

Exercise-induced bronchoconstriction in children with atopic eczema

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Non-specific bronchial hyper-responsiveness has been reported in most of the eczematous children even in the absence of asthmatic symptoms. We therefore investigated the occurrence of exercise-induced bronchoconstriction (EIB) in children with atopic eczema (AE) and the predictors of EIB. Fifty-five children referred to the paediatric clinic for AE and a control group of 17 healthy children were recruited. They all carried out a physical examination and skin prick test (SPT) both to inhalant and food allergens, prior to the exercise challenge test. Their parents filled a questionnaire on atopic diseases. They underwent exercise challenge test that consisted in free running for 6 min. Spirometric measurements were carried out before running and till 11 min after. Exercise challenge test was positive in 13 (23%) children with AE. None of the children in the control group had a positive exercise challenge test [OR (95% CI) = 1.31 (1.13–1.51); $p = 0.030$]. Sixteen (29%) eczematous children had a history of EIB. Such history was not reliable for identifying children who had a positive exercise test. Twenty-nine (52%) children with AE had asthma. Allergic rhinitis affected 33 (60%) of eczematous children and allergic conjunctivitis 28 (50%). EIB was not related to any history of asthma, allergic rhinitis, allergic conjunctivitis, severity of eczema or SPT results. Our study shows that EIB is common in children with AE. Our data also indicate that screening by medical history and physical examination is not a sensitive marker of EIB. This may explain why EIB is often ignored in eczematous children.

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Asthma is common in children with atopic eczema (AE). Asthmatic symptoms have been found to occur in about 50% of eczematous children at 5 yr of age (1, 2). Moreover, the presence of non-specific bronchial hyper-responsiveness has been commonly reported in eczematous children free of asthmatic symptoms (3–5).

Physical activity is an important trigger of asthma in childhood. The prevalence of exercise-induced bronchoconstriction (EIB) in asthmatics varies from 40% to 90% (6). Among other atopic disorders, it has been shown that EIB occurs in up to 40% of patients with allergic rhinitis (7). The incidence of EIB in children with AE is unclear, ranging from 0% (8) to 69% (9).

The diagnostic work-up of suspected EIB includes medical history, physical examination and exercise challenge test.

Several types of exercise challenge tests have been used as objective measures of EIB in children. Among them, free running exercise test is considered the most effective for demonstrating an airway hyper-responsiveness to exercise (10, 11).

The aim of this study was first to assess the percentage of eczematous children attending a paediatric clinic with positive free running exercise test and then to identify predictors of EIB such as medical history or sensitization to allergens in children with AE.

Materials and methods

Execution of study and subjects

Fifty-five consecutive children referred to the paediatric clinic of the University Hospital of Parma for AE were asked to participate in this study. There was no decline. Children fulfilling the following selection criteria were invited: diagnosis of AE according to the criteria of Hanifin and Rajka (12); cooperation for the exercise test. Parents completed a questionnaire on baseline data and atopic diseases.

All children visited a physician where history, physical examination, diagnosis of atopic diseases and assessment of the validity of the questionnaire were recorded. To identify any association between EIB and the extent of a child's eczema, each child's eczema was classified as follows: (i) distribution: diffuse (either morbilliform or erythrodermic), or predominantly localized (either predominantly flexural, nummular, predominantly facial, or other patterns, not predominantly flexural); (ii) overall severity: mild, moderate, or severe. Grade of severity of AE was assigned according to a modified Investigator's Global Assessment (IGA) score: mild = score 2, mild erythema and mild papulation/infiltration; moderate = 3, moderate erythema and moderate papulation/infiltration; severe = 4, severe erythema and severe papulation/infiltration, severe and 5, severe signs with oozing/crusting (13). No child had an IGA score less than 2 (mild) was included in the study. Children with AE performed SPT to common food and inhalant allergens. All children performed exercise testing.

In order to ascertain whether exercise challenge test results may be influenced by environment, 17 children were selected as controls. Control group comprised children with neither atopic diseases (AE, asthma, oculorhinitis, urticaria) on examination or a personal history of atopic diseases.

