

EARLY CHILDHOOD ALLERGY LINKED WITH DEVELOPMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER

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Abstract

Background: Previous studies reported controversial results regarding the association between allergic disorders and ADHD/ASD. The aim of this article is to investigate whether allergic disorders are associated with ADHD/ASD in a large cohort of pediatric patients. Methods: A retrospective study using the pediatric (0-18 year) database (ICD-9-CM codes) of Clalit Health Services during the years (2000-2018). Diagnosis of all disorders was made by specialist physicians. Results: 117,022 consecutive non-selective allergic children diagnosed with one or more allergic disorder (asthma, rhinitis, conjunctivitis, skin, food, or drug allergy) and 116,968 non-allergic children were enrolled to our study. The mean follow-up period was 11 ± 6 years. The presence of allergic disorders in early childhood (mean age of allergic diagnosis 4.5 ± 4.3 years) in boys as well as in girls, significantly increased the risk to develop ADHD (O.R 2.45, CI 2.39-2.51; $P < 0.0001$), ASD (O.R 1.17, CI 1.08-1.27; $P < 0.0001$) or both ADHD+ASD (O.R 1.5, CI 1.35-1.79; $P < 0.0001$). Children with more than one allergic comorbidity revealed a much higher risk. In a multivariable analysis (adjusted for age at study entry, number of yearly visits and gender) the risk of allergic children to develop ADHD and ADHD+ASD, but not ASD alone, remained significantly higher. Conclusion: Allergic disorder in early childhood significantly increased the risk to develop ADHD, and to a less extent ASD, in later life.

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ABSTRACT:

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Conclusion: Allergic disorder in early childhood significantly increased the risk to develop ADHD, and to a less extent ASD, in later life.

KEYWORDS:

pediatric allergic disorders, risk factor, ADHD, ASD, gender.

INTRODUCTION

Allergic disorders including allergic dermatological diseases especially atopic dermatitis (AD), rhinoconjunctivitis, asthma, food, and drug allergies are common chronic morbidities in pediatric patients. The prevalence of allergic diseases is constantly increasing in the last decades especially in high developed countries.¹ Though the exact pathogenesis of allergic disorders is not yet defined, it appears that genetic and environmental factors play a role in their development.² In addition to physical discomfort, chronic allergic disorders in early childhood may cause mental and behavioral problems.³ Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder characterized by inattention and hyperactivity that appear before to age of 12.⁴ The prevalence of ADHD in American population (<18 years) is about 9-12%.⁵ A study from Israel reported ADHD prevalence of 15.2%.⁶ Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by deficits in social interaction, language communication with

repetitive problems.⁴ Its prevalence of in children is about 2.47%, in the USA,⁷ whereas an Israeli study reported a prevalence of 0.65%.⁸ ADHD as well as ASD are more common in boys compering to girls.⁵⁻⁷ In some pediatric patients the symptoms of ADHD and ASD overlap, thus they have features of both disorders.⁹

As was shown for allergic disorders,¹ the prevalence of ADHD and ASD is steadily increased over the past decades.⁵⁻⁸ Furthermore, as was reported for allergic disorders,² genetic and environmental factors were shown to play a role in the pathogenesis of ADHD and ASD.¹⁰⁻¹³ Indeed, several studies did investigate the association between allergic disorders and ADHD and/or ASD with controversial results.¹⁴⁻²⁶ Differences in size of the studies, follow-up period and diagnostic criteria which were used in the various studies as well as the specific types of allergic disorders that were investigated are most probably the causes for the conflicting reports.

We, therefore, conducted a very large cohort study (about 240,000 pediatric patients) with a long follow up period (from birth to 18 years of age) of consecutive non-selective allergic (rhinitis, conjunctivitis, asthma, food, drug, and skin allergy) and non-allergic patients in order to define the relationship and the association between allergic disorders (all allergic disorders and each one separately) and the development of ADHD, ASD, or both neurological disorders.

