

Attention deficit hyperactivity disorder may be a highly inflammation and immune-associated disease (Review)

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Abstract. Attention deficit hyperactivity disorder (ADHD) is a common behavioral disorder. Previous research has indicated that genetic factors, family education, environment and dietary habits are associated with ADHD. It has been determined that in China many children with ADHD also have allergic rhinitis or asthma. These children are more susceptible to the common cold or upper respiratory infections compared with normal healthy children. Additionally, the common cold or an upper respiratory infection may lead to disease recurrence or worsen the symptoms in these children. Previous studies have determined that ADHD may have a close association with allergic disease. Based on the clinically observed phenomenon and previous studies, it was hypothesized that ADHD is a high inflammation and immune-associated disease. Therefore, the authors designed clinical and animal experiments to test this hypothesis in the future. Immune system disorders may be a novel part of the etiology of ADHD. The current report may have implications for future clinical practice.

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common behavioral disorder with an onset during childhood. Currently, ADHD has a prevalence of 5.9% worldwide (1). The core symptoms of ADHD are inattention, impulsiveness and hyperactivity (2,3). These negative effects may cause serious problems to the individual, family and society. Previous studies have revealed that ADHD has been associated with criminal activity (4-6). Although previous studies have indicated that genetic factors (7,8), streptococcal infection (9,10) and environmental factors (11-13) were closely associated with ADHD, to the best of our knowledge, the causes of ADHD remain to be fully elucidated. However, the theory of dopamine (DA) deficiency in ADHD currently widely accepted (14). In addition, other mechanism-based hypotheses, involving norepinephrine (NE) (15) and serotonin (16,17) have also been proposed for ADHD. However, these hypotheses require further investigation for confirmation. Currently, pharmacological and psychosocial interventions are the most frequently used methods of treatment (18). Methylphenidate (MPH) is the first choice and first-line medical treatment for ADHD for adults and children (18). However, it has a number of serious side effects, such as depression, anxiety and obsessive compulsive symptoms (19,20), parents are disinclined to use MPH and nonadherence to therapy is high (21) under these circumstances, novel insights into the causes and treatment methods for ADHD are necessary.

In China, many children with ADHD have also been diagnosed with allergic rhinitis (AR) or asthma. In addition, children with ADHD are more susceptible to the common cold or upper respiratory infections compared with normal healthy

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Abbreviations: ADHD, attention deficit hyperactivity disorder; DA, dopamine; NE, norepinephrine; MPH, methylphenidate; CNS, central nervous system; AE, atopic eczema; AR, allergic rhinitis; BBB, blood-brain barrier; SHR, spontaneously hypertensive rats; WKY, Wistar Kyoto mice; HPLC, high-performance liquid chromatography; TH, tyrosine hydroxylase; SNAP25, synaptosome associated protein 25; VMAP2, vesicle-associated membrane protein 2; DAT, dopamine transporter; DDC, DOPA decarboxylase; syntaxin1A, synaptic fusion protein 1A; TNF- β , tumor necrosis factor- β

Key words: ADHD, allergic disease, immune system, clinical treatment

children. In children with ADHD with controlled clinical symptoms, common colds or upper respiratory infections may lead to AR or asthma disease relapse and reduced immune function. This may result in the recurrence or exacerbation of ADHD symptoms (22,23). Additionally, this phenomenon is common rather than the exception and the underlying reasons for this occurrence remain to be elucidated. At present, clinicians have not devoted sufficient attention to this phenomenon. Nonetheless, it has a major role in other complex genetic diseases, such as AR and asthma (24). A previous study indicates that AR and asthma, which are immune-associated diseases may also be associated with ADHD (25). Therefore, it is possible that ADHD may be associated with the immune system and that the immune system may underlie ADHD onset or recurrence. Therefore, the immune system should receive more attention and consideration in the clinical treatment of ADHD.

2. Potential relationship between ADHD and allergic disease

ADHD is deemed to be a neurobehavioral disorder, DA deficiency in the central nervous system (CNS) is one recognized as part of the pathogenesis of ADHD (14). Previous studies have revealed that ADHD may impair affected children and impose a significant economic burden on their families and society in general (1,26,27). In addition, a previous study has indicated that ADHD has a moderate association with criminal activity, a significant risk of suicide, and has a negative effect on the labor market outcomes. Therefore, ADHD requires more attention. AR, which is an immune-associated disease, which has recently been shown to have an association with ADHD (25). However, the association between CNS diseases and allergic diseases remains to be elucidated.

