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# Impact of allergy on children with Attention Deficit Hyperactivity Disorder

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## KEYWORDS

*allergy; attention deficit hyperactivity disorder; skin prick; asthma; allergic rhinitis*

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## Summary

*Attention deficit hyperactivity disorder (ADHD) has gained importance lately, because it has become common and has caused serious implication to those affected. DSM-IV-TR defined ADHD by symptoms of inattention, hyperactivity and impulsivity (1).*

*Studies estimated that 4% to 8% of children worldwide have ADHD, which is more prevalent in boys than girls by three folds (2). In Egypt, the prevalence raised to 9.4% (3).*

*There are many speculations about the possible relationship between ADHD and allergy, owing to the fact that ADHD children had allergic disorders. It is putative that ADHD might be a complication of allergy, as it was found that allergic reactions led to a sequence of imbalanced cholinergic/adrenergic activity in the central nervous system (4). On the other hand, ADHD can occur secondary to side effects of antiallergic drugs (5).*

*The pathogenesis of allergy and ADHD both rely on gene-environment interaction, which is complex in nature (6).*

*Surprisingly, ADHD and allergy share the hypersensitivity phenomenon. When exposed to certain stimuli which are tolerated by normal subjects, a sequence of symptoms occur. As inhalants like mite or ingestants like milk can trigger an allergic reaction, certain foods and pollens can activate ADHD symptoms (7).*

*Due to this hypersensitivity concept in pathogenesis of both allergic disease and ADHD, integrated evaluation, proper diagnosis, prevention and management should be revised and put in consideration to improve quality of care of these patients (5).*

*Therefore, the aim of this work was to investigate the percentage of allergic conditions among clinically diagnosed children with ADHD, and to study the effect of allergy on symptom patterns, severity and its association with demographic variables in ADHD children.*

*Secondary outcomes were to detect the most common allergens in ADHD children with concurrent allergic disorders.*

## Subjects and methods

This case-control study included 127 ADHD children and 60 healthy children. The patients were recruited from the Outpatient Clinic of the Child Psychiatry, Institute of Psychiatry, Faculty of Medicine in Ain Shams University, Cairo, Egypt, over a six month period from September 2014 to March 2015. The

patients were then referred to the Allergy and Clinical Immunology Clinic for further assessment for allergic diseases. The clinics are located in eastern Cairo and serve as catchment area for about a third of greater Cairo. The Clinic serves both rural and urban areas, including areas around greater Cairo as well. The age of patients ranged between six and twelve years. They were diagnosed according to DSM-IV criteria (8). Patients with

co-morbid neuropsychiatric disorders, below average IQ, and chronic illnesses were ineligible for the study. An informed consent was taken from all guardians of the participants prior to enrollment in this study. The study was approved by the Ain Shams Medical Research Ethics Committee.

Participants were subjected to the following:

1. detailed history taking and full general examination for exclusion of any medical condition that might interfere with the process of the study.
2. psychiatric assessment using (M.I.N.I. Kid) for diagnosis of ADHD and exclusion of other psychiatric co-morbidities in the patient and control group. There were two screening questions. If the patient/informant responded positively to one or both of the screening questions, more detailed symptom questions were asked (9). The version used in this study was the Arabic version and it was translated into Arabic language. In addition, the reliability and validity tests were done (10).
3. IQ assessment using Wechsler Intelligence Scale for Children (WISC) to exclude children with below average IQ. The version used in this study was the Arabic version. It was translated into Arabic language and the reliability and validity tests were done (11).
4. assessment of ADHD severity using Conners' parent rating scale-revised, long version. Its main use was assessment of the severity of ADHD, response to treatment, follow up studies, and DSM-IV diagnostic correspondence (12).
5. assessment for allergy. Both the patients' group and the control group were referred to the Allergy and Clinical Immunology Clinic of Ain Shams University, and were subjected to:
  - a) history for allergy and clinical assessment, which included previous diagnosis of allergy, atopic manifestations of the disease, history of food allergy or food induced attacks, past history of illnesses, immunizations, history of child being breastfed or on artificial milk, and family history of allergy.
  - b) Skin prick test, puncturing the skin with a calibrated lancet (1 mm) held vertically, or a hypodermic needle or blood lancet at an angle of 45°, and introducing a drop of diluted purified allergen. All patients were also introduced with prick of a drop of histamine as positive control, and a drop of normal saline as negative control. An itchy wheal should develop at the histamine puncture site within 10 minutes. Test solutions were standardized to give a mean wheal diameter of 6 mm. The maximum or mean diameter of the wheals to various allergen extracts, including mites, moulds, and mixed pollens extracts, were read at 15 minutes. A wheal of 3 mm or more in diameter was considered to represent a positive response (indicating sensitization to the allergen) (13).

