. In DSM II, the disorder was known as hyperkinetic reaction of childhood [14], while in DSM-III, it was called attention deficit disorder (ADD) with or without hyperactivity [15]. From DSM-IV onward [16], ADHD has been categorised into four main types, including ADHD with (1) predominant inattentive presentation, (2) predominant hyperactive/impulsive presentation and (3) combined presentation or (4) other specified or unspecified ADHD. All four types can be further classified into mild, moderate or severe. Therefore, the symptoms of ADHD mainly are those related to inattention, hyperactivity and impulsivity. On the other hand, the International Classification of Diseases 11th Revision (ICD-11) defines ADHD as a "persistent pattern (at least 6 months) of inattention and/or hyperactivity-impulsivity that has a direct negative impact on academic, occupational or social functioning" [17].

Epidemiology of ADHD

In the developed countries, such as the United States (US), ADHD is a common behavioural disorder in children and adolescents. A population-based, cross-sectional study known as the National Health Interview Survey (NHIS), has conducted surveys on a yearly basis from 1997 to 2016. Children and adolescents from four to seventeen years old were included in the surveys. The estimated prevalence of diagnosed ADHD in the US showed an increasing trend over the years from 6.1% (in 1997–1998) to 10.2% (in 2015–2016). Boys (14.0%) showed a higher estimated prevalence than that of girls (6.3%), whereas the estimated prevalence rates for Hispanic individuals, non-Hispanic white individuals and non-Hispanic black individuals were 6.1%, 12.0% and 12.8%, respectively. Increasing trends in the prevalence were observed across the subgroups based on demographic data, such as age, gender, ethnicity, geographic regions and family income [2].

On the other hand, the worldwide pooled prevalence of ADHD generated from a meta regression analysis consisting of 102 studies with 171,756 subjects $\leq$ 18 years

was estimated to be 5.29% in an earlier study [18]. In a meta-analysis that included 175 studies over 36 years, an overall prevalence pooled estimate of 7.2% was reported, with no significant differences observed between different DSM editions [19]. More recently, a systematic review and meta-analysis reported the 2020 global estimated prevalence of persistent adult ADHD (ADHD with an onset in childhood) to be 2.58% and symptomatic adult ADHD (ADHD regardless of an onset in childhood) to be 6.67%. Both types of adult ADHD were reported to have a decreased prevalence with increasing age [20].

Aetiology

Just like many other psychiatric disorders, one cannot pinpoint a single, definite cause for ADHD. It has been linked to many genetic and environmental factors, and an interplay of both. Exposure of a risk factor does not necessarily mean that one will be affected by ADHD as certain risk factors only affect a proportion of the cases.

Parental age

Several studies have reported that a younger parental age is generally associated with a higher risk of having an offspring with ADHD. For example, Hvolgaard Mikkelsen and colleagues conducted a large population-based study in Denmark and demonstrated that parents who were ≤ 20 years had a greater-than-twice risk of having an offspring being diagnosed with ADHD compared to those between 26 and 30 years of age [21]. These findings coincided with an earlier study that reported a 1.5-fold increased risk of having children with ADHD for fathers < 20 years when compared with those aged 25–29 years. Similarly, a 1.4-fold increased risk ($p = 0.0009$) was observed for mothers < 20 years. An inverse association between advanced maternal age and ADHD was also observed in the same study ($p = 0.02$) [22]. On the other hand, an earlier study reported an association between higher severity of hyperactivity/impulsivity and lower paternal age and advanced maternal age. However, the parental age was not associated with inattentiveness in ADHD [23].

Genetic factors

The heritability of ADHD has also been studied in family and twin studies. In one recent study that extracted data from two sizable health care systems in the US, a higher likelihood to be diagnosed with ADHD was reported in later-born siblings of children who had ADHD compared with later-born siblings of those who did not have ADHD. They also demonstrated a higher likelihood to be diagnosed with ASD in the absence of ADHD [24], suggesting that later born siblings of those with ADHD had an increased risk of not only ADHD but also ASD.

On the other hand, an earlier twin and sibling study demonstrated the highest tetrachoric correlations were observed for same-sex twin pairs, whereas the tetrachoric correlations were lowest for non-twin siblings of the opposite sex. The heritability estimates were higher for males than females. A probandwise concordance rate of 17.8–63.7% was obtained for male dizygotic, male monozygotic, female dizygotic and female monozygotic twins [25]. Substantial heritability in adults has also been demonstrated in another study [26].

