

Prodromal features of asthma

S BEER, J LAVER, J KARPUCH, S CHABUT, AND M ALADJEM

Pediatric Pulmonary-Allergic Service and Departments of Pediatrics B and Clinical Epidemiology, Assaf Harofeh Medical Center, Sackler School of Medicine, Tel Aviv University, Israel

SUMMARY One hundred and thirty four ambulatory children with bronchial asthma were investigated in the Pediatric Pulmonary-Allergic Service. In 95 patients an interval characterised by prodromal respiratory symptoms (cough, rhinorrhoea, and wheezing), behavioural changes (irritability, apathy, anxiety, and sleep disorders), gastrointestinal symptoms (abdominal pain and anorexia), fever, itching, skin eruptions, and toothache preceded the onset of the attack of asthma. Each child had his own constant set of prodromal findings.

A significant age related increase in serum IgE concentrations was observed in these patients. No such relation was observed in children with an acute onset of attack of asthma without any preceding symptoms. We suggest that awareness of these prodromal symptoms may lead to an early introduction of treatment, thus avoiding or abbreviating some of the acute attacks of asthma.

The overt attack of asthma is often preceded by a variety of prodromal symptoms, some of which are not related to the respiratory system.¹⁻⁴ The aim of this study was to characterise these prodromal findings and thus enable an early introduction of treatment for asthma, an approach that may, in some patients, either avoid or abbreviate the attack of asthma.

Patients and methods

One hundred and thirty four patients (90 boys and 44 girls), presenting to the outpatient clinic of the Pediatric Pulmonary-Allergic Service at our centre, were studied. Mean (SD) age was 7.0 (1.8) years (range 1.5–14 years). Ninety three had seasonal and the remaining 41 perennial bronchial asthma. All the patients had bronchial asthma based on the criteria set by the American Thoracic Society.⁵

A standardised questionnaire that recorded the symptoms that preceded the attack of asthma was completed by the parents. The attack of asthma was defined as an acute onset of noisy breathing associated with wheezing, tachypnoea, and intercostal and/or suprasternal retractions. Symptoms preceding the attack of asthma, such as rhinorrhoea, cough, fever, skin eruption, irritability, apathy, anxiety, sleep disorders, loss of appetite, abdominal pain, itching, and toothache were recorded according to their chronological occurrence. Duration of

asthma and total number of attacks and admissions to hospital during the last year were documented. The chronic or sporadic use of oral antihistamines, theophylline, steroids, or inhalation treatment with betasympathomimetics or sodium cromoglycate was recorded. To minimise errors due to the parents' memories, data recording was limited to the year preceding the first examination at our outpatient clinic.^{3,6}

History of asthma, atopy, hay fever, or a specific allergic reaction to dust, pollen, or foods in either parents or siblings, or both, was considered positive only if diagnosed by a physician. Atopy was considered present if the patients had a personal and/or a family history of an atopic condition (eczema, hay fever, food allergy, or asthma) and a positive prick test to one or more of 10 common allergens. An asthma history severity score from 1 to 4 was computed for each child as described by Murray *et al.*⁶

Determination of serum IgE concentrations was performed during the symptom free intervals while children were on treatment with bronchodilator alone or without prophylactic treatment. Serum samples were stored at -20°C until analysed. IgE was assayed by a commercial solid phase radioimmunoassay (Prist, Pharmacia Ltd, Uppsala, Sweden).

Statistical analysis was performed by Student's *t* or Fisher's exact tests. Due to the considerable

variation, IgE concentrations were transformed into logarithmic values and presented as geometric means. The Pearson coefficient was used to test the correlation between the log (IgE) and the age of the patients and *p* for the null hypothesis was obtained from statistical tables.⁷

Results

The study comprised 134 children attending the outpatient service. In 91% of the patients with seasonal asthma and 34% of the patients with perennial asthma the acute attacks occurred from March to June and from September to November. The duration of asthma ranged from one to seven years.