- c) open food elimination challenge to common food allergens including milk, egg, fish, nuts, wheat, maize, chocolate and banana. After elimination of the food tested for two weeks, re-introduction of the food was done in very small amounts with gradual increase in amount until allergic symptoms appear.
- d) serum total IgE concentration (IU/mL) was evaluated using the total IgE enzyme immunoassay (ELISA) kit (DRG International Inc., USA), according to the instructions of the manufacturer. The minimum detectable concentration was 5 IU/mL. The normal limit of total IgE in children was 50 IU/ml.

#### *Statistical analysis*

Data was collected tabled and statistically analyzed using SPSS version 16. The sample size was determined by the ethic committee, based on the following assumptions: alpha error = 0.0500 (two-sided), power of study = 0.8000, and percentage of positive prick test in ADHD = 0.6700. Therefore, the estimated required sample size was = 100. Parametric data were expressed as means  $\pm$  SDs and non-parametric data were expressed as number and percentage. Comparison of data was done using Student's t-test for parametric data and chi-square test for non-parametric data. Analysis of variance (ANOVA) was used to analyze the differences between groups. Two tailed p value of  $> 0.05$  was insignificant,  $p \leq 0.05$  was significant,  $p \leq 0.01$  was highly significant and  $p < 0.001$  was very highly significant.

#### **Results**

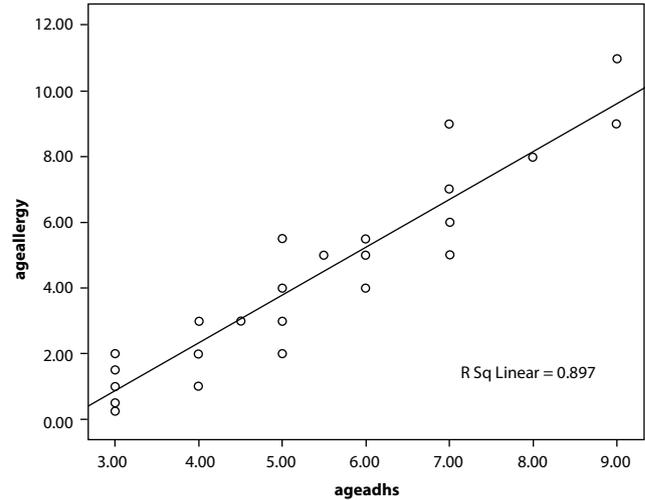
One hundred and twenty-seven children were enrolled. Twenty-seven patients dropped out of the study due either presence of co-morbidities or refusal to continue in the study, with a total of 100 male and female patients, of whom 83 of the children were males (83%) and 17 were females (17%) with male to female ratio 4.8:1 in the ADHD group. The control group consisted of 60 healthy children of whom 47 male (78.3%) and 13 female (21.7%) with male to female ratio 3.6:1 without significant statistical difference between the ADHD and the control ( $\chi^2 = 0.536$ ,  $p = 0.46$ ). The mean age was 8.54 ( $\pm 1.9$ ) years in ADHD patients and 8.77 ( $\pm 1.82$ ) in healthy control ( $p = 0.62$ ) without significant statistical difference. Among the ADHD patients, most of the children (86%) lived in urban areas, while only 14 children (14%) lived in rural areas, and the rest of the children (86%) lived in urban areas. 35 children (35%) were clinically diagnosed to have allergy. The mean age of onset of ADHD was 6.0 ( $\pm 1.5$ ) years, while the mean age of onset of allergy was 4.0 ( $\pm 2.6$ ) years. 36 (36%) of the total sample had positive family history of allergy. Positive skin prick test was found in 16 (16%) of patients and 3 (5%) of the controls ( $p$  value 0.037), 45 (45%) of the patients and 11 (18%) of controls showed high total IgE ( $p$  value 0.0006).

