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Risk of Attention-Deficit/Hyperactivity Disorder in Children with Atopic Dermatitis

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ABSTRACT Atopic dermatitis (AD) is a common, chronic, inflammatory, pruritic skin disorder that affects up to 20% of the children in Western countries. Attention-Deficit/Hyperactivity disorder (ADHD) has been reported to be more frequent in children with AD. The purpose of this study was to explore the risk for ADHD in our population of patients with AD**.** A population-based case-control study, using the medical database of Clalit Health Services (CHS), the largest healthcare provider organization in Israel. The study included 840 patients with AD between the age of 0-18 years and 900 age and gender frequency-matched patients without AD. The proportion of ADHD in patients with AD was 7.1% as compared to 4.1% in controls. ADHD was more frequent in boys with AD (9.6% vs. 5.2%, odds ratio (OR) 1.9, 95% confidence interval (CI) 1.1-3.2) but not in girls with AD (4.6% vs. 2.9% OR 1.5). In multivariate analyses, AD was associated with ADHD (OR 2.1, 95% CI 1.3-3.4). The current study demonstrated an association between AD and ADHD. This report and earlier observations emphasize the need for detection and treatment of ADHD in atopic patients.

KEY WORDS: atopic dermatitis, attention-deficit/hyperactivity disorder, allergy, eczema, pruritus, sleep disturbances

INTRODUCTION

Atopic dermatitis (AD) is a common, chronic, inflammatory, pruritic skin disorder that affects up to 20% of the children in the western countries (1). The eczematous, itchy skin leads to an "itch-scratch" cycle that in turn may cause sleep loss and psychosocial impairment in childhood (2-5).

Attention-Deficit/Hyperactivity disorder (ADHD) is a neurodevelopmental disorder that begins in childhood and manifests with difficulties in sustaining attention and modulating the level of activity with or without impulsive actions. ADHD is considered to be the most frequent psychiatric disorder in childhood, with prevalence of up to 15% in Western countries (6). It causes impairment of quality of life, psychosocial maladaptation, and economic burden through social services (6).

The association and comorbidity between atopic diseases and ADHD had been reported in recent years. Earlier studies failed to establish an association between atopy and ADHD (7), but accumulating data, including a systematic review by Schmitt (8) and other recent publications (9-12), have demonstrated a relationship between atopic diseases and ADHD.

The purpose of this study was to examine the association between AD and ADHD in Israeli children, using a population-based, case-control study, as comorbidities in AD may have different characteristics in different cultural or geographic populations.

PATIENTS AND METHODS

The study was designed as a retrospective case-control study using data mining techniques in the Clalit Health Services (CHS) database. CHS is the largest healthcare provider organization in Israel, serving a population of about 4 400 000 enrollees (13). CHS has a comprehensive computerized database with continuous real-time input from pharmaceutical, medical, and administrative computerized operating systems.

In the CHS database, the diagnoses of chronic diseases such as atopic dermatitis (AD) and attention deficit/hyperactivity disorder (ADHD) are based on data from hospital and primary care physician reports. These diagnoses are validated using a systematic methodology and proven to be accurate (14). The CHS perform the process of validation through logistic checks (such as comparing diagnoses from various sources) and by direct validation of the diagnoses by the treating physicians of each patient.

Study patients were defined as subjects with at least 1 documented diagnosis of AD in the medical records registered by the CHS dermatologist or pediatrician. The control group consisted of a computer-generated randomly selected age- and sex-matched list of subjects from the CHS database, excluding patients with AD, thus sampling the general population. Minor differences in sex and age distribution were corrected using multivariate analyses. Data available from the CHS database included body mass index (BMI), age, sex, comorbid diagnoses, socio-economic status (SES) and use of methylphenidate. According to the CHS regulations, prescriptions for methylphe-

Table 1. Baseline characteristics of the study population (N=1740)

