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ADHD and atopic diseases

van der Schans, Jurjen

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Chapter 1

GENERAL INTRODUCTION

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADULTS

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders in children. ADHD is a neurodevelopmental disorder characterized by symptoms of inattention and/or impulsivity-hyperactivity (see for description box 1). Although often seen as a disorder based on a modern societal construct, a German physician already described ADHD in 1775.¹ The first diagnostic criteria were established in 1968.² Currently, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)³, a persistent pattern of inattention and/or hyperactivity-impulsivity alongside with functional impairments warrants a diagnosis of ADHD. In addition, several symptoms need to be present prior to the age of 12 years and in two or more settings like home, school, and work. Different combinations of symptoms lead to the distinction between three presentations of ADHD, i.e. the predominantly inattentive presentation, the predominantly hyperactive/impulsive presentation, and the combined presentation.³ However, over the course of the development these presentations are not stable and tend to shift from being predominantly hyperactive to being predominantly inattentive. The symptoms of individuals with predominantly inattentive ADHD symptoms tend to be more stable over time compared to those in individuals with the predominantly hyperactive presentation and the combined presentation.⁴ Besides the presence of different ADHD presentations, most individuals also differ in the severity of the disorder, ranging from few symptoms with only slight impairment of functioning to the presence of most if not all symptoms with significant impairment of functioning.³ Because DSM-5 criteria of ADHD require the symptoms to be present before the age of 12 years, ADHD is often seen as a childhood disorder. However, symptoms and impairments related to ADHD often continue to have impact into adulthood, which has raised more awareness of ADHD in adults and even of adult-onset ADHD.⁵

Epidemiology of ADHD

The prevalence of ADHD during childhood is estimated to vary between 3% and 7% of children and adolescents.^{6,7} Approximately 65% of children with ADHD continue to have symptoms of ADHD as an adult and ADHD is therefore seen as a chronic disorder.⁸ Over the last decades there has been both a scientific and societal discussion about the possible overdiagnosis and overtreatment of ADHD⁹, mainly caused by a rise in number of prescriptions of ADHD medication¹⁰. The overall prevalence of ADHD, however is similar between different countries around the world and does not appear to increase over time.^{6,11} Taken into account the chronic character of ADHD it is likely that the annual incidence rate of ADHD has remained stable over the last years. However, improved awareness of the disorder may have caused the increase of ADHD related drug prescriptions.⁶

Relevance of ADHD

Overall, the course of ADHD into adulthood shows a decrease of symptoms, independent of the severity of the symptoms in childhood¹² A part of the individuals with ADHD-symptoms grow up without any significant problems; however, ADHD is associated with high rates of school dropout, poor relationships with peers, and substance misuse, all leading to high economic and social burdens.¹³ ADHD is also associated with adverse long-term outcomes ranging from school related problems during childhood, to social and psychological dysfunction in adolescent, and health-related comorbidities in adulthood.² The extent to which treatment of ADHD, especially in the long term, contributes to the improvement of symptoms and real-world outcomes like school performance is being discussed.¹⁴

Box 1: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) symptoms of ADHD.

Attention:

- Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities.
- Often has difficulty sustaining attention in tasks or play activities.
- Often does not seem to listen when spoken to directly.
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace.
- Often has difficulty organizing tasks and.
- Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort.
- Often loses things necessary for tasks or activities.
- Is often easily distracted by extraneous stimuli.
- Is often forgetful in daily activities.

Hyperactivity and impulsivity:

- Often fidgets with or taps hands or feet or squirms in seat.
- Often leaves seat in situations when remaining seated is expected.
- Often runs about or climbs in situations where it is inappropriate.
- Often unable to play or engage in leisure activities quietly.
- Is often “on the go,” acting as if “driven by a motor”.
- Often talks excessively.
- Often blurts out an answer before a question has been completed.
- Often has difficulty waiting his or her turn.
- Often interrupts or intrudes on others.