Patients were divided into two groups according to allergy workup into allergic and non-allergic groups. There were no statistically significant differences when analyzing the socio-demographic data between the two groups, except for a statistically significant difference in past history of tonsillectomy and sinus problems, in the allergic group (as shown in **table I**).

According to the allergy-immunology questionnaire; 16% (16 patients) of the ADHD group and 5% (3 individuals) in the healthy control group had SPT +ve results to one or more of the allergens examined ( $\chi^2 = 0.15$ ,  $p = 0.7$ ). The most common allergic diseases in ADHD group were mixed allergic diseases 25% (the most common was allergic rhinitis and bronchial asthma, followed by bronchial asthma and urticaria, then allergic rhinitis and urticaria), followed by urticaria 8%, then asthma 2.0%, while there were no ADHD cases with pure atopic eczema or allergic rhinitis. Sensitization to mixed allergens comprised the vast majority of cases, followed by aeroallergens including mites and pollens and lastly food allergens (wheat, nuts and banana). There was strong positive correlation between onset of allergy symptoms and onset of ADHD symptoms ( $r$  value = 0.947, where the correlation is significant at  $r$  value = 0.01) as shown in **figure 1**.

The co-existence of allergy in ADHD children revealed a statistically significant difference with type of ADHD (combined, DSM- IV hyperactive-impulsive, DSM-IV inattentive), se-

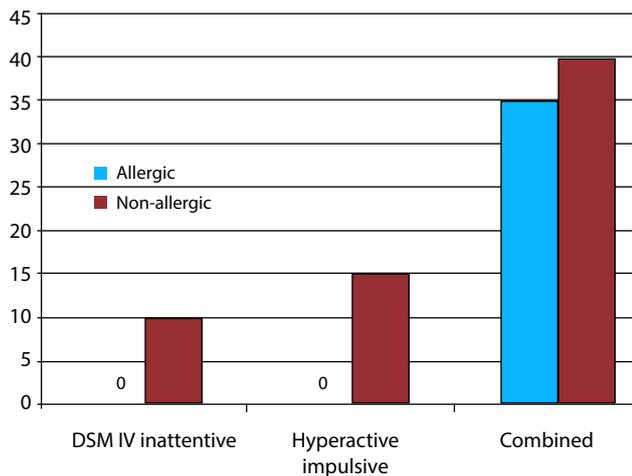
**Figure 1** - Correlation between onset of allergy and onset of ADHD symptom.



verity of ADHD symptoms (oppositional, cognitive problem, DSM IV inattentive, lability, hyperactivity, DSM IV hyperactive-impulsive, psychosomatic, Conner's global index: total, and DSM-IV total score) and the presence of co-morbid psy-

**Table I** - Sociodemographic data of both groups.

Socio-demographic data		ADHD children		Total	p-value (significance)
		allergic	non allergic		
gender	male	count	31	52	p = 0.2 non significant $\chi^2 = 1.1$
		%	88.6%	80.0%	
	female	count	4	13	
		%	11.4%	20.0%	
age (years)	mean	8.15	8.22	p = 0.867 non significant $\chi^2 = 0.17$	
	stand. deviation	± 1.89	± 2.1		
residence	urban	count	29	57	p = 0.5 non significant $\chi^2 = 0.4$
		%	82.9%	87.7%	
	rural	count	6	8	
		%	17.1%	12.3%	
past medical history	none	count	26	60	p = 0.03 significant $\chi^2 = 6.7$
		%	74.3%	92.3%	
	previous surgeries	count	8	5	
		%	22.9%	7.7%	
	sinus problem	count	1	0	
		%	2.9%	.0%	

**Figure 2** - Impact of allergy on ADHD type.

chiatric symptoms (anxiety, oppositional defiant) (as shown in **figure 2** and **table II**).