Different approaches have been used to identify the genetic markers associated with ADHD. Such approaches may involve genome-wide association studies (GWAS) or candidate gene association studies. In a meta-analysis of previous GWAS studies consisting of 20,183 ADHD cases and 35,191 controls, 12 independent loci that surpassed the genome-wide significance were identified [27]. On the other hand, candidate gene association studies are less frequently pursued as more advanced genomic tools emerge. Unlike GWAS, predetermination of single nucleotide polymorphisms (SNPs) lowers the probability of gene identification. In a review by Hayman and Fernandez [28], 105 ADHD candidate genes from genetic studies of ADHD were reported. These genes were included if they showed a statistically significant association with ≥ 1 ADHD subtype diagnosis in ≥ 1 association study. Some examples of genes that play a role in ADHD include *ADRA2A*, *DAT1*, *DRD4*, *DRD5*, *5HTT*, *DBH*, *HTR1B*, *SNAP25* and *TPH2* [29].

Environmental factors

Although ADHD is a highly heritable disorder, it has also been linked to a large number of environmental factors during the pre-, peri- and postnatal periods in the published literature. The list of these environmental factor is exhaustive and is beyond the scope of this review. Some examples of these factors include childhood stroke, lead exposure, traumatic brain injury, low birth weight, prematurity, postmaturity, postnatal jaundice, maternal smoking and alcohol consumption during pregnancy, maternal medical diseases during pregnancy, complications during pregnancy and labour, prenatal exposure to illicit drugs and antidepressant drugs [30–32]. In addition, maternal psychological conditions before and during pregnancy, such as anxiety, depression and sleep disorders, have also been indicated in ADHD [33].

Clinical aspects of ADHD

School-aged children with ADHD are often seen by primary care physicians, child psychiatrists or psychologists when teachers or parents raise concerns regarding their behaviours or school performance. Several organisations such as the American Academy of Paediatrics (AAP) and

American Psychiatric Association (APA) have developed guidelines for the diagnosis and treatment of ADHD. This section gives an overview on the diagnostic criteria, clinical features, co-morbidities and treatment of ADHD.

Diagnosis

According to DSM-5, the diagnosis of ADHD must be made before the age of 12 years and the symptoms of the disorder must have lasted for a period of ≥ 6 months in ≥ 2 settings (for example, home, school and other settings). Symptoms are grouped into two main categories, which are those of inattention and those of hyperactivity/impulsivity [34]. As such, an individual can have ADHD that predominantly presents with symptoms of inattention or those of hyperactivity/impulsivity, or both. In the inattention category, ≥ 6 symptoms in are required. As for hyperactivity and impulsivity, again, ≥ 6 are required for those < 17 years, and ≥ 5 for those ≥ 17 years [34]. When using the ICD-11, symptoms of inattention or symptoms of hyperactivity and impulsivity or a combination of both must persist at least for 6 months before a diagnosis of ADHD is made. The symptoms occur prior to the age of 12 years, typically in early or mid-childhood. The clinical presentation of inattention and/or hyperactivity and impulsivity must be beyond limits of normal variation expected for age and the intellectual development of the patient [17].

Co-morbidities

Psychiatric disorders may share similarities in familial links and neurobiological factors. It is worth mentioning that ADHD may exist alone, or it may co-occur with other neurodevelopmental disorders, such as ASD. When criteria are met, the DSM-5 allows dual diagnosis of ADHD and ASD [34]. In addition, many other conditions may co-occur with ADHD. These include anxiety disorder, bipolar disorder, conduct disorder, depressive disorder, learning disorders, oppositional defiant disorder, personality disorders and tic disorders (reviewed by Gnanavel and colleagues) [35].

Research has also shown a close relation between patients with ADHD and epilepsy, and ADHD with electroencephalogram (EEG) changes in the context of psychiatric comorbidity (for example, anxiety, depression and conduct problems) [36]. Furthermore, paediatric patients with ADHD and epilepsy were shown to have a lower performance IQ when compared to children in the control group or other studied groups (for example, children with ADHD with or without EEG changes and children with epilepsy alone). Patients with ADHD and epilepsy were also shown to have a lower socioeconomic status and quality of life in the same study [37].

The presence of co-comorbidities in ADHD has implications in terms of diagnosis and treatment. This is because when ADHD occurs with co-morbidities, diagnosis becomes more challenging due to overlapping symptomatology. Therefore, early diagnosis and treatment of both ADHD and co-morbidities are important, as this may alter the course and outcome of the condition later in life [38].