Children with respiratory tract infection in the preceding month were excluded from the study. Informed consent was obtained from parents of all children.

Exercise challenge

The exercise challenge test consisted of free running up and down a 45 m straight corridor (14). Children ran as fast as they could for 6 min. At the end of the run, measurement of children heart rate was postponed after heart and lung examination. Because of this interval, we agree on a lower increase in heart rate to at least

120 beats/min to establish the adequacy of the exercise (15). Spirometric measurements were carried out before running and repeated 1, 6, 8 and 11 min after the end of exercise using a computerized spirometer (Microloop, Markos, Milan, Italy). The best of three FEV₁ values was used to evaluate the response to exercise. Results of FEV₁ were expressed as percentage of predicted. Its post-exercise values were expressed as percentage changes from baseline at individual time points. Maximum FEV₁ falls were calculated as follows: $[100 \times (\text{pre-exercise value} - \text{lowest value after exercise}) / \text{pre-exercise value}]$. A positive exercise test was defined as a maximum percentage fall in FEV₁ $\geq 15\%$ from the baseline (16). All exercise challenges were conducted in the same conditions of temperature (20–22°C) and humidity, at a similar time of the day. Exercise test was performed only in patients with FEV₁ $> 80\%$ of the predicted value at baseline. β_2 -agonists and inhaled corticosteroids were withheld for at least 12 h before each testing session; chromones, theophylline, anti-leukotrienes for 24 h. Exercise tests were performed out of the pollen season.

Questionnaire

Parents filled a questionnaire which was simple in design. The questions on allergy concerned the presence or absence of a history of atopic disease in parents or siblings, and the presence of atopic symptoms (asthma, allergic rhinitis or conjunctivitis) in the children. A history of allergic rhinitis was elicited by asking whether their child had ever had any 'allergic-like' symptoms affecting the nose (e.g. itching, sneezing, running or blocking the nose) not associated with a cold. The occurrence of allergic conjunctivitis was sought by asking, 'Has your child ever had any "allergic-like" symptoms affecting the eyes (e.g. itching, redness, tearing)?'. Asthma was identified by the question, 'Has your child ever had asthma or wheezing, that is noisy breathing with a whistling sound coming from the chest not associated with a cold?' Parents were asked whether their child had recurrent cough at night or first thing in the morning (unrelated to colds). EIB was identified by asking whether the child has ever been more breathless than you would expect during or after exercise and whether the child coughed during exercise. Severity of asthma was classified as follows: severe (at least one attack per month), moderate (at least one attack every 3 months), mild (at least one attack every year). Parents were also asked about the number of hospital admissions and any past and current

medication taken for asthma. Further information was obtained by asking about age of onset of allergic symptoms, household pets and parental smoking habits. Symptoms were considered current if they had occurred during the previous 12 months.

Skin prick test

Children with atopic eczema underwent skin prick tests (SPT) with commercial extracts (1:10 w:v; Bayropharm, Milan, Italy) for hen's egg, cows' milk, goats' milk, pea, cereals, bean, peanut, banana, pear, peach, apple, cherry, soy, tomato, spinach, potato, carrot, beef, pig, lamb, chicken, cod, tuna, salmon and common inhalant allergens. The positive control was histamine 10 mg/ml, the negative diluent of extract. The results were evaluated after 15 min. The test was considered positive if it elicited a weal at least 3 mm greater in diameter than the weal at the site of negative control, and more than half the size of the wheal produced with histamine.

Statistical analysis

The expected frequency of children with EIB in the general population is around 10% (17, 18). We wanted to detect a 100% increase in positive exercise challenge test in the group with AE. Using 17 controls, a sample size of at least 26 eczematous children gives a 90% power of detecting a difference at 5% significance.

Chi-square test, with Yates' correction, or Fisher's exact test, when appropriate were used to compare proportions. Odds ratios (ORs) and confidence intervals (CIs) were calculated. Mann-Whitney test was used to compare continuous variables. Results were considered statistically significant at a value of $p < 0.05$.