The odds of those who had positive skin test to those who had more severe Conner's global total score was 34.25 (95% CI, 3.7 to 315) times to those who had negative skin prick test, which was statistically highly significant (Wald  $\chi^2$  (1) = 9.7,  $p$  = 0.002). While those who had positive skin test had a more severe Conner's DSM IV total score which was 18.3 (95% CI, 2 to 167.7) times to those who had negative skin prick test, which was also statistically highly significant (Wald  $\chi^2$  (1) = 6.6,  $p$  = 0.01).

## Discussion

ADHD and allergic disorders are both hereditary diseases involving gene-environment interactions that may share a common biological background. Although children with ADHD have increased prevalence of allergic diseases, studying the association between allergic disorders and ADHD has received less attention (14).

Schmitt et al. (2010), identified and systematically reviewed 20 epidemiological studies that investigated the relationship between atopic disease and ADHD/ADHD symptoms.

Many studies suggested a positive association between eczema and ADHD (15,16). Furthermore, studies by Romanos and colleagues found an association between asthma and ADHD (17). Other published studies found no relation between ADHD and allergic rhinitis (18). This was in agreement with Schmitt et al., who found weak to moderate strong association between asthma and ADHD; however, they found no relationship between ADHD and allergic rhinitis (19).

In contrast to the previous studies, recently two cross sectional studies found that allergic rhinitis has a strong association with ADHD (20). Suwan et al. (2011), revealed that the most common allergic disease was allergic rhinitis (21). Also, Brawley et al. (2004) found that most patients with ADHD had atopic manifestations and skin prick test findings to common aeroallergens, which were consistent with a diagnosis of allergic rhinitis (22).

Camfferman et al. found a significant association between allergic eczema, allergic rhinitis and allergic conjunctivitis, and to a lesser extent with asthma in association with ADHD (23).

**Table II** - The impact of clinically diagnosed allergy on ADHD severity of symptoms of ADHD.

			mild	moderate	severe	Total	significance
Conners ADHD index	ADHD children	allergic	0%	18%	17%	35%	$p$ = 0.018
		non allergic	13%	27%	25%	65%	$\chi^2$ = 8.040
Conners global index: restlessness-impulsive	ADHD children	allergic	0%	14%	21%	35%	$p$ = 0.069
		non allergic	5%	34%	26%	65%	$\chi^2$ = 5.346
Conners lability	ADHD children	allergic	0%	0%	35%	35%	$p$ = 0.001
		non allergic	9%	50%	6%	65%	$\chi^2$ = 77.486
Conners global index	ADHD children	allergic	0%	16%	19%	35%	$p$ = 0.03
		non allergic	10%	31%	24%	65%	$\chi^2$ = 6.998
Conners DSM-IV inattentive	ADHD children	allergic	0%	0%	35%	35%	$p$ = 0.001
		non allergic	13%	46%	6%	65%	$\chi^2$ = 77.486
Conners DSM-IV hyperactive-impulsive	ADHD children	allergic	0%	0%	35%	35%	$p$ = 0.001
		non allergic	2%	45%	18%	65%	$\chi^2$ = 47.750
DSM-IV total score	ADHD children	allergic	0%	12%	23%	35%	$p$ = 0.001
		non allergic	18%	24%	23%	65%	$\chi^2$ = 14.286

Conversely, only one cross-sectional study did not observe the association (24).

In our study we found a statistically significant difference between ADHD patients and the healthy control group, regard both the SPT reactivity and the serum total IgE levels, and that the most common allergic diseases were mixed allergic diseases 25%, followed by urticaria 8%, then asthma 2.0%, while there were no ADHD cases with pure atopic dermatitis, allergic rhinitis or allergic conjunctivitis.

The present study revealed that sensitization to mixed allergens comprised the vast majority of cases, followed by aeroallergen then food allergen; these results matched the results of Suwan et al. (2011), that sensitization to aeroallergens was higher than for food allergens in both ADHD and healthy control groups. In agreement with previous studies, food allergen sensitization was most prevalent during the first years of life, diminishing in prevalence in later childhood. Conversely, the risk of sensitization to aeroallergens increased with age (25).