Treatment

According to the American Academy of Paediatrics, ADHD is a chronic condition and children and adolescents diagnosed with the condition should be viewed as individuals with special health care needs. Treatment can be pharmacological and non-pharmacological (for instance, counselling, behavioural therapy and environmental modifications). The age of the patient is a key determinant for treatment recommendations. For children aged 4–5 years, behavioural therapy is the first-line treatment with or without methylphenidate (a type of stimulant medication) prescription. For those aged 6–11 years, approved medications (such as stimulant medications, guanfacine, extended-release clonidine) and/or behavioural therapy are recommended. Adolescents aged 12–18 years can be treated with the approved medications or behavioural therapy. However, it is preferred that both pharmacologic and behaviour therapy are prescribed for the last two groups of patients [39].

For adults, a combination of pharmacological and psychosocial approaches is recommended. Psychosocial approaches may involve education for the patient and his or her family, as well as condition-specific cognitive behavioural therapy. These may be delivered by psychologists or psychiatrists. For pharmacological strategies, stimulant drugs (such as methylphenidate) are considered first-line pharmacotherapy, while non-stimulant drugs (such as atomoxetine, clonidine and guanfacine) are second-line options. Non-stimulant drugs can be combined with stimulant drugs, used alone or used in the treatment of co-morbid conditions [40].

Role of inflammation in ADHD

There is plenty of evidence that points to the role of inflammation in ADHD from various sources. The inflammatory response may be local or systemic and several immune-mediated conditions such as autoimmune diseases, allergic diseases and maternal immune activation (MIA) have been linked to ADHD, which are believed to contribute to the psychopathology of ADHD. This section discusses the role of inflammation in ADHD based on these immune-related perspectives.

Oxidative stress and neuroinflammation

An imbalance between free radical production and antioxidant species results in oxidative stress [41]. The accumulated reactive oxygen species (ROS) and reactive nitrogen species (RNS), in turn, cause damage to cells and tissues and may lead to inflammation. In the brain, accumulation of ROS leads to microglia and astrocyte activation (a key feature of neuroinflammation) and secretion of proinflammatory chemokines and cytokines [42]. It is worth mentioning that neuroinflammation also produces ROS and RNS, which may, in turn, intensify the inflammatory processes initiated by oxidative stress and lead to a vicious cycle.

N-3 polyunsaturated fatty acids (n-3 PUFA) are long-chain PUFA that possess anti-inflammatory and antioxidant properties. In an earlier study, the frontal cortex of hyperactive rats were subject to membrane phospholipid fatty acid profile examination and correlated with the main symptoms of ADHD. Significant correlations were observed between amounts of n-3 PUFA and locomotor responses to novelty and nocturnal locomotor activity, which are indicators of hyperactivity. Hyperactive rats also demonstrated a lower amount of n-3 PUFA than the hypoactive ones. The study inferred that spontaneous hyperactivity in rats predicted the frontal cortex n-3 PUFA content and that PUFA may play a role in the psychopathology of ADHD [43]. On the other hand, findings of a systematic review and meta-analysis further supported the role of n-3 PUFA in ADHD. N-3 PUFA supplementation in youth with ADHD enhanced clinical symptom scores in seven randomised clinical trials (RCTs), whereas in three RCTs, improvement in attention associated cognitive measures was observed with n-3 PUFA supplementation [44].

In one study, indicators of oxidative stress in children or adolescents with ADHD were compared with those of healthy children. These indicators include serum levels of glutathione S-transferase (GST), xanthine oxidase (XO), nitric oxide synthase (NOS) and paraoxonase-1 (PON-1) activities. Adenosine deaminase (ADA) activity, which is an indicator of cellular immunity, was also examined. Children with ADHD showed significantly higher levels of ADA, NOS and XO activities and significantly lower levels of GST and PON-1 activities when compared to those of healthy children. The study concluded that altered oxidative metabolism and cellular immunity might play a part in the pathogenesis of ADHD [45].

In another study, the total oxidant status (TOS), total antioxidant status (TAS) and oxidative stress index (OSI) arylesterase (ARE) activity and paraxonase-1 (PON-1) activity of ADHD children were compared with those of healthy children. Significantly, higher levels of TOS and OSI were observed in children with ADHD when compared to control. On the other hand, TAS, ARE activity and PON-1 activity were significantly lower in the former than those of the latter. These findings imply that children with ADHD had increased oxidative stress when compared to healthy children [46].

