
Common behavioral problems among children with asthma: Is there a role of asthma treatment?

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Background: An increased prevalence of behavioral problems has been described among children with asthma.

Objective: To investigate those associations between common behavioral problems and asthma, with an emphasis on the roles of medications used for asthma.

Method: We studied 409 children who had been followed-up in pediatric allergy clinics and 157 age-matched healthy controls. A diagnostic and statistical manual disorder–referenced symptom inventory was used to assess “attention deficit-hyperactivity disorder” (ADHD), “attention deficit” (AD), “hyperactivity and impulsivity” (HI), and “oppositional defiant disorder” (ODD) behavioral problems.

Results: The study group consisted of 409 patients (male: 251, female: 158), with a mean age of 9.0 ± 2.67 years, and the control group consisted of 157 children (male: 75, female: 82), with a mean age of 9.0 ± 2.86 years. Prevalences of AD, hyperactivity, ADHD, and ODD were not significantly different between the study and control groups. Among those patients receiving leukotriene antagonist (LA) drugs adjunctive to inhaled corticosteroids (ICS), duration of treatment was correlated with total scores calculated for hyperactivity ($P = .035$, $r = 0.432$), AD ($P = .044$, $r = 0.414$), ADHD ($P = .042$, $r = 0.418$), and ODD ($P = .032$, $r = 0.439$). Among patients with asthma, children with ODD had a significantly longer duration of LA+ICS use ($P = .024$) compared with those with no ODD. Patients with hyperactivity had a longer duration of ICS+LA use compared with those with no hyperactivity ($P = .009$). Patients with asthma receiving LA+ICS treatment had a higher risk for oppositional behavior (4.282 times compared with the control group [$P = .042$, confidence interval (CI): 1.542–15.949]) and 8.3 times compared with patients with asthma not using any drug ($P = .021$, CI: 1.419–48.543).

Conclusion: Rather than asthma itself, adjunctive use of ICS+LA therapy appears to be related with symptoms of common behavioral problems, including hyperactivity, AD, ADHD, and ODD and to increase the risk of ODD.

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INTRODUCTION

A number of studies have demonstrated a higher prevalence of psychiatric disorders in patients with asthma compared with that seen in the general population. Data generated from the World Mental Health Survey showed that, after adjusting for age and sex, those adults with asthma were more likely to have depressive and anxiety disorders.¹ In a population-based survey of 355,710 subjects that investigated the relationship between current asthma and poor mental health, for every incremental increase in days of poor mental health, there was a corresponding increase in risk of currently having asthma.² Studies on children have shown similar patterns. Data from

the National Survey of Children’s Health showed significantly higher ORs for developmental or behavioral problems in children with asthma. This association had a dose response relationship; the greater the severity of asthma, the higher the risk of behavioral problems.³

Studies of behavioral problems in asthma are confounded to some extent by the potential adverse effects of medications to treat this disorder. Apart from symptoms of asthma, a variety of medications used in its treatment have been reported to cause behavior-related side effects, including restlessness, sleep disturbance, headache, and emotional and mood lability.^{4–6} Interpreting the association of behavioral symptoms with severity of asthma is further complicated by the escalation of treatments with disease exacerbation. Identifying behavioral problems of children with asthma is essential for optimal disease control, because they can simply cause maladjustment and can decrease an asthma patient’s ability to self-monitor and comply with treatment, resulting in serious asthma complications.^{7–9}

In this study, we aimed to investigate some disruptive behavioral symptoms among children with asthma, particularly of attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) and to assess whether

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medications used to treat asthma have a role in those important psychiatric disorders of childhood.