Likelihood ratios have been calculated to determine the effectiveness of atopic respiratory symptoms in identifying those who have positive or negative exercise tests.

Results

In the 55 children of the AE group, the mean age was 9.1 yr (range 5 yr 9 months to 15 yr 10 months). Sixty-three percent of the AE group were boys. Fifty-eight percent of children had a positive family history of atopic diseases in at least one parent. In 32 (58%) of the children with AE, the disease had first appeared before the age of 1 yr, and in 44 (80%), before the age of 2 yr. Eczema was diffuse in 12 (21%) and localized in the remaining 43 (78%) children. The overall severity of eczema was 'mild' in 29 (52%), 'moderate' in 20 (36%), 'severe' in 6 (10%). Every questionnaire was fully completed.

Prevalence of EIB and features of atopic dermatitis

Exercise challenge test was positive for EIB in 13 (23%) children with AE.

No association was found between age, sex, age of onset of eczema or the severity of eczema and the occurrence of EIB (Table 1).

None of the 17 children in the control group had a positive exercise challenge test. EIB was significantly more common in AE group than in control group ($p = 0.030$).

The mean age was 8.5 yr (range 5–13 yr) for the control group. Seventy percent of the control group were boys. There was no significant difference in age and sex in controls compared with eczematous children.

The median (range) maximum percent FEV₁ fall after exercise was significantly higher in children with AE than in the control group

Table 1. Age, sex, age of onset of atopic eczema, extent of atopic eczema in eczematous children with positive exercise tests

	Positive exercise test group (n = 13)	Negative exercise test group (n = 42)	Odds ratio (95% CI)	P-value
Median Age (range) (yr)	8.88 (6 yr 1 months to 15 yr 11 m)	8.80 (5 yr 10 months to 15 yr 8 months)		0.758
Male/female	7/6	28/14	0.58 (0.16–2.06)	0.610
Median age of onset of atopic eczema (range) (yr)	1 (1 month to 6 yr)	0.52 (1 month to 8 yr)		0.626
Extent of atopic eczema				
Distribution				
Diffuse [n (%)]	4 (30)	8 (19)	1.88 (0.46–7.71)	0.448
Localized [n (%)]	9 (69)	34 (80)		
Severity				
Mild [n (%)]	4 (30)	25 (59)	0.30 (0.08–1.14)	0.134
Moderate [n (%)]	6 (46)	14 (33)	1.71 (0.48–6.07)	0.513
Severe [n (%)]	3 (23)	3 (23)	3.90 (0.68–22.32)	0.136

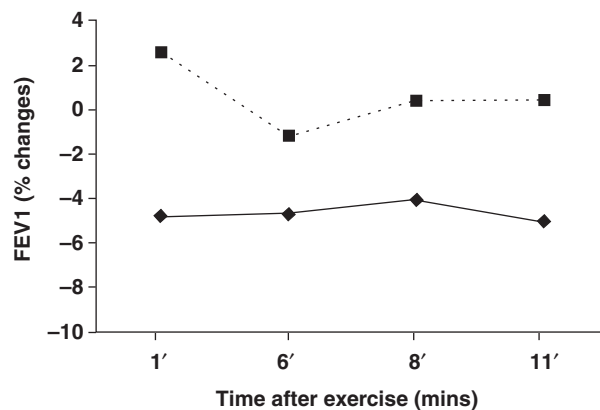


Fig. 1. Mean percentage drop in FEV₁ at 1, 6, 8 and 11 min after end of exercise in atopic eczema group (—◆—) and in control group (—■—). There was no statistical difference between groups at all time points.

[−7.1 (−45.4, 10.5) vs. −5.16 (−12.5); $p = 0.017$]. Post-exercise percentage changes in FEV₁ values were lower in eczematous children than in controls at all time points, but this did not reach a statistical significance (Fig. 1).

Association between asthma, atopic symptoms and positive exercise test

Frequency of symptoms of atopy and EIB in eczematous children with and without positive exercise test, as reported in the questionnaire and confirmed by medical examination, are shown in Table 2. Sixteen (29%) eczematous children had a history of EIB. Such history was not reliable

for identifying children who had a positive exercise test (Table 2).