Allergic diseases, such as atopic eczema (AE), AR and allergic asthma, are common childhood chronic illnesses that are estimated to affect 7 to 40% of children worldwide (28). With the deterioration of the environment due to pollution, the morbidity of allergic diseases has increased over time (29-31). Recently, researchers have paid close attention to the connection between ADHD and allergic disease (32,33). Previous reports have revealed potential associations between ADHD and allergic diseases (34-36). AE, AR, and allergic asthma are considered to be the most common chronic diseases worldwide and represent the three major clinical manifestations of atopy (37). The characteristic symptoms of AR are itching, rhinorrhea, and nasal congestion and obstruction. These symptoms may result in daytime inattention, irritability and hyperactivity, which are also symptoms of ADHD. Previous studies have indicated that there are associations between ADHD and AR (38-40). Brawley *et al* reported that 10 out of 23 (43%) children with ADHD had typical physical signs of AR (41). A population-based study from Taiwan indicated that patients with ADHD had an increased occurrence of AR compared with normal healthy subjects (42). Children with AR have hyperactivity and impulsivity (43). Risk factors for inattention and impulsivity in children with AR may lead to comorbidity with ADHD (43). AE, which is another allergic disease, has also been identified to have a significant association with ADHD in a large population-based sample (44).

Schmitt *et al* reported that AE is independently associated with ADHD (45). In addition, an epidemiological survey revealed that children with AE have a significantly higher risk for ADHD-symptoms (38). The potential mechanisms underlying the comorbidity of AE and ADHD may be associated with high levels of psychological stress (46), genetic factors (47) and interference of inflammatory cytokines with the maturation of the prefrontal cortex regions and neurotransmitter systems involved in ADHD pathology (37). Allergic asthma, a leading cause of childhood chronic medical illness, affects 7-15% of children worldwide (48). Previous population-based studies (28,49,50) have indicated significant associations between allergic asthma and ADHD. Children with asthma have a higher incidence of ADHD compared with normal healthy children. Based on the aforementioned evidence, allergic diseases, such as AE, AR and allergic asthma may have a significant connection with ADHD. However, the potential mechanisms underlying the comorbidity of allergic diseases and ADHD remain to be elucidated.

3. Potential mechanisms

At present, the specific association between allergic diseases and ADHD is in the hypotheses and preliminary study stage. Therefore, the potential mechanisms underlying the comorbidity of allergic diseases and ADHD remain to be determined. Previous investigations using molecular biology have provided some possible explanations for the association between allergic diseases and ADHD. Buske-Kirschbaum *et al* (51) have proposed that children with atopic disease are exposed to higher levels of inflammatory cytokines released during the atopic response and these cytokines may then pass through the blood-brain barrier (BBB) (52) and interfere with the development of brain regions, such as the prefrontal cortex, the corpus striatum, and the DA system, which have crucial roles in executive functions, such as attention, motivation motor, and cognitive control (37,53-55). Conversely, Rosenkranz *et al* (56) revealed that emotional behaviors are mediated by the prefrontal cortex, such as attention, are activated during atopic episodes, as demonstrated by functional magnetic resonance imaging. Inflammatory mediators significantly affect the evaluation of sensory stimulation and the regulation of homeostatic responses in the prefrontal cortex and the insula. Therefore, inflammatory mediators levels may be used to identify children vulnerable to the risk of developing ADHD symptoms. Studies (47,57) have stated that genetic factors are associated with ADHD and allergic diseases, and that AE and ADHD are complex multifactorial traits with substantial genetic components. Prenatal stress has been reported as another factor contributing to ADHD. A previous study revealed that maternal stress during pregnancy may be associated with psychopathology later in life, including symptoms of attention deficit, compulsive behavior and hyperactivity (58). There are various theories on the potential mechanisms underlying the comorbidity of allergic diseases and ADHD. The aforementioned theories identified the relationships among inflammation, immunity and allergic diseases. Although these theories vary substantially, they are unanimous regarding the presence of a clear connection between ADHD and allergic diseases and provide evidence for this idea. ADHD and allergic

diseases may share molecular mechanisms, which may need to be determined in future studies.