As regards the most common allergens causing sensitization, we found that mites comprised the commonest allergen, followed by pollens. These results are also consistent with those reported in an earlier study conducted by Suwan et al. (2011), who reported that the commonest allergen in both ADHD and healthy control groups was house dust mites. This result supports the finding from previous studies that house dust mites are the most important allergens in Thailand.

The mean age of the ADHD group in the current study was 8.54 years. The male to female ratio was about 4.8:1. Tsai et al. (2013) found a strong association between atopic disease below 7 years and ADHD (26). Also, these results matched the findings of Genuneit et al. (2014), who analyzed data of a population-based, prospective birth cohort study among 770 children included at baseline in 2000/2001 with follow-up up to age 11, and found that Atopic eczema (AE) was associated with an increased risk of subsequent ADHD only within the first few years after AE diagnosis, and possibly to a greater extent in early compared to later childhood (27). Despite the fact that most of our patients selected were above 7 years of age, according to the history of start of allergic disease and ADHD, we found that the earlier the age of onset of allergy in these patients, the earlier the symptoms of ADHD happened to those prone. We also found that presence of family history of allergy affected significantly the onset of ADHD. Suwan et al. (2011) also found that positive atopic family history was significant in ADHD children.

There are several explanations for the observed co-morbidity between early age of onset of ADHD and atopic disease. Some experimental evidence supported a theory of a link of both diseases, in a way, through neuro-immune pathways. The brain is still immature in early life, allowing allergic induced cytokines to pass and affect the ADHD-relevant brain circuits (28).

It is noteworthy that allergic ADHD patients in this study had history of tonsillectomy. Several studies demonstrated an association between allergy and tonsillar hypertrophy. Moreover, family history of allergy and clinical allergic disorders are related to early onset of tonsillar hypertrophy (29). This raises the question should children with history of tonsillar hypertrophy be evaluated for allergy and in turn screened for ADHD, and furthermore what is the response of allergy and ADHD symptoms after tonsillectomy.

The results of the current study found that the co-existence of allergy in ADHD children was significantly associated with severity of symptoms (oppositional, cognitive problem, inattentive, lability, hyperactivity, hyperactive-impulsive), type of ADHD (combined, hyperactive-impulsive, inattentive), and the presence of co-morbid sub-threshold symptoms (anxiety, oppositional defiant). The present results agreed with those reported by Suwan et al. (2011), who found a strong association between the presence of allergy and the severity of ADHD symptoms and decreased response to psycho-stimulants. Shyu et al. (2012), reported that allergic children (including those with AR, bronchial asthma, atopic dermatitis) had a more severe symptom pattern and a higher prevalence percentage in ADHD than the general population, and the impulsivity took the upper hand more than inattention in the AR children.

The strengths in this study are that the study looked at the percentage of allergic conditions among clinically diagnosed children with ADHD and studied the effect of allergy on symptom patterns and severity. Also demonstrating the effect of age of onset of allergy and presence of positive family history is crucial in determining the progress of ADHD. Limitations is that the study did not cover the whole range of ADHD patient, and therefore a large scale cohort study is recommended. Therefore, assessment and understanding the relationship between ADHD and allergy is important for early and proper diagnosis of these patients. Performance of workup necessary as regards allergy and ADHD will provide correct management, decrease the use of psychostimulants and prevent worsening and non-responsiveness of the condition. Determination and avoidance of the culprit allergen, either airborne or food, may be a turn point in improvement of ADHD patient with allergic disease along with proper care and treatment of allergy symptoms. In addition, screening of siblings of patient may help in prevention and decrease incidence of the disease.

## Conclusion

Children with ADHD had an increased prevalence of allergic diseases. Allergic ADHD children had more severe ADHD symptoms (oppositional, cognitive problem, inattentive, lability, hyperactivity, hyperactive-impulsive) and more co-morbid sub-threshold disorders (anxiety, oppositional defiant). A bet-

ter relationship between atopic diseases and development of ADHD, especially at the biological, molecular and genetic level, is of significant public health relevance as it may lead to targeted treatments and improved preventive measures for those children with atopic disease who are at increased risk to develop ADHD.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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