Treatment of ADHD

Most current European guidelines suggest a stepped care approach of ADHD, starting with non-pharmaceutical treatment, i.e., psychological education, behavioral therapy, or parent training, and progressing to pharmaceutical care when there are more severe symptoms, higher impairments associated with the disorder, or when there is insufficient response to the non-pharmaceutical approach.¹⁵ The use of psychotropic drugs has steeply increased over the

past years^{10,16-19}, an issue of considerable debate. Although often effective in the short-term treatment of psychiatric disorders, concerns have been raised regarding the limited long-term effectiveness of psychotropic drugs due to adverse effects, and lack of clinical significance by reducing symptoms without improving the associated functional impairments.^{13,20-22} On the other hand, without proper treatment, individuals with ADHD are at risk of severe adverse outcomes, both on the long and short term.

The multimodal treatment study of children with ADHD, a 14-month randomized clinical trial, assessed the effectiveness of different pharmaceutical and non-pharmaceutical treatment strategies and concluded that combining non-pharmaceutical therapies like behavioral therapy with pharmaceutical treatment did not give clear additional benefits over the sole use of pharmaceutical treatment.¹⁴ The main advantages of pharmaceutical therapies like psychostimulants are their clear, strong, and rapid effect. The unwanted adverse effects may, however, be substantial such as a delayed onset of sleep, nervousness, headache, decreased appetite, nausea, and dry mouth often occurring with the use of stimulants.^{14,23}

Although ADHD is thought to be chronic, the effectiveness of treatment beyond a period of two years is not well established. In a follow-up on the MTA study the outcome of the originally randomized types of treatment did not lead to differing in functioning after 6 to 8 years of enrolment in the study. The severity of symptoms at the start of the study, the socioeconomic status of the family, and the best initial response to any of the treatments showed the best long-term prognosis of ADHD related outcomes.^{13,23} Also, little is known about the long-term adverse effects of psychostimulants. Concerns have been raised regarding the long-term safety, like reduced growth, adverse brain development, cardiovascular problems, and risk of other psychiatric problems.²⁴ To what extent treatment is warranted of adults with ADHD is unclear, partially because ADHD related medication is not registered for adults.¹⁵ In addition, the outcome of the pharmacological intervention is dependent on the treatment adherence of the patient, which is generally poor in ADHD treatment.²⁵ As in all pharmacological interventions it is essential to consider treatment adherence in the evaluation of the efficacy and effectiveness, because the effectiveness stands apart from the fact whether or not the efficacy of the drug has been proven. Studying adherence in specific populations can therefore lead to better treatment.²⁵

Moreover, it is estimated that annual costs of ADHD lie between €9,860 and €14,483 per patient. Additional education, healthcare, and productivity and income losses of family account for the largest proportion of the cost made in ADHD.²⁶ Because of the substantial economic burden of ADHD and the variety of treatment options and related effectiveness of the treatment, assessing the potential cost-effectiveness of specific treatment strategies could make the distinction between the added value of different treatment options.²⁷

Risk factors & pathology of ADHD

Although the precise etiology of ADHD is unknown, ADHD is highly heritable and multifactorial, with genes and non-inherited factors contributing to the disorder. Even though

the specific genes underlying ADHD have not been identified, heritability is estimated to be around 80%.²⁸ However, it has been suggested that genetic factors may be different for ADHD in childhood and in adulthood.²⁹

Also non-hereditary risk factors play a role in the etiology of ADHD, like low birth weight, maternal smoking and alcohol use during pregnancy, and birth complications. There is a clear difference in childhood between male and female prevalence rates (3:1), but this gender difference is not seen during adulthood.³⁰ Also lower socioeconomic status is associated with higher rates of ADHD, but it is not clear whether low socioeconomic status is a risk factor for ADHD or that the heritability of ADHD together with related impairments lead to an overall lower socioeconomic status in the ADHD population.³¹ This shows that identifying specific environmental factors is difficult because of the possible influence of genetics on the environment and the likely presence of gene-environment interactions.² Each individual risk factor only has a small effect on the causal pathway associated with ADHD. It is therefore likely that cumulative vulnerability plays a role in the etiology of ADHD, in which a certain threshold needs to be reached for the disorder to unfold.²