METHODS

Study Population

The study group consisted of 409 children aged 6 to 17 years who had been followed-up for asthma in three different pediatric allergy clinics. The patients' conditions were classified as mild intermittent, mild persistent, or moderate persistent asthma. Two additional patients who had severe persistent asthma were not included in the analyses because of the small number of this subgroup. The control group consisted of 157 age-matched healthy children with no history of asthma, other allergic disorders, or any chronic disease, who were admitted to Yeditepe University Hospital for acute symptoms. Asthma was diagnosed according to guidelines for the diagnosis and treatment of asthma (GINA 2006 guidelines).¹⁰ Severity of disease was defined according to GINA guidelines as "mild intermittent," "mild persistent," "moderate persistent," or "severe persistent." Patients with intermittent asthma were treated with inhaled salbutamol or terbutaline on an "as needed" basis. Patients with persistent asthma who were assigned for an anti-inflammatory therapy were treated with inhaled budesonide/fluticasone for a daily total dose of 800 µg/500 µg for a month. At the end of 1 month, if an improvement was achieved, the dose was decreased to a total daily dose of 400 µg. During the follow-up period, the dose of medication needed for control of respiratory symptoms was adjusted to find the effective dose. No patient was treated with long-acting beta agonists.

Children who had a previous diagnosis of ADHD or a comorbid chronic illness were excluded. A structured questionnaire was completed by parents of all patients, requesting sociodemographic information (age, sex, education of parents, and family income), exposure to smoke, family history of psychiatric illness, prematurity, comorbid conditions, usage and duration of medications used for asthma (inhaled corticosteroids, leukotriene antagonist drugs), and duration of asthma. Duration of asthma was defined as the time elapsed after the diagnosis by a pediatric allergist. The study was approved by the Yeditepe University Ethical Committee. Written consent was obtained from parents of all participants.

Behavioral Assessments

The questionnaire contained statements about behavior, using a scale based on child and adolescent behavior disorders screening and assessment for the DSM-IV. This scale was developed on the basis of DSM-IV diagnostic criteria by Atilla Turgay,¹¹ and its validity and reliability studies have been done for Turkish children.¹² This scale included 41 questions; 9 for attention deficit, 9 for hyperactivity and impulsiveness, 8 for ODD, and 15 for conduct disorder. Each item was scored using the following scale: 0: none; 1: little; 2: some; 3: much. Each score was recorded into final score by the researchers as 0 or 1 point into "0," 2 or 3 points into "1." The final scores for each domain were added up to obtain

total scores. Diagnosis of a particular behavioral problem was made if the total score for that domain is 6 or higher, as hyperactivity, AD, or ODD. Diagnosis of ADHD was made if the criteria for both AD and hyperactivity were fulfilled.

Statistical Analysis

Results are presented as mean $\pm$ SD, median or number, and percentage of children as appropriate. Mann Whitney *U*-test, chi-square tests were used to determine the statistical significance of the differences between the two groups. Spearman correlation coefficient was used for the correlation analysis. The level of statistical significance was set at $P < 0.05$. Statistical analysis was performed by the SPSS 13.0 (Chicago, Illinois) computer program.

RESULTS

The study group consisted of 409 children (251 male, 158 female) with a mean age of 9.0 ± 2.67 years. The control group consisted of 157 children (75 male, 82 female) with a mean age of 9.0 ± 2.86 years. For patients with asthma, the mean duration of disease was 2.89 ± 2.13 years. Prevalences of behavioral problems were not significantly different between the study group and the control group (Table 1). The presence of behavioral problems was not associated with the age at onset of asthma symptoms.

Among the study group, 79.2% of patients were currently receiving antiasthmatic medications (90.4% inhaled corticosteroids, 2.2% leukotriene inhibitors, and 7.4% adjunctive inhaled corticosteroids [ICS]/leukotriene antagonist [LA]). When analyzing the associations between use of anti-asthma medications and presence of behavioral disorders, the prevalence of oppositional behavior was significantly different between the four groups ($P = .024$) (Table 2); it was highest among asthma patients receiving adjunctive ICS/LA drugs. Patients with asthma receiving adjunctive ICS+LA drugs had a 4.28 times higher risk for ODD than the control group ($P = .042$; confidence interval [CI]: 1.542–15.949). Patients with asthma receiving adjunctive ICS+LA drugs had 8.3 times higher risk for oppositional behavior than those with asthma who did not use any drug ($P = 0.021$, CI: 1.419–48.543).

Significant correlation was found between duration of LA use and hyperactivity scores ($P = .03$, $r = 0.390$). However, no significant correlation was found between the total scores calculated for each behavioral problem and the duration of ICS treatment.

Duration of adjunctive ICS+LA treatment was significantly longer in patients with hyperactivity compared with those without (24 months vs 12 months) and in patients with ODD compared with those without (24 months vs 12 months).