The patients were divided into two distinct groups according to the presence or absence of prodromal symptoms preceding the overt attack of asthma by hours or days. Group A comprised 95 (71%) patients who showed prodromal symptoms six hours or more before the attack of asthma. Group B comprised 39 (29%) patients with a rapid evolution of symptoms that led to the overt attack of asthma within six hours. No significant difference in any of the variables listed in Table 1 was observed between the two groups. In group A the mean (SD) number of prodromal symptoms per patient was 2.84 (0.86) and the mean (SD) interval between the occurrence of the initial prodromal symptom and the overt attack of asthma was 23.5 (11.1) hours. The patients were classified according to the occurrence of the initial prodromal symptoms in time ranges of six to 12, 12 to 24, 24 to 36, 36 to 48, and 48 to 60 hours before the onset of the overt attack of asthma. In computing time averages and standard deviations the mean of a range was taken to represent the time of occurrence of the individual prodromal initial symptom.

The type of the initial prodromal symptom and its

Table 1 Comparison of individual characteristics in patients with (group A) or without (group B) prodromal symptoms before the attack of asthma

| | Group A (n=95) | Group B (n=39) |
|---|-------------------|-------------------|
| Sex (M:F) | 66:29 | 24:15 |
| Mean (SD) age (years) | 6.7 (2.8) | 7.7 (3.6) |
| No. of patients with family history of allergy | 56 | 24 |
| Mean No. of admissions per patient during the last year | 0.55 | 0.56 |
| Mean (SD) No. of attacks of asthma per patient during the last year | 6.8 (2.6) | 7.3 (2.4) |
| Type of asthma: | | |
| Seasonal | 68 | 25 |
| Perennial | 27 | 14 |

Table 2 Initial prodromal symptom and its time relation to the overt attack of asthma

| Symptom | No. of patients | Interval (hours) between initial symptom and onset of overt attack | |
|--------------------|-----------------|--|-------|
| | | Mean (SD)* | Range |
| Rhinorrhoea | 39 | 26.76 (12.00) | 6-60 |
| Cough | 23 | 20.73 (0.42) | 6-48 |
| Irritability | 7 | 28.28 (4.53) | 12-36 |
| Apathy | 7 | 28.28 (4.13) | 12-36 |
| Anxiety | 3 | 30 | 24-36 |
| Sleep disorders | 2 | 18 | 12-24 |
| Fever (above 38°C) | 5 | 16.2 (4.0) | 6-24 |
| Abdominal pain | 2 | 13.5 (6.4) | 6-24 |
| Loss of appetite | 2 | 18 | 12-24 |
| Itching | 3 | 9 | 6-12 |
| Skin eruption | 1 | 9 | 6-12 |
| Toothache | 1 | 9 | 6-12 |

*The means and standard deviations were computed according to average representative values of the appropriate time ranges.

time relation to the overt attack of asthma is recorded in Table 2. As shown the most common symptoms (62%) were related to the respiratory tract (rhinorrhoea and cough), which were followed in frequency (20%) by behavioural changes (irritability, apathy, anxiety, and sleep disorders). Fever, gastrointestinal symptoms (loss of appetite, and abdominal pain), itching sensations, skin eruptions, and toothache were fairly rare. In 92 (97%) of the patients the initial symptoms was followed by additional ones; they were polysymptomatic and usually more than one system was involved (Table 3). Any given child presented with a constant initial symptom and a characteristic set of additional prodromal findings. Not all the additional prodromal findings were present, however, during any given attack of asthma. Eighty two (86%) of the 95 patients in group A constantly showed the same prodromal features before each attack of asthma, while the other 13 (14%) showed a variable number of prodromal symptoms in each subsequent attack of asthma.