Despite the identification of multiple factors associated with ADHD it is unclear how these factors affect the biological mechanism and pathophysiology of ADHD. At group level individuals with ADHD show a delayed cortical maturation and dysfunction of specific pathways in the brain related to among others the control of attention, and response to reward.^{2,32,33} This specific pathophysiological process of ADHD is supported by the effect that methylphenidate, a commonly used psychostimulant, has on neurotransmitter levels in the brain. Methylphenidate and other psychostimulants, the first line pharmacological treatment of ADHD, increase the level of dopamine available to synaptic transmission by inhibiting the dopamine transporter. This results in a stronger signal sent from the dopaminergic system.³⁴

Because of the uncertainty surrounding the etiology and pathology of ADHD, the overlap and possible associations with comorbid diseases, and the relative lack of knowledge in this area warrants more research. The assessment of possible associations with other diseases could lead to a better understanding of the origins of ADHD as well as the best treatment.

Psychiatric comorbidities

Contrary to most physical diseases, mental health problems are mainly based on a construct of symptoms partly because there is a lack of valid biomarkers. Diagnosis is therefore more subjective and relying on observed and reported behavior, cognitions, and emotions.¹³ The classification and diagnosis of mental health problems in general is grounded on clinical consensus, which may be subject to change over time, and is often based on arbitrary boundaries on a spectrum of symptoms.^{2,35} Moreover, psychiatric comorbidities are often a consequence of the classification system used for psychiatric disorders, and not necessarily pointing to the true existence of separate disorders.^{35,36} Comorbidity with other psychiatric disorders is common in individuals with ADHD and it is estimated that only a third of the ADHD population is without any other comorbid psychiatric disorder.³⁷ This makes the ADHD population very heterogeneous. Psychiatric comorbid disorders most often seen together with ADHD in childhood are oppositional defiant disorder

(47%), mood disorders (28%), conduct disorder (19%), and anxiety disorders (17%), and in adulthood also substance use disorder (45%) together with mood and anxiety disorders.³⁸

Case of comorbid ADHD and atopy

David is a twelve year old boy who received a diagnosis of Attention-Deficit/Hyperactivity Disorder at the age of ten. He was born after an uneventful pregnancy. However, at the age of 6 weeks atopic dermatitis evolved and class two local corticosteroids were needed to relieve the symptoms.

At the age of six years he was admitted to the hospital because of an asthma attack. At follow up it appeared that sometimes he experienced shortness of breath in playing and running. Because of these symptoms, short acting bronchodilators were prescribed. At first, this treatment was sufficient but at the age of eight years he had to use his medication almost daily. Therefore, inhaled corticosteroids (ICS) were added to his medication regimen. The starting dose of ICS was not sufficient and therefore the dose was doubled. Unfortunately, the double dose also did not have the desired effect and therefore David was referred to a paediatrician. The diagnosis of asthma was established formally by spirometry. However, the paediatrician noticed that David did not inhale the ICS medication correctly; instead of 10 breaths, he only took one inhalation. Despite the fact that he had received multiple instructions he did not take the time to inhale properly. In addition, his mother was instructed to help him, but she could not convince him to take his medication properly; after one or two inhalations he was distracted and ran away or started talking.

His mother also reported that the school teacher had contacted her about the dropping school results of David. The teacher described him as hyperactive and impulsive, not being able to follow direct instructions and having difficulty in taking turns with peers. On top of that, he could not sit still during explanations or even during tests, and concentrating was very hard.

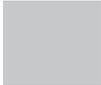
David was referred to a child psychiatrist who established the diagnosis of ADHD. The parents received parent training in group sessions and the David was prescribed methylphenidate. The morning dose ICS was given half an hour after taking methylphenidate and the evening dose ICS was given around 5 o'clock. By doing so David was more relaxed and could take the ICS properly. His asthma symptoms resolved and the dose of ICS could be halved. Currently, he is doing well and his school results have improved.