Neuroinflammation refers to inflammation involving the CNS, consisting of the brain and the spinal cord. Traditionally, it was believed that the CNS is immunologically inert and privileged, because immune substances from outside the CNS had no access to the CNS [47]. However, it is now increasingly evident that immune responses do occur in the CNS and that peripheral immune responses are in communication with the CNS. A crosstalk exists between blood-borne innate and adaptive immune cells, which provides immunological and homeostatic support to the CNS [8].

Neuroinflammation has been implicated in various neurological conditions including traumatic brain injuries, neurodegenerative disorders and movement disorders [48]. Although, there is no direct evidence of neuroinflammation in ADHD, there is indirect evidence that indicates neuroinflammation may play a role in ADHD. For example, Mittleman and colleagues investigated the inflammatory markers present in the cerebrospinal fluid (CSF) of children with neuropsychiatric diseases, such as ADHD, obsessive–compulsive disorder and schizophrenia. Among the 44 children with ADHD, detectable levels of IL-2, TNF-β, IFN-γ, IL-5 and IL-10 were observed in the CSF in varying degrees [49].

Peripheral or systemic inflammation

Other than local inflammation that occurs within the CNS, research has found that peripheral or systemic inflammation is also associated with an increased risk of ADHD. This section discusses various immune-mediated conditions linked to ADHD. These conditions may be present in children with ADHD or in mothers of ADHD children during pregnancy, which impose an increased risk of ADHD in the offspring.

Immune-related and autoimmune diseases

Maternal immune activation refers to immune response to infections or stimuli resembling infections in the mother during pregnancy. The resultant cytokines and immune alterations may exert their adverse effects on the developing foetus, particularly in the CNS and leads to adverse neurodevelopment and behaviour phenotypes [50]. Although an earlier Danish study that examined data on 89,146 pregnancies found no overall association between maternal exposure to fever and infections during pregnancy with ADHD in the offspring, it was reported that increased rates of ADHD was observed for certain periods of pregnancy. These

include fever during 9–12 weeks of gestation and genitourinary infections during 33–36 weeks of gestation. [51].

Another study examined 15,465 pairs of mothers and children using data from the Millennium Cohort Study (MCS, a UK sample representative of the population) concerning the association between ADHD and maternal-reported prenatal infections or hospital-recorded prenatal infections. Maternal-reported infections were found to be associated with ADHD and ASD, but not co-occurrence of both conditions. On the other hand, there was no observed association between hospital-recorded infections and (1) ADHD, (2) ASD or (3) co-occurrence of both conditions. The study concluded that prenatal infections might increase the odds of both ADHD and ASD. However, it is important to draw reliable data from multiple sources to determine the infection status [52].

In a population-based case–control study, several maternal immune-related disorders were reported to be related to ADHD in the offspring. These diseases include asthma, hyperthyroidism, multiple sclerosis, type 1 diabetes mellitus and rheumatoid arthritis. On the contrary, there was no significant association between non-immune-related conditions, such as type 2 diabetes mellitus and chronic hypertension and ADHD [53]. More recently, Nielsen and colleagues conducted a population-based cohort study and a meta-analysis of five studies to investigate the relationship between maternal autoimmune diseases (ADs). In the cohort study, children whose mother with an AD (for example, psoriasis, type I diabetes mellitus, rheumatic fever/carditis) were more likely to be diagnosed with ADHD in comparison with the control group. The meta-analysis reported similar findings in which ADHD was associated with mothers with an AD, such as type I diabetes mellitus, hyperthyroidism and psoriasis [54].

Interestingly, a recent study has reported the co-aggregation of ADHD and ADs among biological relatives [55]. Thirteen ADs (namely, ankylosing spondylitis, psoriasis, celiac disease, Crohn's disease, systemic lupus erythematosus, Grave's disease, Hashimoto's disease, multiple sclerosis, rheumatic arthritis, sarcoidosis, type 1 diabetes mellitus, Sjogren's syndrome, and ulcerative colitis) were studied. There was an association with any AD and specific ADs with odds ratio between 1.11 for ulcerative colitis and 1.79 for Sjogren's syndrome. When analysing for familial co-aggregates, there was an increased odd of any AD in all relatives (mother, father, sibling, aunt and uncle). These findings suggest familial co-aggregation of ADHD and ADs exists among biological relatives, which may be attributed to shared genetic risk factors. However, the familial co-aggregation patterns do not point to maternal immune activation (MIA).