Sixty two patients whose initial prodromal symptoms were respiratory in nature—that is, rhinorrhoea or cough—had a mean (SD) age of 7.3 (2.8) years and a mean (SD) interval between the initial symptom and the overt attack of asthma of 24.5 (12.2) hours. The 33 patients in group A whose initial symptoms were not of a respiratory nature had a mean (SD) age of 5.2 (2.1) years and a mean (SD) interval between the initial symptom and the overt attack of asthma of 21.5 (8.5) hours. The prodromal symptoms were observed by the mother in 64 (67%) patients, by the father in 12 (13%), and by both parents in 19 (20%).

In 30 (77%) of the 39 patients in group B the initial symptom occurred half an hour to an hour

Table 3 Relation of initial prodromal symptom to additional ones preceding the overt attack of asthma

| Initial prodromal symptom* | Additional prodromal symptoms | | | | | | |
|-------------------------------|-------------------------------|-------|-------------------|-------|----------------------------|----------------|-----------|
| | Rhinorrhoea | Cough | Behaviour changes | Fever | Gastro-intestinal symptoms | Skin eruptions | Toothache |
| Rhinorrhoea (39) | — | 39 | 10 | 5 | 3 | 2 | 1 |
| Cough (23) | 11 | — | 6 | 5 | 1 | 2 | 1 |
| Behavioural changes (19) | 5 | 19 | — | 1 | 5 | 2 | 0 |
| Fever (5) | 3 | 5 | 1 | — | 0 | 0 | 0 |
| Gastrointestinal symptoms (4) | 2 | 4 | 2 | 0 | — | 0 | 0 |
| Skin eruption (4) and itching | 1 | 4 | 1 | 0 | 0 | — | 0 |
| Toothache (1) | 1 | 1 | 0 | 0 | 0 | 0 | 0 |

Numbers in parentheses refer to the number of patients presenting with the particular set of symptoms.

before the attack of asthma without any premonitory warning. In the remaining nine (23%) respiratory symptoms, seen as rhinorrhoea, cough, and strong wheezing, occurred one to six hours before the overt attack of asthma. The history asthma severity score was 2.18 (0.85) for the patients in group A and 2.15 (0.90) for those in group B.

Serum samples for the determination of IgE concentrations were available in 82 patients (53 of the 95 patients in group A and 29 of the 39 patients in group B). Sex distribution, mean age, and type of asthma were similar in these patients compared with those who had no serum samples available for IgE determinations. The interpretation of serum IgE concentrations in the 82 patients with serum samples available was therefore considered to be representative of the whole study group. No significant difference in the serum log (IgE) values between patients with (2.56 (0.32)) or without prodromal symptoms (2.64 (0.34)) was observed.

A significant age related increase in log (IgE) values was observed in patients who had prodromal symptoms; no such relation was observed in the patients in group B (Figure). Prick tests were performed in 65 of 118 patients with personal and/or family atopic history. Fifty three of them showed positive reactions to one or more allergens. Of

these, 39 belonged to group A and 14 to group B ($\chi^2=0.135$, p =not significant).

Discussion

The presence of prodromal symptoms preceding the overt attack in some of the patients with asthma has been recognised previously but not studied carefully.¹⁻⁴ These symptoms may not be confined to the respiratory tract alone and may often involve other systems as well. In 95 of the 134 patients followed by us the attack of asthma was preceded by prodromal features that were usually constant for any given patient. The most commonly affected system in our study was the respiratory tract, followed by behavioural changes. Other symptoms such as fever, abdominal pain, or skin eruption were rare. Itching, a common symptom in other studies,^{2,3} was observed in only three patients, though this was probably due to the younger age of our population. The mean (SD) interval between the occurrence of the initial prodromal symptom and the attack of asthma was 23.5 (11.1) hours for the 95 patients with prodromal symptoms. The interval for patients whose initial prodromal symptom was of a respiratory nature was not significantly longer than for those whose initial prodromal

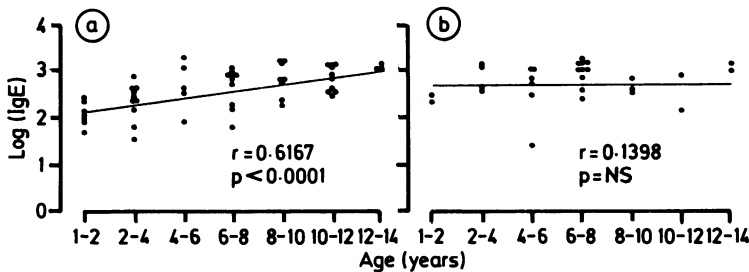


Figure Individual serum IgE concentrations according to age in patients with (a) and without (b) prodromal symptoms.