Twenty-nine (52%) of the children with AE had asthma. Asthma was 'mild' in 18 (32%) cases, 'moderate' in eight (14%), 'severe' in three (5%). Eczematous children with asthma and without asthma have very similar age [mean 8.7 yr (range 6 yr 2 months to 13 yr 6 months) vs. 9.5 (5 yr 10 months to 15 yr 11 months)]. A positive family history was reported by parents of 17/29 (58%) eczematous children with asthma and 18/26 (69%) without asthma ($p = \text{NS}$). There was no significant association between severity of eczema and occurrence of asthma. Eczematous children with asthma were more likely to have a positive history of atopic disease than those without asthma [21/29 (72%) vs. 11/26 (42%); $p = 0.047$]. We could not find any significant association between occurrence of asthma, severity of asthma, medications taken for controlling asthma and the prevalence of EIB (Table 2).

Allergic rhinitis affected 33 (60%) of eczematous children and allergic conjunctivitis 28 (50%). Allergic rhinitis or allergic conjunctivitis did not occur more frequently in eczematous children with EIB than in those who had a negative exercise test (Table 2).

We have analysed the usefulness of clinical symptoms in detecting children with EIB. A history of EIB symptoms, asthma or allergic rhinitis are considered risk factors for EIB in clinical routine. Forty-two (76%) eczematous children with such symptoms were designated as 'at risk' (Table 3). Ten (23%) of at-risk children

Table 2. Positive exercise test and history of exercise-induced bronchoconstriction (EIB), features of asthma, allergic rhinitis or conjunctivitis

	Positive exercise test group (n = 13)	Negative exercise test group (n = 42)	Odds ratio (95% CI)	P-value
History of EIB [n (%)]	6 (46)	10 (23)	2.74 (0.74–10.07)	0.165
Asthma				
Asthma [n (%)]	8 (61)	21 (50)	1.60 (0.44–5.70)	0.682
Current asthma [n (%)]	7 (53)	17 (40)	1.71 (0.49–6.00)	0.597
Median age of onset (range) (yr)	3.5 (2–7 yr)	3 (3 months to 10 yr)		0.537
Severity				
Mild [n (%)]	4 (30)	14 (33)	0.88 (0.23–3.39)	1.000
Moderate [n (%)]	3 (23)	5 (11)	2.22 (0.45–10.91)	0.376
Severe [n (%)]	1 (7)	2 (4)	1.66 (0.13–20.01)	0.562
Hospital admissions [n (%)]	1 (7)	4 (9)	0.79 (0.81–7.78)	1.000
Medications for asthma [n (%)]	8 (61)	22 (52)	1.45 (0.40–5.18)	0.794
Allergic rhinitis				
Rhinitis [n (%)]	5 (38)	28 (66)	0.31 (0.08–1.13)	0.136
Current rhinitis [n (%)]	4 (30)	25 (59)	0.30 (0.08–1.14)	0.134
Median age of onset (range) (yr)	5 (3–9)	4 (1 year 6 months to 13 yr)		0.414
Allergic conjunctivitis				
Conjunctivitis [n (%)]	6 (46)	22 (52)	0.77 (0.22–2.71)	0.940
Current symptoms [n (%)]	3 (23)	16 (38)	0.48 (0.11–2.04)	0.506
Median age of onset (range) (yr)	4 (3–9 yr)	4 (1–13 yr)		0.588

Table 3. Likelihood ratios (LR) of a positive exercise test in eczematous children for atopic symptoms or exercise-induced symptoms