Allergic diseases

Wang and colleagues examined the link between allergic conditions and ADHD risk among 216 children with ADHD. Rhinitis and eczema were significantly associated with an increased risk of ADHD. Using blood samples, four biochemical markers were also found to be associated with ADHD such as higher immunoglobulin (IG)-E level ($p < 0.001$), increased eosinophil count ($p = 0.001$) and lower levels of serotonin (5-HT; $p < 0.001$) and haemoglobin ($p = 0.001$) when compared with the control. The presence of more risk factors was related to a higher likelihood of ADHD diagnosis with a higher odds ratio observed with increasing number of biochemical risk factors [56].

A cohort study with 27,780 ADHD individuals revealed the association between parental asthma, asthma exacerbations and ADHD in the offspring. A higher risk was observed in offspring born to mothers with asthma, as well as offspring born to fathers with asthma. In addition, a higher risk was observed in ADHD offspring born to mothers with asthmatic exacerbations after delivery and during pregnancy when compared to mothers with exacerbations before pregnancy. However, the risk of ADHD in offspring was not increased with anti-asthmatic drug treatment [57].

Biochemical markers of inflammation

Several studies have analysed the biochemical markers in the serum/blood of patients with ADHD. In one study, blood samples were collected from 600 prematurely born children (< 28 week gestation) 1, 7 and 14 days after birth and were subject to analysis of 25 inflammation-related markers. At 2 years of age, behavioural problems were assessed using Child Behaviour Checklist for Ages 1.5–5 (CBCL/1.5–5) based on parents' responses. It was found that among these prematurely born children, blood IL-6, IL-8 and TNF-RI were persistently elevated in the postnatal period and this was associated with an attention problem later in life at 2 years of age [58].

Donfranscesco and colleagues investigated the serum inflammatory profile of ADHD children and healthy children. Out of the 58 children with ADHD, 45 demonstrated presence of antibodies against Purkinje cell (anti-Yo antibodies), whereas only 2 out of the 34 healthy children were positive to anti-Yo antibodies. Significant higher levels of serum IL-6 and IL-10 were detected in ADHD children when compared with