4. Hypothesis: ADHD may be a highly inflammation and immune-related disease

There is substantial evidence that allergic diseases, such as AE, AR, and allergic asthma, have significant association with ADHD. The majority of children with ADHD have a strong association with allergic diseases (25). Allergic diseases and the allergic response are associated with the immune system and inflammation (59,60). Typical allergic diseases, such as AE, AR, and allergic asthma lead to significant responses reflected in the immunoglobulin (Ig)E or IgG levels and T cell changes in clinical studies (24,61,62). Researchers (23,63,64) reported that ADHD has high comorbidity with helper T cell (Th)1- and Th2-mediated disorders, such as ear infections, eczema and asthma. Substantial alterations occur in the immune system and the epigenetic regulation of gene expression in ADHD. Overall, it is evident that different types of allergic diseases are heterogeneous with respect to the role of the immunopathology underlying the cause of these diseases. Although ADHD has never been postulated as an allergic disorder, the present study hypothesizes that ADHD has an etiologic connection with the immune system and inflammation. Therefore, it is possible that ADHD is an inflammation and immune-associated disease.

The current study has presented sufficient evidence to support this hypothesis. Mervan Bekdas (65) performed a clinical study on patients with ADHD and healthy children and quantified their IgG levels. The findings indicated that ADHD is associated with a significant immune reaction ($P=0.044$). Another study (66) revealed a significant positive association between ADHD and the anti-Yo antibody immunoreactivity in the Purkinje cells of the cerebellum in children and suggested the presence of immune dysregulation in children with ADHD. These clinical studies offered additional evidence that may be used to identify relationships between ADHD and immunity. It has been previously reported (23) that patients with ADHD have elevated concentration of the innate pro-inflammatory cytokine tumor necrosis factor (TNF)- β and reduced levels of anti-inflammatory cytokines interleukin (IL)-4, IL-2 and interferon γ (IFN- γ). In addition, mothers suffering from inflammatory and immune system diseases during the prenatal period have an increased the risk of their offspring developing ADHD (67). Inflammatory cytokines may interfere with the maturation of the prefrontal cortex regions and neurotransmitter systems (51) associated with DA systems. Peripheral inflammation may lead to the occurrence of ADHD. This may be due to microglial activation and TNF- α production mediating altered CNS excitability (68). The microbiota-gut-brain axis (MGB) theory has been previously proposed and provided evidence regarding the connection between ADHD and maternal inflammation (69). Previous studies have determined that gut microbes are associated with the body's immune system and that gut microbes aid in the maintenance of homeostasis and ensure the normal operation of the immune system by mutual exchange of cytokines with the intestinal epithelium and intestinal mucosal cells (70,71). The gut microbiota may also pass through the BBB and

influence the CNS immune system (72). It is of note that children with ADHD have been recorded to have abnormalities in the MGB (73). This supports the hypothesis that ADHD is an immune-associated disease.

The previous studies provide evidence that the immune system and inflammation may be associated with the underlying mechanisms of ADHD. Based on the aforementioned evidence the present study hypothesized that ADHD may be closely associated with the immune system and inflammation, and that ADHD is an inflammation- and immune-associated disease.

5. Testing the hypotheses

There are two methods to test the hypotheses: Clinical research and animal experiments. T-lymphocytes have an important role in the immune system. The CD4⁺ (helper) to CD8⁺ (cytotoxic) ratio has been used to assess a person's level of immunity. For preliminary clinical research, the CD4/CD8 ratio in blood samples of children with ADHD may be quantified using flow cytometry. This ratio may then be compared to that obtained from normal children to provide basic evidence that may be used to prove our hypotheses. For further research, the levels of other T, B and natural killer (NK)-cells, and immune-associated proteins should also be quantified in future studies. Detailed research methods for the above experiments are presented in Fig. 1. For animal experiments, the spontaneously hypertensive rats (SHR) model is deemed the best recognized ADHD animal model (74), which may be compared with normotensive Wistar Kyoto (WKY) control rats (75). SHR rats have typical ADHD symptoms at 3-4 weeks of age (76). Flow cytometry may be used to quantify the blood and spleen T, B and NK-cell levels in the rats. Furthermore, DA levels in the striatum and prefrontal cortex may also be quantified using high-performance liquid chromatography. IgG quantification may be performed using enzyme-linked immunosorbent assay or reverse transcription-polymerase chain reaction, whereas tyrosine hydroxylase (TH) levels may be determined using immunofluorescence or immunohistochemistry. Detailed research methods are presented in Fig. 2. The aforementioned research design may aid in elucidating the association between ADHD and immunity, and determine whether ADHD is an immune-associated disease.

