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The Relationship between Allergy, Clinical Symptoms and Bronchial Responsiveness in Atopic Dermatitis

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Atopic Dermatitis (AD) and asthma are closely associated with respect to epidemiology, hereditary factors and occurrence in the same individuals. Bronchial Hyperresponsiveness (BH), the hallmark of asthma, can also be a physiopathological feature of AD, even in the absence of clinical asthma. We studied 78 subjects with AD. A follow-up study was performed in 27 of these. Data on respiratory and dermatologic symptoms were collected by means of a standardized questionnaire. Skin reactivity was evaluated by prick testing, and in 57 subjects BH was assessed with a methacholine test (Mch). Twenty-one subjects had asthma and 36 showed a positive skin reaction. A PC20 FEV1 was measurable in 38 subjects. Males were found more likely to be Mch responders than females ($p<0.05$). Mch responders also showed an earlier age at onset of AD than non-responders (2.1 yrs vs. 6.2, $p=0.03$). Determinants of the degree of BH were evaluated by a stepwise multiple regression analysis, taking the log of the slope of the concentration response curve as dependent variable. In the final model we found that the degree of BH was directly related to wheezing ($p=0.0017$) and coughing ($p=0.04$) and inversely related to lung function ($p=0.0082$) and age ($p=0.0008$). Neither skin reactivity nor grading of AD were statistically significant. The longitudinal study demonstrated that the courses of AD and BH seem to run parallel only in skin-negative subjects, whereas an increase in BH was observed in skin-positive subjects. ***Key words: Atopic dermatitis, bronchial asthma; bronchial hyperresponsiveness.***

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INTRODUCTION

In childhood, Bronchial Asthma (BA) and Atopic Dermatitis (AD) share many features as regards epidemiology, immunology, clinical findings, and physiopathological features. At present the two diseases are commonly classified as atopic diseases because the increased levels of IgE in the serum have been proposed as common etiological factor (1). However, it has recently been suggested that increased IgE may not be causal, either in AD (2) or in BA (3). Moreover, in recent years, numerous epidemiological, clinical and experimental studies have improved our knowledge on AD and BA. Consequently the linking factors between these two diseases should be reconsidered.

In Tables I and II we summarize the epidemiology, the natural history, the immunology and some physiopathological aspects of BA and AD.

Physiopathological aspects are worth a few brief comments. Skin hyperreactivity to histamine (11) and to cholinergic stimuli (2, 11) occurs in patients with AD in a manner similar to that observed in asthmatics who develop bronchoconstriction following histamine or methacholine challenge (3). However, a skin hyperreactivity has been found in asthmatics (47) and a bronchial response to cholinergic stimuli has been shown in subjects with AD (24, 45, 46). Also, a reduced beta-adrenergic activity has been found in lymphocytes both in BA (50, 51) and in DA (48, 49). Lastly, an abnormality in epidermal permeability barrier has been demonstrated in patients with AD with increased transepidermal water loss through both dry and clinically normal skin (38). In BA an increase in permeability has been observed in the bronchial epithelium after various stimuli (39). These studies strongly suggest that there is an overlap between the physiopathological aspects of BA and DA, not accounted for the increase in IgE alone. Thus, subjects with AD may have an increased airway reactivity even if clinical symptoms of BA are present in some subjects with other risk factors (i.e. family history, respiratory infections in early age).

We performed a detailed study on a sample of subjects with AD in order to evaluate the prevalence of respiratory symptoms and of Bronchial Hyperresponsiveness (BH) and the relationship to certain risk factors (i.e. age, sex, skin test positivity and clinical factors related to AD).

METHODS

Sample selection, anamnestic data and clinical examination

We studied 78 subjects with AD (38 males, mean age 11 years, range 5–29) from the Out-patient Department of a pediatric dermatology unit (Policlinico Gemelli, Roma).