Characteristic	Patients with atopic dermatitis (N=840)		Control patients (N=900)		P value
	N	%	N	%	
Age (years):					
Mean ± SD	9.48±3.65		10.84±3.81		
Median	9		10		<0.0001
Range	2-18		2-18		
Boys	426	50.7%	458	0.490	
SES:					
Low	241	35.0%	455	51.9%	<0.0001
Intermediate	257	37.4%	311	35.5%	
High	190	27.6%	111	12.7%	
	688		877		
BMI					
Mean ± SD	17.94±4.13		18.56±4.76		0.016
up to 18.5	367	65.0%	393	58.7%	
18.5-24.9 159	159	28.1%	212	31.7%	
25.0-29.9	27	4.8%	38	5.7%	0.200
30.0-34.9	4	0.7%	10	1.5%	
35.0-39.9	1	0.2%	4	0.6%	
40+	7	1.2%	12	1.8%	
	565		669		
Received Ritalin®	53	6.3%	34	3.8%	0.010
Received Concerta®	18	2.1%	15	1.7%	0.290
Received Ritalin or Concerta®	60	7.1%	37	4.1%	0.004

SD: Standard Deviation; BMI: body-mass index

Table 2. Atopic dermatitis (AD) and attention-deficit/hyperactivity disorder (ADHD) among boys (N=884)

Subgroups	N	ADHD in Atopic Dermatitis cases (n=426)	ADHD in controls (n=458)	OR (95% CI)	P value
All	856	41 (9.6%)	24 (5.2%)	1.92 (1.14-3.24)	0.009
Age					
1-4	48	0 (0.0%)	0 (0%)	-	-
5-14	722	33 (7.7%)	16 (3.5%)	2.16 (1.17-4.01)	0.009
15-18	114	8 (1.9%)	8 (1.7%)	1.97 (0.67-5.71)	0.163
SES					
Low	340	11 (2.6%)	7 (1.5%)	3.11 (1.17-8.25)	0.018
Intermediate	293	13 (3.1%)	12 (2.6%)	1.34 (0.59-3.05)	0.309
High	160	15 (3.5%)	4 (0.9%)	2.69 (0.85-8.54)	0.065
BMI					
up to 18.5	419	16 (3.7%)	10 (2.2%)	1.83 (0.81-4.14)	0.101
18.5-24.9	170	13 (3.1%)	8 (1.7%)	2.55 (0.99-6.52)	0.040
25+	39	4 (0.9%)	3 (0.6%)	2.93 (0.55-15.63)	0.194

SES: socio-economic status; BMI: body-mass index; OR: odds ratio; CI: confidence interval

nidate (Ritalin® or Concerta®) can be issued only after the diagnosis has been established by specialists in pediatric neurology or pediatric psychiatry. Thus, potential selection bias related to diagnoses of ADHD by general pediatricians could be excluded. SES and BMI were explored as potential confounding factors for AD and/or ADHD.

The distribution of background factors was compared between patients with and without AD using the chi-square test for categorical variables and t-test for age. The proportions of patients with ADHD were compared between the study groups in the entire study sample as well as in a stratified analysis based on age, sex, and other subgroups using the chi-square test. A logistic regression model was used to measure the association between AD and ADHD in a multivariate analysis. Statistical analysis was performed using SPSS software, version 12.

The study was approved by the Ethics Committee of the CHS.

RESULTS

The study included 840 patients with AD between the age of 0-18 years and 900 age- and sex-matched children without AD (Table 1). Descriptive analyses of the characteristics of patients with and without AD are shown in Table 1. Patients with AD were younger relative to the control group (mean ± Standard Deviation (SD): 9.48±3.65 years vs. 10.48±3.81 years, respectively; $P<0.0001$). Patients with AD were of lower BMI than controls (17.94±4.13 vs. 18.56±4.76, respectively; $P=0.016$) and were from higher SES ($P<0.0001$).

Overall, the proportion of ADHD was 7.1% in patients with AD as compared with 4.1% in the control group ($P=0.004$). Prescriptions for methylphenidate (Ritalin® or Concerta®) were issued more commonly to male patients with AD as compared to male patients in the control group (9.6% versus 5.2%, odds ratio (OR) = 1.9, 95% confidence interval (CI) 1.1-3.2, $P=0.009$) (Table 2). Although both medications were also given more frequently to girls with AD than in the control group, the differences did not reach statistical significance (4.6% vs. 2.9%, OR = 1.5, 95% CI, $P=0.138$) (Table 3).

In a multinomial logistic regression analysis, ADHD was associated with AD among boys (OR = 2.1, 95% CI 1.3-3.4, $P=0.002$). Furthermore, increasing age was associated with increased risk of ADHD by 1.1 (OR = 1.2, 95% CI: 1.1-1.2, $P<0.0001$) (Table 4). In contrast, SES and BMI were not associated with ADHD among boys after controlling for the same confounders.