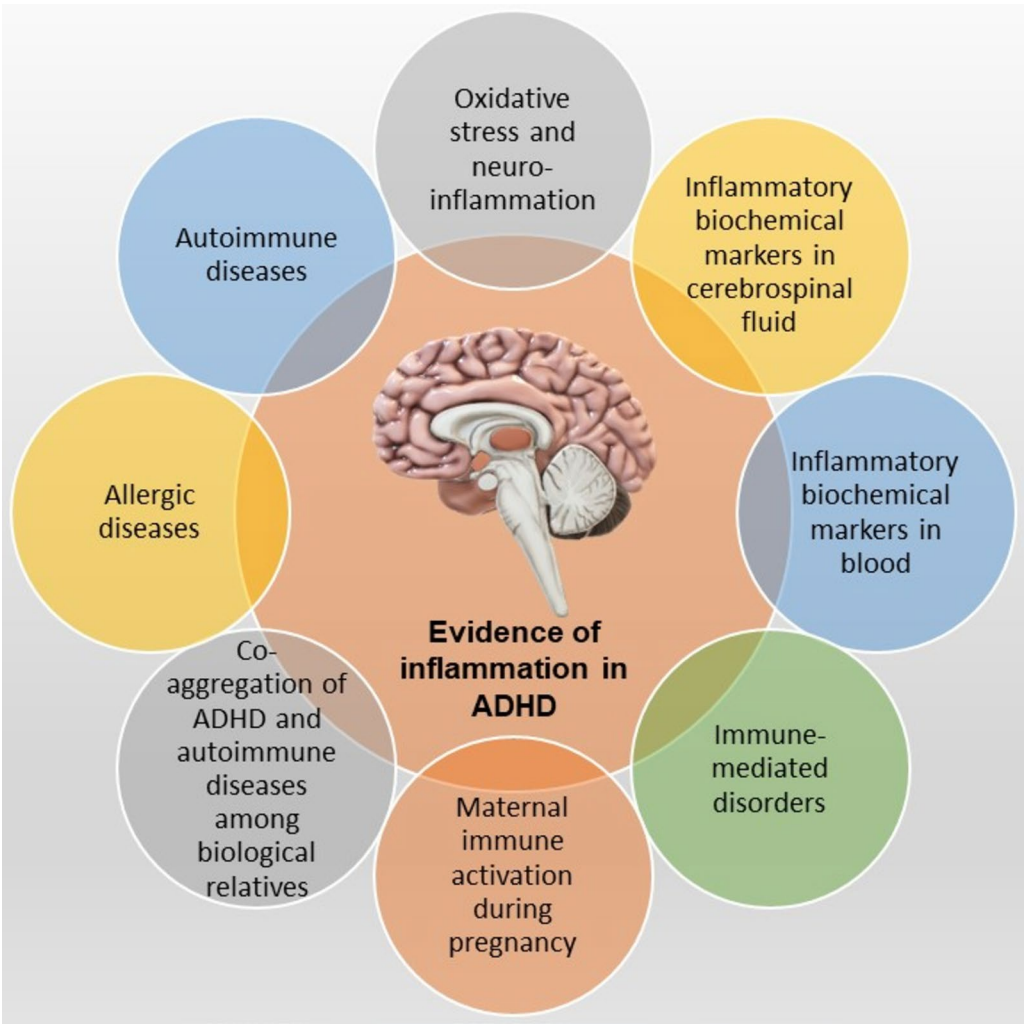

Fig. 1 Evidence of inflammation in ADHD The author declares that Fig. 1 is original. Its copyright belongs to the author, which ispassed to The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

normal children. Figure 1 summarises the evidence of inflammation in ADHD [59].

Conclusions

ADHD is a common neurodevelopmental disorder with an increasing prevalence and economic burden globally. Current literature cannot pinpoint the exact cause of ADHD but suggests that an interplay of genetic and environmental factors plays a role in the pathogenesis and psychopathology of ADHD. To this end, an increasing body of research indicates that inflammation, both locally and peripherally, is associated with psychiatric disorders, including ADHD. It is also increasingly evident that factors such as oxidative stress, neuroinflammation, autoimmune diseases, maternal immune activation, allergic diseases and other immune-mediated conditions are linked to ADHD. However, there are limitations in some of these studies such as a small sample size, a lack of follow-up in different stages of the disease and a lack of correlation with disease severity.

On the other hand, many of the studies that examined the relationship between ADHD and inflammation were epidemiological studies that associated the risk of ADHD with certain immune-related conditions or studies that correlated inflammatory biochemical markers with the risk or clinical features of ADHD. However, the underlying mechanisms are not clearly understood, which warrant further exploration. This has clinical significance in terms of treatment of ADHD. Current treatment approach focusses on behavioural

therapy, stimulant drugs and/or non-stimulant drugs. If the underlying mechanisms of the immune responses are known in patients whose ADHD is associated with inflammation, then inflammation may be a potential therapeutic target and treatment strategies may include immune modulation, antioxidants or anti-inflammatory agents.

The neuroinflammatory process has important implications on the treatment of ADHD. Being a common feature in many CNS pathologies, neuroinflammation has become an emerging therapeutic target. For example, if the signalling pathways involved in neuroinflammation can be clearly delineated, drugs that target these pathways can be potential therapeutic agents for ADHD. Researchers have also explored the use of targeted delivery of nanoparticles to alleviate neuroinflammation [60]. Perhaps, future research can explore this novel therapeutic strategy in the treatment of ADHD.

In addition, pregnant mothers who are at a higher risk of giving birth to offspring with ADHD should be closely monitored, especially if they have immune-related conditions that are associated with ADHD. A potential area of interest in future research may include identification of genes or biomarkers with a predictive value in these pregnant mothers. Furthermore, a better understanding of the underlying mechanisms of how the immune-related conditions contribute to the pathophysiology of ADHD in the developing foetus will allow a better control of inflammatory, allergic and infectious diseases during pregnancy using a targeted approach, which may be another area of interest for future exploration.

Abbreviations

AAP: American Academy of Paediatrics; AD: Autoimmune disease; ADHD: Attention deficit/hyperactivity disorder; APA: American Psychiatric Association; ARE: Arylesterase; ASD: Autism spectrum disorders; CNS: Central nervous system; CSF: Cerebrospinal fluid; DSM: Diagnostic and statistical manual of mental disorders; EEG: Electroencephalogram; GST: Glutathione S-Transferase; ICD: International classification of diseases; IFN: Interferon; IL: Interleukin; MIA: Maternal immune activation; NHIS: National Health Interview Survey; PON-1: Paraoxonase-1; PUFA: Polyunsaturated fatty acid; NOS: Nitric oxide synthase; OSI: Oxidative stress index; RCT: Randomized clinical trial; ROS: Reactive oxygen species; TAS: Total antioxidant status; TNF: Tumour necrosis factor; TOS: Total oxidant status; XO: Xanthine oxidase.

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