A longitudinal study was carried out on 27 subjects, lasting for a mean period of 17 months (range 11–24). The observations were repeated in the same period of the year as regards all the subjects who were found to be skin reactors to seasonal allergens. Anamnestic data were collected by means of a standardized questionnaire that comprised both questions regarding the respiratory system (cough and phlegm apart from colds, wheezing apart from colds, medical diagnosis of BA, rhinitis) and dermatological status (onset of disease, periodic occurrence of symptoms, triggering factors). Moreover, the presence of atopic diseases (BA, rhinitis, AD) in directly related family members was ascertained. The dermatological examination was performed according to Rajka's criteria (20): on the basis of the course, extent and activity, a score system was devised and subjects were classified as having mild, moderate, or severe AD.

Skin prick test

Immediate skin reactivity was evaluated by skin prick tests with six common inhalant allergens (*Phleum pratense* and *Dactylis glomerata*, 10,000 PNU/ml; *D. pteronyssimus*, 5000 PNU/ml; mugwort, 10,000

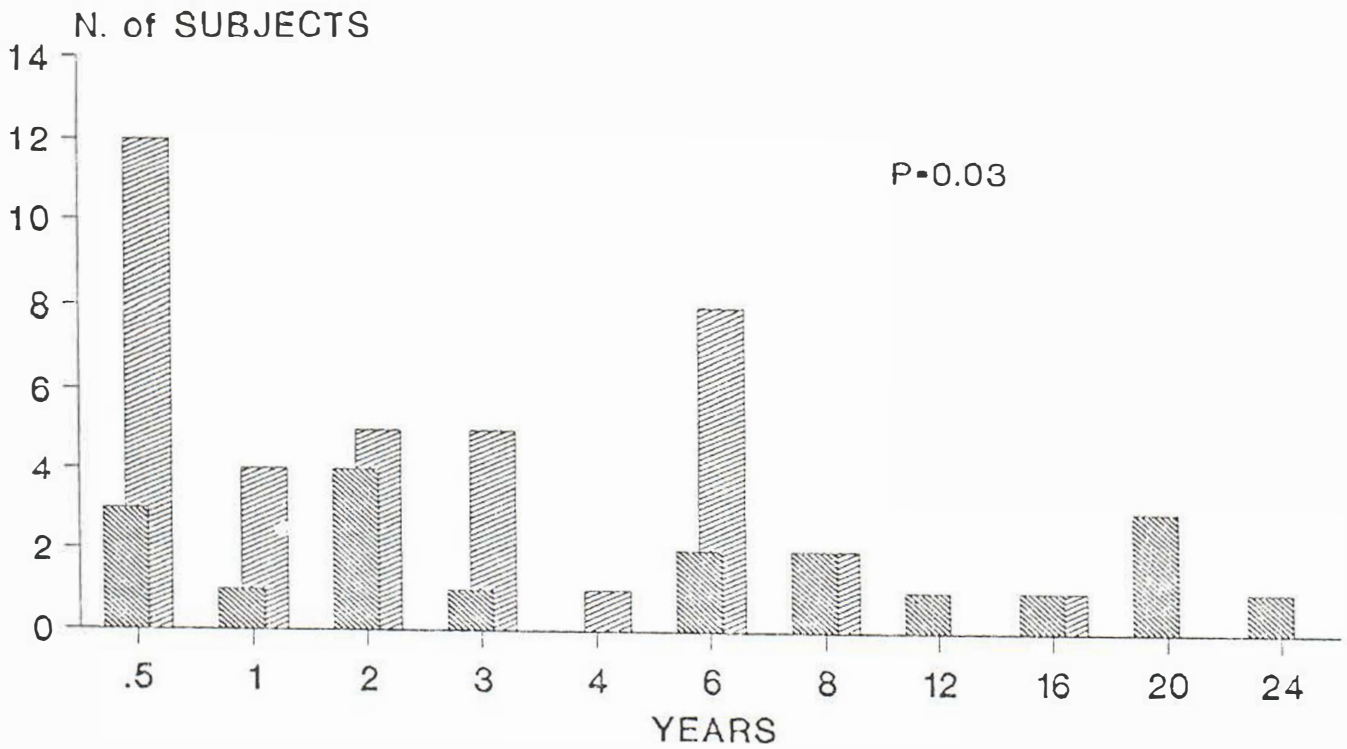

Fig. 1. Response to methacholine test and age at onset of Atopic Dermatitis. ▧, MCH-; ▨, MCH+.