NS=Not significant.

symptom was not respiratory in nature ($p < 0.1$). Prodromal symptoms that were not of a respiratory nature were less common. They occurred in 33 (35%) patients as the initial symptom. The mean age in years of the patients with initial symptoms of a respiratory nature was significantly higher than that of the patients with initial symptoms of a non-respiratory nature ($p < 0.0005$). It is clear, therefore, that in younger patients the prodroma begins more often with initial symptoms that are non-respiratory in nature. A comparison of individual characteristics of patients with or without prodromal symptoms showed no significant difference in the type of asthma (seasonal or perennial), sex distribution, age, family history of allergy, or severity of asthma.

Weather changes and upper respiratory infection are associated with gradual onset of acute attacks of asthma.¹ Most of our patients with prodroma had their acute attack in changing weather periods. The rapid development of the acute attacks in the patients in group B may be due to specific, intermittent, but overwhelming allergic or irritant exposure.

As our study was a retrospective one some degree of mild bronchoconstriction, clinically unrecognisable by the parents, may have existed in some of our patients during their prodromal phase. Obviously, based on our questionnaire we cannot define the exact onset of the attack of asthma. As the vast majority of patients are treated at home, however, it seems, from a practical point of view, that parental recognition of these prodromal symptoms may lead to an early introduction of treatment, thus avoiding or abbreviating some of the attacks of asthma.

Serum IgE concentrations increased with age in patients with prodromal symptoms. In patients without any preceding symptom no such relation was observed. Whether this observation reflects a

basic immunological difference that signifies a different development in the allergy pattern in the two groups of patients remains unclear.

It seems to us that the differentiation of the population with asthma into two groups according to the presence or absence of prodromal symptoms may lead to a different therapeutic approach. In children with an acute onset of asthma continuous prophylactic treatment may be indicated, whereas in children with preceding symptoms treatment may be introduced only at the onset of the initial prodromal findings.

We gratefully acknowledge the suggestions and comments of Dr Ida Boldur in the preparation of the manuscript, the advice of Professor Yanai Kannai in the statistical analysis, the enthusiastic participation of Baruch Yaël RN, and the secretarial help of Mrs Janine Szychman.

References

- ¹ Leffert F. The management of chronic asthma. *J Pediatr* 1980;**96**:1-12.
- ² Orr AW. Prodromal itching in asthma. *J R Coll Gen Pract* 1979;**29**:287-8.
- ³ David TJ, Wibrew M, Hennessen U. Prodromal itching in childhood asthma. *Lancet* 1984;ii:154-5.
- ⁴ Bhagat RG, Grunstein MM. Comparison of responsiveness to metacholine, histamine, and exercise in subgroups of asthmatic children. *Am Rev Respir Dis* 1984;**129**:221-4.
- ⁵ The American Thoracic Society. Definitions and classifications of chronic bronchitis, asthma and pulmonary emphysema. *Am Rev Respir Dis* 1972;**85**:762-9.
- ⁶ Murray AB, Fergusson AC, Morisson B. Airway responsiveness to histamine as a test for overall severity of asthma in children. *J Allergy Clin Immunol* 1981;**68**:119-24.
- ⁷ Ciba-Geigy. *Documenta Geigy*. 7th ed. Geneva: Ciba-Geigy, 1973.

Correspondence to Dr S Beer, Pediatric Pulmonary-Allergic Service, Assaf Harofeh Medical Center, Zerifin 70300, Israel.

Received 10 November 1986