6. Implications for clinical practice of this hypothesis

The present study suggests that when clinicians treat children with ADHD, they should consider inflammation and immunity, not just genetic factors or lower dopamine levels. If the patient has an allergic disease such as AR, AE, or allergic asthma, then more attention should be paid to the inflammatory cytokines and the immune system. An immunological clinical inspection and an accurate and timely allergy and immune system diagnosis are required and important for treating the patient in an appropriate manner (77). The present study provides a novel way of examining the clinical treatment of ADHD. Therefore, physicians should also consider the immune system. The clinical phenomenon observed in China, where children with ADHD are more susceptible to the common cold or upper respiratory infections, to the best of our knowledge, not been

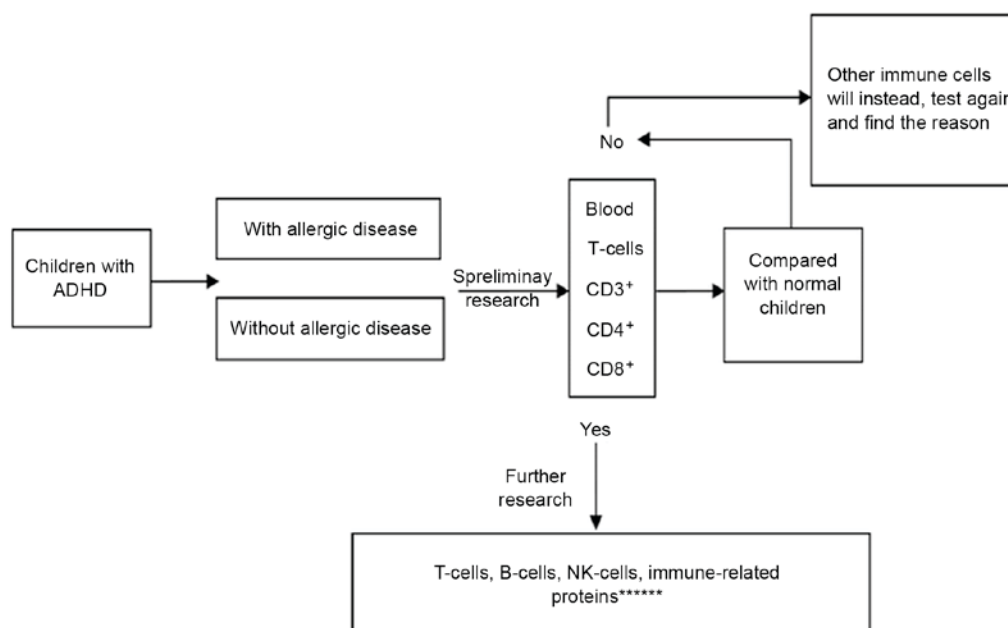


Figure 1. Clinical research design. Children with ADHD will be divided into two groups depending on presence of allergic disease and blood samples will be compared with those from normal children. For preliminary research, T-lymphocytes CD3/CD4/CD8 will be detected. In case of a significant change in immunity, additional immune-associated indicators will be quantified. If not, other immune cells or immune-associated factors will be tested to determine the underlying mechanisms. ADHD, attention-deficit hyperactivity disorder; NK, natural killer.