PNU/ml; Parietaria, 10,000 PNU/ml; birch, 10,000 PNU/ml; olea, 10,000 PNU/ml). Histamine dihydrochloride at 10 mg/ml concentration was taken as positive control. The diluent (0.03% human serum albumin in phosphate-buffered saline) was the negative control. The site of application of allergen extracts and controls on the forearms was randomized. Any wheal reaction was outlined with a soft ballpoint pen, and the markings were transferred to square millimetre recording paper by means of a tape. After subtraction of any wheal response to the diluent control, wheals measuring $\geqslant 3$ mm^2 area were arbitrarily termed positive. The ratio between each allergen wheal and the histamine wheal was calculated and the grading of skin reactivity was defined according to following scale: mild = allergen wheal $\leqslant 0.5$ with respect to the histamine; moderate = allergen wheal > 0.5 but less than or equal to the histamine wheal; severe = wheal with an area greater than that of the histamine wheal. The greatest wheal observed was arbitrarily taken as the index of skin reactivity.

Respiratory function tests and bronchial provocation test

Lung volumes were measured with a water-filled spirometer. Bronchial hyperreactivity was assessed by methacholine challenge according to the method described by Ryan et al. (52). Twelve concentrations (from 0.03 up to 64 mg/ml McH) were delivered via a De Vilbiss 646 nebulizer attached to a dosimeter (Mefar, Brescia, Italy). The output of aerosol was 9.1 (±0.8) microlitres per nebulization of 0.8 s. The subjects were given five breaths of each concentration of methacholine by taking slow deep breaths from functional residual capacity to inspiratory capacity. Initially we administered a control aerosol of buffered saline diluent. A $\geqslant 20\%$ drop in FEV1 was selected to categorize patients into responders and non-responders. In the responder group, results were expressed as the methacholine-provocative concentration causing a 20% fall in FEV1 (PC20 McH). This index was regarded as a categorical index (PC20 McH $\leqslant 64$ mg/ml, and PC20 Mch>64 mg/ml) in the statistical analysis of the overall sample. In the follow-up study, the methacholine test response was expressed by an ordinal index for degree of hyperreactivity (PC20$\leqslant 0.5$ mg/ml = severe PC20$\leqslant 2$ mg/ml = pronounced, PC20$\leqslant 8$ mg/ml = moderate, PC20$\leqslant 64$ mg/ml = mild, PC20>64 mg/ml = normal reactivity). It is possible, however, to express the response to methacholine test in terms of the slope of the dose-response curve (53). This index presents a continuous and log-normal distribution over a population.