PATIENTS AND METHODS

Data Sources

In the present retrospective study, we used the pediatric (0-18 years of age) database of Clalit Health Services which is the largest health care provider in Israel during the years 2000-2018. The database contains comprehensive information of all insured subjects including demographic characterizations, dates and details of all hospitalizations and all clinical visits with diagnosis (for each clinical visit/hospitalization) which were coded according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CD). The follow up period was defined from the date of the first to the date of the first to the date of last clinic visit reported for each patient.

We intend to enroll to the present study a large number of consecutive nonselective pediatric subjects - 120,000 subjects with a diagnosis of allergic disease designated as "allergic patients" and 120,000 control subjects without any diagnosis of allergic disease - "non-allergic patients" from that database.

Allergic disease was defined in the present of one (or more) of the following: asthma (ICD-9-CM code 493) diagnosed by pulmonologist, allergist or pediatrician; allergic rhinitis (ICD-9-CM code 477) diagnosed by allergist, pediatrician or otolaryngologist; allergic conjunctivitis (ICD-9-CM code 372) diagnosed by ophthalmologist, allergist or of pediatrician; skin allergy including atopic dermatitis (ICD-9-CD code 691,692,708) diagnosed by dermatologist, allergist, or pediatrician; food allergy (ICD-9 CM code 693) diagnosed by allergist; drug allergy (ICD-9 CM code 995) diagnosed by allergist or pediatrician. ADHD (ICD-9-CM code 314) and ASD (ICD-9-CM code 299) where diagnosed by pediatric psychiatrics or pediatric neurologists according to the current version of the diagnostic and statistical manual of mental disorders (the DSM-5).²⁷

ETHICAL APPROVAL:

The study was approved by the Clalit Health Services Ethics Committee in Israel, and was conducted in accordance with all rules of the Declaration of Helsinki.

Statistical analysis

Data is presented as mean \pm standard deviation (SD). For between group comparisons the independent t-test was used for continuous variables and the Pearson Chai-squared test for categorical variables. We performed, first, univariable analysis to calculate the unadjusted odds ratios (OR) and the 95% confidence intervals (CI) of allergic patients to develop ADHD, ASD or both. (Tables 1, 2, 3; Figure 1). To control for possible confabulations, a multivariate logistic regression analysis adjusting for age at study entry, number of yearly visits per patient and gender was performed (Model 1), (Table 4). A two-tailed p-value equal or less

than 0.05 was considered statistically significant. All data processing and statistical analysis were performed with Statistical Package for Social Science (SPSS 27).

RESULTS

234,170 pediatrics patients (119,874 males, 114,323 females) were enrolled to our study. During the time of the study (2000-2018), a total of 23,690,318 clinical visits (including hospitalizations) were recorded. The mean ($\pm SD$) number of yearly visits per patient was 10.3 ± 10.7 and the mean ($\pm SD$) follow-up period, for all enrolled patients was 11 ± 06 (range 2-18) years.

117,022 patients were diagnosed with at least one allergic disorder during the time of the study ("allergic patients") whereas the other 116,968 control patients were not diagnosed with any allergic disorder ("non-allergic patients"). As can be seen in Table 1, allergic skin diseases, conjunctivitis, and asthma, were the most prevalent allergic disorders (49.6%, 41.5% and 32.8%, respectively). About 40% of our allergic patients had two or more types of allergic disorders (Table 1). During the years of the study, 33,008 of our patients (14%) were diagnosed with ADHD, 2341 (0.99%) with ASD and 816 (0.34%) with both, ADHD and ASD (Table 1).