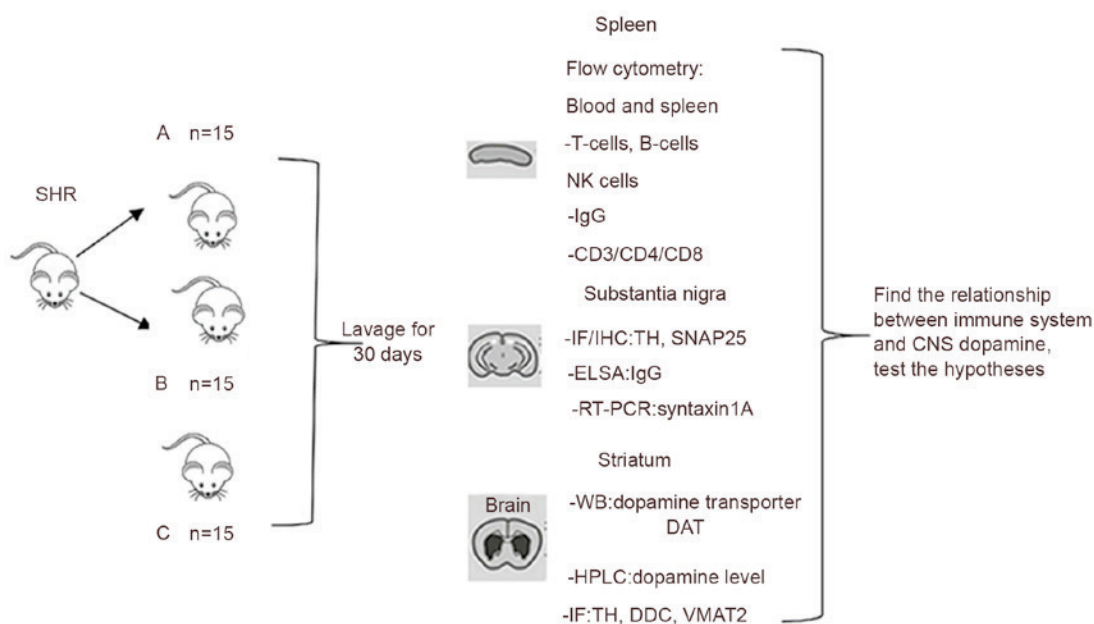


Figure 2. Animal experimental design. Mice will be divided into 3 groups, the control group A (lavage with Ritalin), the model group B (lavage with saline) and the blank group C (lavage with saline), with and will be treated with lavage for 30 days. Blood and spleen samples will be tested using flow cytometry for CD3/CD4/CD8, B and NK cells, and IgG to determine whether ADHD model mice have immune problems. Immunofluorescence or immunohistochemistry, ELISA and reverse transcription polymerase chain reaction will be used to detect ADHD-associated proteins, such as syntaxin1A, DDC, VMAT) and SNAP25 in the substantia nigra. The striatum dopamine levels will be confirmed using HPLC. Other appropriate methods, including microdialysis technology, gene chip technology and metabolomics technology will be used to determine the association between the immune system and CNS dopamine levels in the CNS. SHR, spontaneously hypertensive rats; ADHD, attention-deficit hyperactivity disorder; NK, natural killer; IF, immunofluorescence; IHC, immunohistochemistry; WB, western blotting; CNS, central nervous system; syntaxin1A, synaptic fusion protein 1A; DDC, DOPA decarboxylase; VMAT2, vesicular monoamine transporter 2; SNAP25, synaptosome associated protein 25; DAT, dopamine transporter; HPLC, high-performance liquid chromatography.

widely considered in the medical community. The present study is based on this clinical phenomenon, if it is confirmed children with ADHD may be divided into immune-associated and non-immune-associated ADHD. Subsequently, therapies aimed to regulate immunity instead of central stimulant

drugs such as methylphenidates may be used. This may aid in reducing the application of psychiatric drugs and the mental stress in children with ADHD and their families, and improve the quality of life for children and adults with ADHD in the future.

7. Conclusions

ADHD is deemed to be a neurobehavioral disorder due to CNS DA deficiency, the specific etiology and pathogenesis remain to be elucidated. The association among ADHD, allergic diseases and the immune system have not been fully investigated in the clinical and laboratory setting. In the clinical setting in China, many children with ADHD also suffered from allergic diseases, such as AR and asthma and children with ADHD are more susceptible to the common cold or upper respiratory infections compared with normal healthy children. They also have relapses of AR or asthma, which may lead to ADHD symptom recurrence or deterioration. This phenomenon also exists in other countries, including Korea and Germany (38,42). Based on the aforementioned findings the present study determined that ADHD may be associated with allergic diseases and that it may be immune-associated disease. However, not enough attention has been devoted to this phenomenon by clinicians. Investigating this phenomenon may provide clinicians with a novel way of thinking in terms of the clinical treatment of ADHD. Clinicians may alter their clinical conception and investigate the immune system extensively. To test the connection between ADHD and the immune system, the present study designed preliminary clinical and animal experiments. In the clinical research proposal, children may be divided into two groups: Children with ADHD and normal children. Blood IgG, CD4/CD8 ratio, NK cell levels, and other immune-associated factors may be quantified using flow cytometry to indicate the association between ADHD and the immune system. In the animal experiments, the aforementioned immune-associated factors would also be measured. In addition, the relationship between the immune system and CNS dopamine levels may be investigated in order to find out whether immunity may influence the DA levels in the CNS. This hypothesis may have a significant effect in the clinical setting, where children with ADHD may be divided into immune-associated and non-immune-associated ADHD groups. Methods to regulate immunity may be used instead of central stimulant drugs such as methylphenidates. This may reduce the application of psychiatric drugs and the mental stress in children with ADHD and their families, and improve the quality of life for children and adults with ADHD in the future.

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