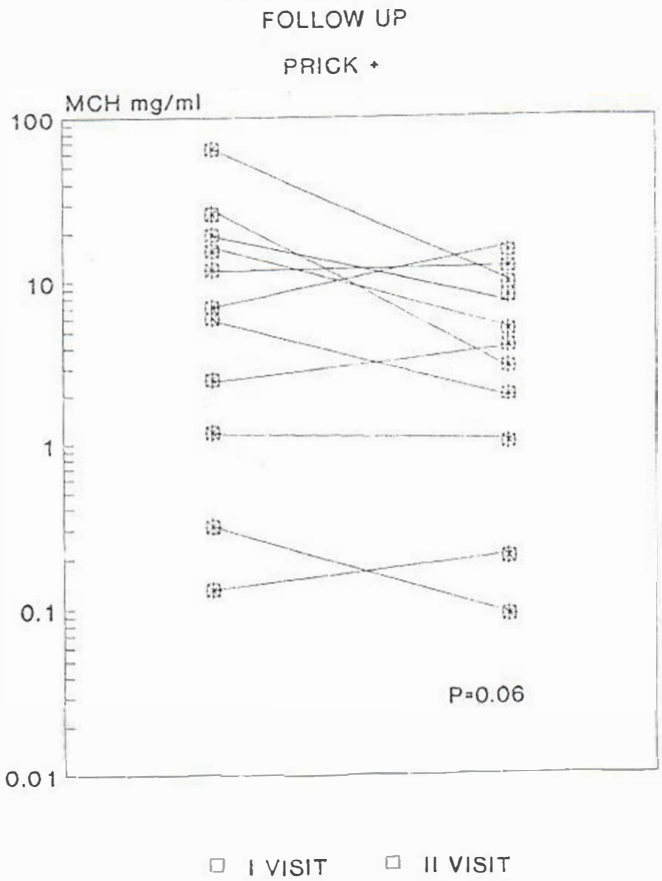

Fig. 2. Change in bronchial response to methacholine test in skin-negative subjects.

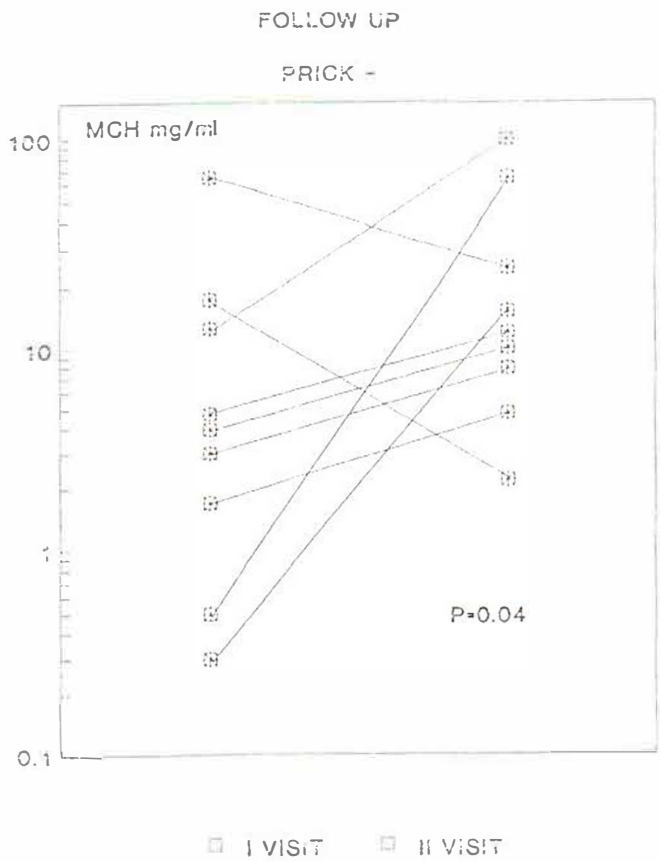

Fig. 3. Change in bronchial response to methacholine test in skin-positive subjects.

Statistical analysis

Comparisons were made by means of one-way variance analysis, Kruskal Wallis, χ^2-test and Fischer's exact test, according the distribution of the variable examined. The determinants of the response to the methacholine test were assessed by means of multiple regression, with the log of the slope of the dose-response curve being considered as a dependent variable. A history for asthma (0 = No, 1 = Yes), wheezing not associated with common cold (0, 1), cough (0, 1), rhinitis (0, 1), family history of atopic disorders (0, 1), age, age of onset of the dermatitis, sex (M = 0, F = 1), baseline lung function (FEF25–75, maximum mid-expiratory flow rate) and skin test reactivity (at least one positive reaction = 1, negative = 0), were included in the model as independent variables. The severity of the skin lesions assessed according to Rajka (20) was included in the model by means of three dummy variables. The same conversion was performed for the degree of skin reactivity.

The follow-up data were analysed by the two-way variance analysis for pulmonary function, and Wilcoxon's test for paired data for skin reactivity, clinical degree of disease and bronchial reactivity.

RESULTS

The analysis of the questionnaire revealed that 21 subjects (27%) presented BA, while rhinitis (36 subjects), cough not associated with common cold (23 subjects), and wheezing not associated with common cold (28 subjects) were more prevalent. Twelve subjects reported a family history of atopic disorders. The asthmatic subjects differed from the controls regarding earlier onset of the AD (11 months vs 2 years 6 months, $p=0.008$) and a greater prevalence of rhinitis (71% vs. 24%, $p=0.0001$), whereas no differences were observed as regards sex and family history.