	No. of patients positive/negative	Positive patients with EIB [n (%)]	Sensitivity	Specificity	LR+	LR–
No at-risk*	13/42	3 (23)	0.23	0.76	0.95	1.01
At risk*	42/13	10 (23)	0.76	0.23	0.98	1.04
Asthma	29/26	8 (27)	0.61	0.50	1.22	0.78
Allergic rhinitis	33/22	5 (15)	0.38	0.33	0.57	1.87
Asthma without allergic rhinitis	9/46	5 (55)	0.38	0.90	3.8	0.68
Allergic rhinitis without asthma	13/42	2 (13)	0.15	0.73	0.55	1.02
Asthma + allergic rhinitis	20/35	3 (15)	0.23	0.59	0.56	1.13
EIB symptoms	16/39	5 (31)	0.38	0.73	1.40	0.84

*At risk on the basis of presence of asthma, allergic rhinitis or exercise-induced bronchoconstriction (EIB) symptoms.

had a positive exercise challenge test. Three (13%) of the 23 children who were not considered at risk had EIB. There was no difference between at risk children and non at risk children for having a positive exercise challenge test [OR (95%CI = 3.03 (0.79–12.6); $p = 0.213$]. Among at-risk children, five (55%) of nine with isolated asthma and two (15%) of 13 with isolated allergic rhinitis and three (15%) of the 20 with asthma plus allergic rhinitis had a positive exercise challenge test. All 16 children with AD who have exercise-induced symptoms suffered from asthma. Positive and negative likelihood ratios of a positive exercise test for each symptom and for overall symptoms is given in Table 3.

Association between background data, SPT and positive exercise test

No association was found between having pets at home or environmental tobacco smoke exposure and occurrence of EIB (Table 4). Fifty-three per cent of the AE group with positive exercise test (AE group with negative exercise test: 59%) stated that their child had a history of atopic disease in at least one parent.

Forty-five (80%) of the eczematous children had at least one positive SPT reaction. In 27 (49%) of the AE children, SPT was positive to at least one food antigen. Forty-two (76%) children with AE had at least one positive SPT reaction to inhalant allergen. There was no significant difference between children with positive and negative SPT reactions in the prevalence of EIB (Table 4).

Eczematous children with asthma had significantly greater frequencies of positive SPT than

Table 4. Positive exercise tests and animals at home, smoking by parents and skin prick test results in children with atopic eczema

	Positive exercise test (n = 13) [n (%)]	Negative exercise test (n = 42) [n (%)]	Odds ratio (95% CI)	P-value
Domestic animals	4 (30)	16 (38)	0.72 (0.19–2.73)	0.749
Smoking by parents	2 (15)	13 (30)	0.40 (0.07–2.09)	0.477
Skin prick tests				
At least 1 positive	10 (76)	35 (83)	0.66 (0.14–3.06)	0.685
At least 1 positive to foods	8 (61)	19 (45)	1.93 (0.54–6.91)	0.478
At least 1 positive to inhalants	9 (69)	33 (78)	0.61 (0.15–2.46)	0.480

those without asthma [29/29 (100%) vs. 16/26 (61%); $p = 0.001$], including both food allergens [19/29 (65%) vs. 8/26 (30%); $p = 0.021$] and inhalant allergens [27/29 (93%) vs. 15/26 (57%); $p = 0.006$].

Discussion

The results of this study provide evidence that spirometrically diagnosed EIB is common and often ignored in children with AE. Furthermore, our results show that in eczematous children EIB can only be suspected by medical history and physical examination. In the current investigation, EIB was defined objectively by using methods including trained medical staff and standardized exercise challenge. We decided to perform serial spirometry instead of peak expiratory flow rate (PEFR) measurements after exercise as PEFR has greater within-subjects variability than forced expiratory volume in 1 s (FEV₁) (19). Subsequently, diagnosis of EIB by PEFR yields many false-positive results (20). Moreover, EIB was defined as a fall in FEV₁ after exercise to > 15%, which is considered the most accurate diagnostic criteria (16).