As can be seen in Table 1, significantly more pediatric patients with a diagnosis of at least one allergic disorder, compared to the non-allergic group of patients, were also diagnosed with ADHD (19.3% Vs. 8.9%; $P < 0.0001$), with ASD (1.1% Vs. 0.9%; $P < 0.0001$) or with both, ADHD and ASD (0.4% Vs. 0.3%; $P < 0.0001$). The vast majority of those patients (95% of ADHD and 97% of ASD patients) were diagnosed with one or more allergic disorders prior to their neurological diagnosis. Furthermore, the mean age of the patients at the time of their first allergic disorder diagnosis (4.5 ± 4.3 years) was lower than the ages of ADHD (8.5 ± 3.4 years), ASD (5.1 ± 3.5 years) and both ADHD and ASD (5.0 ± 2.9 years) diagnosis. Therefore, we investigated whether allergic disorder in early childhood is associated with the development of ADHD, ASD or both disorders in later life. The presence of any (one or more) allergic disorder significantly increased the risk of those pediatric patients to develop ADHD (OR 2.25; 95% CI 2.39-2.51), ASD (OR 1.17; 95% CI 1.08-1.27) or both, ADHD and ASD (OR 1.56; 95% CI 1.35-1.79) (Table 1). Interestingly, the mean age at the time of ADHD or ASD diagnosis was similar in the allergic and non-allergic group of patients (Table 1).

Table 2 clearly demonstrates that any allergic disorder (evaluated separately) significantly increased the risk of the develop ADHD as compared to the risk observed in non-allergic patients. The early diagnosis of rhinitis and conjunctivitis was associated with the highest risk to develop ADHD (OR 3.958; 95% CI 3.801-4.122 for rhinitis and OR 3.36; 95% CI 3.53-3.74 for allergic conjunctivitis). Early diagnosis of skin, drug and especially food allergy were associated with a significant risk to develop ASD. All types of allergic disorders were significantly associated with an increased risk to develop both, ADHD and ASD, except for drug allergy that almost reached statistical significance (Table 2).

We further investigated the association between early diagnosis of allergic disorders and the development of ADHD, ASD or both neurological disorders. To this end, we studied the effect of the number of allergic disorders (for each patient) on the risk to develop ADHD or ASD. As can be seen in Figure 1A, the risk to develop ADHD, significantly increased in patients with several allergic comorbidities. Thus, a patient with five or six allergic disorders demonstrated higher risk to develop ADHD as compared to patients without any allergic disorder or with only one allergic disease. Similar significant results were observed for allergic patients that develop both disorders (ADHD+ASD) (Figure 1C). The association between the number of allergic disorders and the development of ASD was not significant except for patients with six allergic comorbidities that demonstrated significant high OR as compared to the other patients (Figure 1B)

More boys (53.4%) than girls were recruited to our study. Furthermore, both ADHD and ASD are more common in boys.⁵⁻⁷ Therefore, we further evaluated the impact of gender on the association between allergic disorders and the development of ADHD and ASD. Indeed, as can be seen in Table 3, more boys than girls in our study were diagnosed with ADHD and ASD regardless to the presence of any allergic disorder. Nevertheless, the OR to develop ADHD or ADHD with ASD were similar in both genders. The OR to develop ASD alone was significant for boys (1.13; CI 1.03-1.24) but it did not reach statistical significance

in allergic girls (Table 3).

To ensure that allergy in early childhood is an independent risk factor for the development of ADHD, ASD or both disorders, we further preformed a logistic regression multivariate analysis adjusted for gender, age at study entry and the number of yearly visits per patient (Model 1). As can be seen in Table 4, the presence of allergy was shown to be an independent risk factor to develop ADHD (OR 2.08; 95% CI 2.03-2.15) or the combination of both, ADHD and ASD (OR 1.19; 95% CI 1.02-1.38). Although early childhood allergy was shown to be a significant risk factor for ASD development univariable analysis (Tables 1, 4), in the multivariable analysis (Model 1), it did not reach statistical significance (Table 4).

DISCUSSION

The present study demonstrates significant association between various allergic disorders (rhinitis, conjunctivitis, asthma, drug, and food allergy) in early childhood and the development of ADHD. The association with ASD was less significant. The presence of several allergic comorbidities (in one patient) further increases the risk to develop those neurobehavioral disorders.