At the clinical examination, 48 subjects presented a severe degree of AD, while 24 presented a moderate degree. Skin reactions were found to be positive for at least one allergen in 38 subjects (48.7%). Twenty-two subjects out of 38 had a reaction to more than one allergen extract. The prevalence of positive reactions was higher in subjects with asthma (41% vs. 14%, $\chi^2=7.78$, $p<0.01$), with rhinitis (47% vs. 24%, $\chi^2=4.6$, $p<0.05$) and those with a family history of atopic disease (27% vs. 5%, $\chi^2=7.8$, $p<0.01$). No differences were observed in terms of respiratory function or clinical severity of AD.

The Methacholine test was performed in 57 subjects (25 males and 32 females). A positive response to the test (PC20 $\leqslant$ 64 mg/ml) was recorded in 38 subjects (66.6%). A PC20 Mch less or equal to $\leqslant$ 8 mg/ml was found in 25 subjects (44%), while 17 subjects (30%) had a response lower than 2 mg/ml. The positive response to the test was recorded more frequently in males (55% vs. 21%, $\chi^2=5.9$, $p=0.015$) and in subjects with a history of wheezing not-related to common cold (47% vs. 16%, $\chi^2=5.3$, $p=0.02$). No significant differences were found as regards asthmatic subjects (34% vs. 10%, $p=0.057$) or skin reactors (68% vs. 52%) Methacholine responders were found to be significantly younger than non-

Table I. *Atopic dermatitis and bronchial asthma: Natural history and clinical aspects (references in parentheses)*

	Atopic dermatitis	Bronchial asthma
Prevalence in population	4.3–12.2% (4–5)	2–17.2% (6)
Age at onset	81% by 12 months 97% by 3 years (4.7)	42–57% by 2 years 62% by 3 years (8, 9)
Ratio M/F	1.3:1 (7)	1.8:1 (8, 10)
Family History	+++ (7, 11, 12)	+++ (9)
% remission	57–90% (12, 13)	52–70% (9, 14, 15)
Seasonal susceptibility	+++ (16)	+ (3, 17)
Persistent disease	Family history + late age at onset Bronchial asthma Gender Severe dermatitis (2, 12, 13, 18)	Family history + early age of onset Atopic dermatitis Gender (Male) Severe asthma Severe atopy (8, 9)
Skin test reactivity	80% (11)	71–93% (3, 17, 19)
Food allergy	++ (20)	+ (19,21)
Inhalant allergens	++ (22–24)	+++ (3, 17)
Exercise-induced asthma	+ (25)	+++ (3)
Provoking factors	Emotional stress Overheating Enviromental allergens Food (7, 12)	Environmental irritants Psychological stress Environmental allergens Viral infections Weather Exertion (3, 17, 26)
Asthma <> D.A.	29–34% (7, 12)	40% (10, 19, 21)

Table II. *Atopic dermatitis and bronchial asthma: Immunological and physiopathological features*

	Atopic dermatitis	Bronchial asthma
Cell-mediated immunity	Decreased T-cell numbers Deficient T8+ cytotoxic T-cell function (2, 11, 27, 28)	Deficient T8+ cytotoxic T-cell function (29, 30)
Basophil releasability	Increased (+++) (31)	Increased (+++) (32)
Basophils	Increased (±) (33)	Increased (±) (33)
Eosinophils	Increased (+) (27)	Increased (+++) (19)
Serum IgE	Increased (+++) (1, 2)	Increased (+++) (19)
Other immunological features	IgG immune complexes Decreased chemotactic migration of both neutrophils and monocytes (34–35)	Decreased H2-receptor-bearing lymphocytes with abnormal histamine induced suppressor cell responses (36–37)
Epithelium permeability	Increased (38)	Yes/no (39, 40)
EFA metabolism	Increased [ ] of linoleic acid and low levels of its metabolites in red cells and plasma (41, 42)	Changes of [ ] of linoleic acid in PMN (+) and lymphocytes (−) (43).
Specific challenge	Early and late response (Food) (44)	Early and late response (inhalant) (24)
Histamine reactivity	Increased (+++) (11)	Increased (+++) (3)
Cholinergic hyperreactivity	Skin (+++) (2, 11) Bronchial (+) (24, 45, 46)	Bronchial (+++) (3) Skin (+) (47)
Beta-adrenergic response	Reduced (+++) (48, 49)	Reduced (+++) (50, 51)