Patients with asthma diagnosed as having hyperactivity ($P = .009$) or ODD ($P = .024$) had a significantly longer duration of adjunctive ICS/LA treatment compared with those who did not have a diagnosis of hyperactivity or ODD. A significant correlation was found between the duration of adjunctive ICS/LA treatment and hyperactivity, attention def-

Table 1. Characteristics of Study and Control Groups

	Study group (n = 409)	Control group (n = 157)	P-value
Age (years)(Mean $\pm$ SD)	9.0 $\pm$ 2.67	9.0 $\pm$ 2.89	NS
Sex			
Female	158 (38.63)	82 (52.22)	NS
Male	251 (61.37)	75 (47.78)	NS
Duration of follow-up (years) (Mean $\pm$ SD)	2.89 $\pm$ 2.13	—	
Behavioral problems (n, %)			
Hyperactivity	65 (15.9%)	21 (13.4%)	NS
Attention deficit	28 (6.8%)	5 (3.2%)	NS
ADHD	11 (2.7%)	3 (1.9%)	NS
ODD	32 (7.8%)	7 (4.5%)	NS
Duration of treatments (mos) (Mean $\pm$ SD)			
ICS monox	22.93 ($\pm$ 15.8)	—	
LA monox	14.28 ($\pm$ 15.6)	—	
Adjunctive LA and ICS	13.12 ($\pm$ 7.2)	—	

icit, ADHD, and oppositional behavior scores ($P = .035$, $r = 0.432$; $P = .044$ $r = 0.414$; $P = .042$, $r = 0.418$; $P = 0.032$, $r = 0.439$).

Patients with asthma who used adjunctive ICS/LA drugs had significantly higher oppositional behavior scores than those who did not receive any asthma medications (4 vs 7, $P = .031$) or received only LA drugs (2 vs 7, $P = .029$) (Table 3).

DISCUSSION

Prevalences of common behavioral problems among asthma patients were similar to those of healthy children. However, investigation into the roles of anti-asthma treatments in behavioral problems found that ODD was significantly more common among patients receiving adjunctive ICS+LA treatments compared with the control group. In addition, those patients with hyperactivity had a longer duration of adjunctive ICS+LA use. Duration of adjunctive ICS+LA therapy appeared to correlate positively with total scores of hyperactivity, attention deficit, ADHD, and oppositional behavior.

Evaluation of behavioral problems using a validated questionnaire for our population revealed that a relatively high proportion of children both with asthma and no asthma exhibit some behavioral problems, particularly hyperactivity, the prevalence of which reached 16%. Although statistically not significant, attention deficit was found to be twofold higher among asthma patients compared with healthy con-

trols. Asthma is a major chronic disease of childhood based on its high prevalence, co-morbidities, and detrimental effects on the quality of life and school performance.^{13,14} The sedative effects of the common medications used to treat allergies of those children further disturb their academic performance and learning capacities.¹⁵ Previous studies proposed higher prevalences of behavioral problems among children with asthma.^{3,6} Asthma and its comorbidities per se might induce psychological problems and contribute to the development of such disorders. Our data failed to demonstrate a significant difference in the prevalence of behavioral problems among asthma patients compared with healthy children. However, medications used to treat asthma might have an effect on some behavioral symptoms.

According to parental reports, every developmental or behavioral diagnosis inquired about was significantly more common in children with asthma compared with children without asthma. Furthermore, the more severe the asthma, the more likely it was that a child would manifest a developmental or behavioral problem. Blackman and Gurka³ reported that children with asthma have higher rates of attention-deficit/hyperactivity disorder; diagnoses of depression, behavioral disorders, learning disabilities, and missed school days. Yuksel et al¹⁶ reported that attention deficit is more prevalent in children with asthma, when compared with healthy control subjects. However, this study did not mention the impact of asthma medications.