In a very large (117,022) cohort of pediatric allergic (with one or more of the following: asthma, rhinitis, conjunctivitis, skin, food, and drug allergy) and non-allergic (116,968) patients from rural and urban communities, we were able to demonstrate significant association between allergic disorders (one or more) in early childhood and the development of ADHD or ASD (Table 1). The OR for ADHD (2.45) and ADHD+ASD (1.56) were higher than for ASD (1.17), but still the later was statistically significant in a univariate analysis. A dose dependent relationship was observed, thus as was previously reported,^{17,28} the risk to develop ADHD or ASD increased in children with several (more than one) allergic comorbidities (Figure 1). The latter, further support the link between allergic disorders and ADHD/ASD. The large number of enrolled patients, the long follow up period (from birth to 18 years of age), the assessment of various allergic comorbidities which were diagnosed by specialist physicians contribute to the strength and validation of our study.

Most previous studies investigated the association of a single allergic disorder,^{15-17,29-33} or up to three allergic comorbidities,^{14,23,24,26,28,34,35} and ADHD/ASD. To the best of our knowledge, the present study is the first study which enrolled children with up to six allergic comorbidities (Table 1) including drug allergy that was not previously studied. Moreover, whereas most previous studies reported the association between allergic disorders and ADHD or ASD,^{15,16,29,31} we investigated the link to ADHD and ASD (or both ADHD+ASD) using our large pediatric cohort, with the same methodological and statistical analysis that add to the validity of our findings.

The presence of each allergic disorder (studied separately) significantly increased the risk to develop ADHD or ADHD+ASD. The fact the association between drug allergy and ADHD+ASD (OR 1.7; 95% CI 0.95-3.03) did not reached statistical significance is most probably due to the relatively low number of patients with drug allergy that were enrolled to our study. The highest OR was observed for children with rhinitis and conjunctivitis (OR of 1.93; 95% CI 1.51-2.47 and 1.86; 95% CI 1.58-2.2; respectively) (Table 2). Although the presence of one or more allergic disorder was significantly associated with the development of ASD (Table 1), when studied separately only skin, food and drug allergy were found to be significant with OR's that were lower compared to the risk (OR) to develop ADHD (Table 2).

The prevalence of ADHD and ASD, diagnosed by pediatric psychiatrics or neurologists, in our study (Table 1, 3), is similar to previous reports.⁵⁻⁸ Moreover, as was previously demonstrated,⁵⁻⁷ more boys than girls were diagnosed with ADHD or ASD (Table 3). Allergic boys and girls revealed similar significant risk to developed ADHD or ADHD+ASD, whereas only boys demonstrated significant risk to develop ASD alone (Table 3). Indeed, after adjusting for age at study entry, number of yearly visits per patient and gender (Model 1) (Table 4), the risk of allergic children to develop ADHD or ASD +ADHD as compared to non-allergic children was significantly higher (OR of 2,08 and 1.19; respectively) whereas their risk to develop ASD alone was not significant in the multivariable analysis (Table 4).

Several previous studies did not find significant association between allergic disorders and the development

of ADHD^{15,17} or ASD,^{25,29}. However, most studies that were done in different parts of the world provide evidence for high risk of pediatric allergic patients to develop ADHD^{17,24,28,30–32} or ASD^{14,17,23,28,32} regardless to the ethnicity of the enrolled patients. A meta-analysis by Schans et al,²⁶ reported that asthma, rhinitis, and eczema were independent risk factors for ADHD development which is similar to our observation. Interestingly, in contrast to our observations (Tables 1, 2, 3, 4), two studies^{17,28} reported that the risk of allergic children to develop ASD was higher than their risk to develop ADHD. Differences in methodology (e.g. cohort type and size, follow up period and mode of diagnosis: self-report Vs. physician) and in the statistical evaluation are most probably the reason for the conflicting results.