DISCUSSION

The finding of a higher proportion of ADHD in our population are in accord with earlier reports of the association of AD with ADHD worldwide (9-12). The significant sex difference in the prevalence of ADHD in our population reflects the generally higher rates of ADHD among men worldwide. This could be explained by the fact that men have 3 to 4 times higher incidence rates of ADHD compared to women (15).

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Table 3. Atopic dermatitis (AD) and attention-deficit/hyperactivity disorder (ADHD) among girls (N=856)

Subgroups	N	ADHD in atopic dermatitis cases (n =414)	ADHD in controls (n =442)	OR (95% CI)	P value
All	856	19 (4.6%)	13 (2.9%)	1.58 (0.77-3.25)	0.138
Age					
1-4	20	0 (0.0%)	0 (0.0%)	-	-
5-14	688	12 (2.9%)	7 (1.6%)	1.74 (0.67-4.47)	0.176
15-18	148	7 (1.7%)	6 (1.3%)	1.80 (0.57-5.66)	0.232
SES					
Low	356	3 (0.7%)	7 (1.6%)	0.81 (0.20-3.21)	0.533
Intermediate	272	7 (1.7%)	3 (0.7%)	1.93 (0.74-11.60)	0.100
High	141	7 (1.7%)	3 (0.7%)	1.22 (0.30-4.95)	0.539
BMI					
up to 18.5	341	7 (1.7%)	2 (0.4%)	3.71 (0.76-18.15)	0.080
18.5-24.9	201	10 (2.4%)	8 (1.8%)	1.68 (0.63-4.46)	0.209
25+	64	1 (0.2%)	2 (0.4%)	0.77 (0.06-8.97)	0.664

SES: socio-economic status; BMI: body-mass index; OR: odds ratio; CI: confidence interval

The retrospective design of our study precluded detection of a definite causal relationship between AD and ADHD. It is plausible that the actual frequency of ADHD is higher in both groups, since at least 25% of children with ADHD do not receive any treatment for the disorder (16). Since patients that were not treated with methylphenidate were not regarded as having ADHD, our findings may underestimate the frequencies of ADHD in both groups. It is unlikely that patients with AD were more often prescribed therapy for ADHD while their skin disease is active, since the diagnostic criteria of ADHD mandate that "other mental or psychotic disorders that could account for the symptoms must be excluded". Therefore, frequency of ADHD may be even higher among patients with AD, as symptoms of attention deficit and hyperactivity could be regarded as related to the insufficiently controlled skin disease.

The age of patients with AD and ADHD was higher as compared with patients with AD but without ADHD. This difference may be attributed to the fact that the definition of ADHD in our study was based on prescription for the medication, which is commonly done at school age (17), while the diagnosis of AD is usually done early in infancy.

In our population, patients with AD were of higher SES. SES disadvantage is associated with higher risk for ADHD (18,19), while in our study the control group had lower SES and yet had a lower prevalence of ADHD. This may indicate that our findings underestimate the true prevalence of ADHD among children with AD.

The higher prevalence of ADHD could be related to the pruritus and sleep disturbances that are both common in AD. AD develops in early childhood and is frequently associated with pruritus and sleep disorder (2-4). Sleep disorder may affect memory, behavior, and the attention spectrum (2), indicating a potential causal risk factor for ADHD in AD. Since AD is a chronic inflammatory disease, the neuroimmune pathway theory may explain the association of ADHD and AD (20). Proinflammatory agents may penetrate the blood-brain barrier and activate behavioral and emotional neural pathways (21,22). Although the majority of patients with AD are usually only treated with topical steroids, some may need systemic courses of steroids that may induce hyperactivity (23). The effect of systemic and topical anti-inflammatory medications and antihistamines on mental health should be further investigated.

The strength of the present study is the use of a large population, including children of all ages, and using logistic regression analysis to control confounders such as BMI and SES. The major limitation of our study is that, due to the retrospective data mining design of the study, we could not correlate the severity of AD with the severity of ADHD symptoms, a matter that should be further investigated in a prospective study.

CONCLUSION

The current study demonstrated an association and comorbidity between AD and ADHD. This report and earlier observations emphasize the need for early detection and treatment of ADHD in atopic patients that may potentially facilitate management of ADHD.

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