Our data show that in children with AE seen in a paediatric clinic, the frequency of spirometrically diagnosed EIB is 23%. This frequency is twofold (17, 18) to fivefold (15) higher than that reported in large-scale studies among children in the general community. Previous investigations (8, 9) have reported contrasting data on the prevalence of EIB in children with AE. However, it is not easy to compare our findings with theirs, because of the different criteria used for the diagnosis of EIB. Using PEFR measurements after exercise, Price et al. (9) found that 33 (78%) of 42 children with AE had EIB. Of 23 children with AE and asthma studied, all had a positive exercise test. However, they did not take into

account that the exposure to relevant airborne allergen may provoke an increase in positive exercise tests in children with allergic asthma. As we decided to perform exercise challenges out of the relevant pollen season in the patients with allergic asthma or rhinitis. This and differences in exercise test procedures may explain why we observed a lower prevalence of EIB, especially among children with AD and asthma.

In contrast to our results, Custovic et al. (8) found that none of six children with isolated AE had a positive free running exercise test. The small number and the selection of patients may explain their different findings.

The value of screening for EIB by medical history and physical examination have not been previously evaluated in children with AE (8, 9). The analysis of the data of our survey shows that such screening is inadequate to detect EIB in eczematous children. Our results found positive exercise tests in one-third of the children who complained of symptoms on exertion and in 20% of children with a negative history for EIB. In addition, risk factors, such as asthma and allergic rhinitis, were not effective for recognizing children with EIB. Three of the 13 eczematous children with a positive exercise test had neither atopic respiratory symptoms or self-reported EIB symptoms. These data confirm previous reports (15, 21) showing that a standard exercise challenge should be considered a more accurate mean for ascertaining EIB than history.

We realize that our patient sample may not represent the spectrum of AE in the general population. However, in agreement with previous findings (8) our data show no association between spirometrically diagnosed EIB and distribution or severity of AE defined by using IGA score (13). The issue arises whether a different severity scoring system of AE (22) may give opposite findings. AE scoring systems do not evaluate the same parameters (22) and have large interobserver variations (23). Therefore, a universally accepted standard for objective assessing and grading of intensity of AE is still a matter of debate. We choose to use IGA score because on the basis of our clinical experience, we hypothesized that overall severity of clinical signs of AE might predict EIB. Furthermore, we rated severity of AE before the exercise challenge test. Therefore, we believe that our results are reliable. As to the risk of a misclassification error as a result of parents recall bias, we validated the questionnaire with a medical visit. Thus, we believe that a data bias is unlikely.

The present survey was not designed to investigate the reason for EIB in eczematous children. Only speculative hypotheses can be offered to interpret the data. Thus EIB is a common feature of asthma (1, 2) and allergic rhinitis (7), it has been suggested that EIB is not associated primarily with AE but with combined atopic respiratory diseases. However, Salob et al. (3) showed that 81% of eczematous children free of asthmatic symptoms, had bronchial hyper-responsiveness to histamine. Along this line, we found that EIB was not significantly more frequent in children with AE who had neither asthma or allergic rhinitis in comparison with those who had respiratory symptoms. These findings rule out that EIB in children with AE is only explained by the concurrence of asthma or allergic rhinitis, supporting the view that EIB is common in children with all atopic diseases. The question arises whether the association of EIB with atopic symptoms could be determined by genetic (24, 25) or environmental factors. A genetic predisposition for EIB is indirectly supported by the lack of association in our study between EIB in the children with AE and environmental factors such as (i) hyper-sensitivity to food or inhalant allergens, as determined by SPT, (ii) presence of pets at home and (iii) passive smoke exposure. Studies on candidate genes associated with atopic disorders are necessary to comment further.

It is unclear whether EIB precedes the onset of asthma in eczematous children. Although EIB in children with AE has been anecdotally reported to be a predictor of asthma (8), exercise test has poor accuracy in identifying children who will develop asthma-related symptoms in the general population (26). Longitudinal studies are needed to clarify the risk of having asthma in eczematous children with isolated EIB.

We conclude that much greater attention should be paid to the occurrence of EIB in children with AE, even in the absence of asthma, allergic rhinitis or respiratory symptoms on exertion. Unrecognized exercise-induced symptoms may limit participation of eczematous children in athletic activities with a negative influence on their physical and social well-being. This is particularly true in competitive athletes. Further investigation on children with AE may help us to understand why EIB is under-diagnosed among adolescent athletes (15, 27).

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