Atopic comorbidity in ADHD

Surprisingly, much less is known about the possible association between ADHD and somatic diseases. As mentioned before, ADHD is a heterogeneous disorder with the majority of individuals experiencing different comorbidities. In a 2010 systematic review 20 studies were reviewed with a total of 170,175 individuals showing that especially eczema, more often co-occurs with ADHD than would be expected on the basis of chance.³⁹ Because ADHD and atopic diseases like eczema are both common diseases in children the possible association between both disorders has gained scientific interest over recent years. Studies into the association of ADHD with other (comorbid) somatic diseases could enhance the knowledge of etiological mechanisms of ADHD and may also improve current treatment approaches or lead to alternative treatment strategies. By investigating the possible association between ADHD and atopic diseases, this thesis has addressed the potential involvement of atopy in the pathophysiology and treatment strategies of ADHD.

The three main atopic diseases, asthma, atopic dermatitis, and allergic rhinitis, all originate from an immune response triggered by allergens, but differ in clinical manifestation of this allergic reaction, i.e., inflammation in the lungs, skin, and nose. The immunological sensitization in all three diseases is mediated by the production of immunoglobulin E (IgE) triggered by environmental allergens, which cause an inflammatory reaction that is typical of atopic diseases.⁴⁰ Because of this link between atopic diseases a common progression is observed known as the atopic march, usually starting with atopic dermatitis and subsequent asthma and allergic rhinitis.⁴¹ An increase of all three diseases over the past decades has resulted in a lifetime prevalence rate between 20 and 30% with the majority having its onset in childhood.⁴² The impairment related to all three atopic diseases is substantial. Atopic diseases affect both individuals' physical health through itching, breathing problems and nose obstruction (both leading to sleep disruption), increase stress, poor school performance but also (recurrent) hospitalization, and individuals' psychosocial health e.g. limiting participation in sports, recreation and other social activities.⁴³

In summary, ADHD is a chronic disorder with high prevalence and despite the availability of effective treatments many problems with ADHD still remain in patients and society associated. A lack of knowledge regarding the etiology of ADHD and the subjective nature of the disorder raises questions about the possible connections with other diseases. The possible association between ADHD and atopic diseases has been the starting point of this thesis. As described in the previous section the pathology of ADHD is likely to consist of a complex interplay between genes and environment. Adding the complexity of the progression of the disorder and the uncertainty around the treatment of ADHD and long-term effects of treatment makes the advancement of scientific knowledge surrounding this topic a difficult matter. This thesis aimed to contribute to these challenges concerning atopy and ADHD focusing on the following objectives:



THESIS OBJECTIVES

Main objective:

To assess the possible association between presence of drug-treated atopic disorders and ADHD.

Sub-questions

- What is the clinical and economic impact of psychotropic drug use in children with ADHD?
- What is the association between childhood atopy and ADHD?
- What is the association between atopy and ADHD among adults?

Thesis outline

The first part of the thesis (**chapters 2-4**) is based on the treatment of children with psychotropic drugs, the related outcomes, treatment persistence, and cost-effectiveness. The following two scientific parts of this thesis (**chapters 5-9**) zoomed in on the possible association between atopic allergies and ADHD. The first chapters (**chapters 5-7**) of this section highlight the possibility of improving treatment of ADHD by looking at somatic comorbidities like atopic allergy and increasing the knowledge of the pathology of ADHD in children. The following part of this section (**chapters 8-9**) focused on the trend of both ADHD treatment and the association of ADHD with atopic diseases like asthma, eczema, and allergic rhinitis into adulthood.

This thesis ends with an overall discussion of our main research questions, taking into account the results presented in the previous chapters of this thesis.

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PART I

The clinical and economic impact
of psychotropic drug use in
children with attention-deficit/
hyperactivity disorder