responders (11 vs. 14.7 years, Kruskal-Wallis test: $H=3.86$, $p=0.049$), and the age at onset of AD in methacholine responders was significantly earlier than in non-responders (2.1 vs. 6.2, $H=4.68$, $p=0.03$, Fig. 1).

The results of the multiple regression analysis are given in Table III. The final model showed that bronchial reactivity was inversely correlated with both respiratory function and the subject's age, while it was directly related to the presence of coughing and wheezing not related to common cold. Neither the clinical degree of the AD nor skin reactivity were included in the model.

In the longitudinal study, the clinical examination evidenced an improvement in skin lesions in 13 subjects. Clinical remission was not accompanied in a significant way by a change of the skin reactivity or bronchial reactivity. However, it was observed that skin-negative subjects presented a significant reduction in the skin lesions ($p=0.03$) and a reduction in bronchial reactivity ($p=0.05$) (Fig. 2). By contrast, skin-positive subjects, in addition to presenting a significant clinical improvement ($p=0.02$) showed an increase in bronchial reactivity barely significant in statistical terms ($p=0.06$) (Fig. 3).

DISCUSSION

Our data demonstrate that bronchial hyperresponsiveness has a high prevalence in AD, and young age of the subject and an early age at onset are important determining factors. Atopic status, defined on the basis of skin test, seems more closely related to clinical symptoms such as wheezing, cough, asthma and rhinitis, than to bronchial hyperresponsiveness. The follow-up study suggests that the courses of AD and bronchial hyperresponsiveness are similar in skin-negative subjects, whereas a further increase in bronchial hyperresponsiveness has been observed in skin-positive patients. These findings confirm previous papers (24, 46) and add further data supporting the hypothesis that bronchial hyperresponsiveness can be considered a linking factor between AD and bronchial asthma. Recently it has been found that subjects with AD without a history of asthma are prone to develop an immediate asthmatic response upon challenge with a specific mite allergen – yet no late asthmatic response (24). In these patients a bronchial response to methacholine was also detected. Authors suggested that in patients with aeroallergen sensitivity, a latent bronchial inflammation can be present such as to increase bronchial reactivity. We found that bronchial hyperresponsiveness was not related to atopic status, thus exposure to allergens could play a role only in certain patients, whereas

Table III. *Determinant factors of bronchial response to methacholine test*

Multiple regression
Dependent variable: Slope (LN) $N=57$ s.
Independent variables: wheezing, cough, family history, FEF 25–75, age, age at onset, sex, atopy, grading of disease, asthma.

Analysis of variance

Source	D.F.	R^2	F	P
Regression	4	0.52	14.16	0.0000
Residual	52			
Variables in the model		Beta	F	P
Wheezing		0.378	11.000	0.0017
FEF 25–75		−0.278	7.604	0.0080
Cough		0.228	4.25	0.044
Age		−0.34	12.661	0.0008
Constant		5.124		

other mechanisms should be hypothesized in skin-negative patients (23, 54, 55). The follow-up study suggests that bronchial hyperresponsiveness is linked to the course of AD only in skin-negative subjects becoming independent when sensitization to aeroallergen occurs.

In conclusion, children affected by AD present an increase in bronchial reactivity regardless of the atopic state. This condition takes on clinical significance over time, both in relation to the exposure to irritant factors, and due to exacerbation of the skin symptoms. Consequently, environmental and therapeutic controls take on a preventive significance.

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