We found that prevalence of ODD was approximately 17% among patients receiving adjunctive ICS+LA. This figure was 8 times higher compared with asthma patients off therapy and 3.7 times higher than controls. Furthermore, total scores for hyperactivity, attention deficit, and ADHD appeared to correlate with the duration of this adjunctive treatment. Psychic adverse effects of ICS have been described before. Hederos¹⁷ described a group of 60 children, of whom 9 (15%) experienced more hyperactivity and aggressiveness after relatively high doses of budesonide (770 μ g daily).¹⁷ In de Vries et al's study,¹⁸ on the basis of parental reports children with

Table 2. Prevalence of ODD Among Patients Receiving Different Treatments

	No ODD	ODD	P
Control group	150 (95.5%)	7 (4.5%)	.024
Patients with asthma receiving no treatment	83 (97.6%)	2 (2.4%)	
Patients with asthma receiving only ICS	267 (91.1%)	26 (8.9%)	
Patients with asthma receiving adjunctive ICS+LA drugs	20 (83.3%)	4 (16.7%)	

Table 3. Total Scores of Each Behavioral Problem Among Patients With Asthma According to Type of Anti-asthma Treatment

	No treatment	Adjunctive ICS+LA	ICS monotherapy	LA monotherapy	P
Hyperactivity score*	5 (2–13)	6.5 (4–14.75)	6 (2–12)	7 (1–18)	.596
Attention deficit score*	4 (2–8)	8 (3.25–11.75)	4 (2–9.5)	2 (0–7)	.057
ADHD score*	9 (6–18)	16.5 (7.25–24.0)	11 (5–21)	8 (1–23)	.376
ODD score*	4 (2–8)	7 (4–11.75)	6 (3–9.5)	2 (0–5)	.025

* Median (25–75 percentile).

asthma on ICS therapy experienced more behavioral problems compared with healthy children. Hyperactivity was reported more often in this group, but aggressiveness was not. However, when compared with those children attending the ear, nose, and throat outpatient clinic, no significant differences were found for any of the axes studied. The researchers concluded that behavioral problems in children with asthma using ICS are simply because they are under specialist care.¹⁸ Because our control group consisted of healthy subjects with no chronic illnesses, we cannot exclude the role of anxiety associated with having a chronic medical condition on behavioral symptoms. Noteworthy in this regard is the potential influence of parental anxiety associated with having a child with asthma or use of corticosteroids on the behaviors of their children. Previous studies have reported high rates of non-compliance in asthma^{19,20} and that parents of young children administer asthma medications irregularly and document more than the actual number of administrations.²¹

The prescribing information of LA drugs has been updated periodically since marketing approval to reflect postmarketing reports of various adverse events²². Several behavioral and mood-related changes have been related to montelukast use, including agitation, bad/vivid dreams, depression, feeling anxious, hallucinations, irritability, restlessness, sleep-walking, suicidal thoughts, tremor, and trouble sleeping. Wallerstedt et al²³ evaluated psychiatric adverse drug reactions (ADRs) associated with montelukast treatment in children. Psychiatric disorders reported more than once included nightmares (n = 15), unspecified anxiety (n = 11), aggressiveness (n = 11), sleep disorders (n = 10), insomnia (n = 3), irritability (n = 3), hallucination (n = 3), hyperactivity (n = 3), and personality disorder (n = 2). The results of studies evaluating potential behavior-related adverse effects of montelukast have been reviewed recently²⁴. Researchers concluded that behavior-related adverse experiences were infrequent with montelukast in clinical trials and were similar between the montelukast and placebo groups. In our study, adjunctive use of ICS and LA drugs appeared to be associated with increased total scores of each behavioral problem.

A limitation to our study is the cross-sectional design and potential confounding effects of asthma symptoms on behaviors of children. To differentiate exact roles of asthma medications on behavioral symptoms, a design involving assessment of patients before and after therapy would be more informative. Moreover, comparison with children with other chronic diseases and studying patients with severe asthma

might be considered. Whether the behavioral changes are solely due to asthma/asthma medications or whether other psychiatric disorders such as anxiety associated with having a chronic illness play a role needs further research.

In conclusion, the results of the current study indicated an association between adjunctive ICS/LA use and increased symptoms of common behavioral problems, especially those related to ODD. Duration of treatment appears to increase these problems. Defining the exact roles of anti-asthma medications on behavioral problems could help physicians choose the most appropriate treatment for their patients in terms of their adverse effects on behavior, particularly in the presence of underlying behavioral symptoms.

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