There are several possible mechanisms, not mutually exclusive, for the association between allergic disorders (Table 1, 2, 3, and 4) and ADHD or ASD. First, allergic disorders and ADHD and ASD may have common genetic and environmental factors that increase the co-occurrence of those disorders. The high rates of ASD in children of mothers with allergic disorders³⁶ and the increased risk for allergic disorders in siblings of ASD patients,³⁷ may support the above mechanism. Indeed, genetic links between allergic diseases and ASD³⁶ or ADHD^{10,38} were reported. In addition, dysregulation of tryptophan and serotonin metabolism was reported to play a role in the pathogenesis of allergic disorders as well and in ADHD³⁹ and ASD.⁴⁰ The fact that we (Table 1), as well as others¹⁷ had demonstrated that allergy preceded the development of ADHD or ASD may point to other mechanism(s). Mast cell activation, high levels of inflammatory cytokines (especially Th2 cytokines) and chemokines (CCXL8, CCL2) observed in patients with allergic disorders can cause neuroimmune microglial and mammalian Target of Rapamycin (mTOR) activation, brain inflammation and neurobehavioral disorders.^{11,13,41,42} In addition, stress, fear (especially in food and skin allergy) and sleep disturbances (observed in allergic children) may also play a role in the pathogenesis of ADHD or ASD. Schmitt et al suggested that the usage of antihistamine agents that pass the brain blood barrier (in early childhood) may contribute to the development of the neurobehavioral disorders.¹⁶

The main limitation of our present study is its retrospective nature rather than a prospective controlled study that may give more valid results. Our study does not provide genetic or environmental data which may be potential confounders. In addition, the prevalence of allergic disorders as well as ADHD or ASD in our study might be underestimated since only those who sought medical services were recruited. Nevertheless, our study presents a very large number of pediatrics patients (237,170; Table 1) from urban and rural areas with a long follow up period (11±0.6 years). Moreover, the diagnosis (allergic, neurological) in our study, was made by specialist physicians, rather than by self or parent reports, leading to a high diagnostic validity. Interestingly, Sohn et al reported recently that individuals with developmental disorders had higher odds of self-reported allergic disease but not of allergic sensitization to foods or environmental allergens.⁴³ The fact that the diagnosis of all diseases, allergic as well as ADHD/ASD, in our study were made by specialist physicians overcome such a confabulation. Finally, we investigated the association between the presence of six allergic disorders (together and each one separately), and the development of ADHD or ASD (Tables 1, 2, 3, 4). Taken together, our study provides solid evidence supporting the association between allergic disorders and ADHD/ASD.

The results of our study have clinical applications for physicians who take care of pediatrics patients. Treatment and reduction of sleep disorders, stress, and all kind of physical discomforts in allergic children, may (though it is not proved) reduce the development of neurobehavioral disorders such as ADHD and ASD. In addition, knowledge of the link and the association between allergic disorders and the development of ADHD or ASD will lead to early diagnosis and better treatment of allergic children with neurobehavioral symptoms.

In conclusion, our study provides strong evidence for the association between allergic disorders in early childhood and the development of ADHD. The risk of those children to develop ASD was less significant.

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KEY MESSAGE:

Early and effective treatment of allergic disorders, including sleep disorders, stress, and all types of physical discomforts found in allergic children, may reduce the development of neurobehavioral disorders such as ADHD and ASD.

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LEGEND TO FIGURE 1

The risk to develop ADHD (A), ASD (B) or both ADHD and ASD (C) in non-allergic patients (0 allergic comorbidities) was defined as 1. Concomitantly with the number of allergic comorbidities per patient (from 1 to 6), the OR to develop ADHD (A) or ADHD and ASD (C) also increased significantly. The number of allergic comorbidities per patient did not reveal significant effect on the risk to develop ASD (B). Allergic comorbidities per Table 1 (Asthma, rhinitis, conjunctivitis, skin, food and drug allergy).

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