

Is serum eosinophil cationic protein in bronchiolitis a predictor of asthma?

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To examine their possible predictive value for the development of asthma, the serum concentration of eosinophil cationic protein (ECP) and the total eosinophil count were measured at admission in 25 children aged 1–17 months hospitalized for their first episode of bronchiolitis. After an average of three years the parents of 23 index patients answered a questionnaire to determine development of asthma. Eight children were defined as having asthma at follow-up based on at least three episodes of wheezing. The remaining 15 children had experienced only one or two episodes of wheezing, and all of these children had been wheeze free for the last year. The serum concentrations of ECP were similar in children who subsequently developed asthma (8.0 µg/l; 3.6 to 14.2 (median; quartiles)) and in those who did not (12 µg/l; 4.5 to 16.8). Moreover, the total eosinophil counts were similar in asthmatic ($0.10 \times 10^9/l$; 0.04 to 0.20) and non-asthmatic patients ($0.09 \times 10^9/l$; 0.02 to 0.13). In conclusion, our study suggest that neither the serum concentration of ECP nor the total eosinophil count can predict the development of asthma when measured in children admitted for their first episode of bronchiolitis, but larger studies need to be carried out to confirm these results.

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Key words: Eosinophil cationic protein; total eosinophil count; bronchiolitis; children; respiratory syncytial virus; asthma; wheezing

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Bronchiolitis or wheezy bronchitis is very common in early childhood and the condition may precede childhood asthma in as many as 40% of affected children (1, 2). However, most children will outgrow their symptoms before school-age (1–3). The prognosis for the individual child is difficult to predict, as there are at present no clinical or biochemical markers that can reliably identify the children that are likely to develop asthma (4).

Asthma is an inflammatory disease where activation of eosinophils is a key event (5). Serum eosinophil cationic protein (ECP) is accepted as a marker of eosinophil activation, and is suggested to reflect pulmonary inflammation in asthma (6). ECP has also been demonstrated in nasal washes and serum in wheezing infants (7–9), suggesting that eosinophil activation may contribute to the pathogenesis of the airway inflammation in this condition. Recently, serum ECP has been suggested as a predictor of asthma in young children with wheezing (10, 11).

Serum ECP and total eosinophil counts were measured in 25 children admitted to hospital for their first episode of bronchiolitis (9). To determine whether these parameters of eosinophil inflammation could predict the subsequent development of

asthma in these children, they were re-evaluated at a three-year follow-up.

Methods

Study subjects

Patients: Twenty-five children aged 1 to 17 months (mean 6.8 months) needing hospitalization for their first episode of bronchiolitis were included (9). Bronchiolitis was defined as acute respiratory illness with tachypnea, dyspnea, prolonged expiration and wheezing on auscultation of the chest. Nasopharyngeal mucus was examined for respiratory syncytial virus (RSV) by direct immunofluorescence in all patients (bioMérieux, Marcy-l'Étoile, France). Twelve of the patients were RSV positive and 13 RSV negative. Seven of the patients with bronchiolitis had serum concentrations of total IgE above the normal age range, and one of these had atopic dermatitis. No patient had signs of bacterial infection, as evaluated by clinical examination, chest X-ray, total leukocyte counts and normal serum C-reactive protein.

About three years after the first examination (mean age 46 months, range 37 to 57) the parents of 23 chil-

dren answered a questionnaire concerning the child's respiratory illness. They were asked about all episodes of wheezing, any anti-asthmatic treatment, chronic cough and if the child had been given the diagnosis of bronchitis or asthma by a doctor. Asthma was defined as three or more episodes of wheezing with no signs of other conditions, with at least one of the episodes during the last year (12).

Controls: Ten non-atopic children without asthma or infection served as controls (mean age 62 months; range 13 to 86 months) (9).

Ethics: The study was approved by the Regional Ethical Committee, and signed statements of informed consent were obtained from all parents.

Laboratory analysis

Venous blood was drawn immediately after admission. Serum was prepared and serum ECP were measured according to the recommendation given by the manufacturer (Pharmacia, Uppsala, Sweden)(9). The reference range for ECP was 2.3 to 16.0 µg/l. Serum total IgE was analysed using Pharmacia's CAP system. Serum-IgE levels > 1 SD above the age related mean value was considered elevated. The total eosinophil count was determined in all study subjects.

Statistical analysis

Significance was determined by the Wilcoxon two sample-test. $P < 0.05$ was considered significant. The results are given as median and quartiles.

Results

Patient characteristics

Eight children were defined as having asthma at follow-up on the basis of at least three episodes of recurrent wheezing and at least one episode during the last year. The remaining 15 children had experienced only one or two wheezing episodes and all of them had been without wheezing in the last year. None of these children had chronic cough that could have been an indicator of undiagnosed asthma. There was no difference in serum total IgE between those who developed asthma (6.5 kU/l; 2.5 to 21) (median; quartiles) and those who did not (2 kU/l; 2 to 8). However, four of eight patients who had developed asthma and three of fifteen who had not developed asthma had elevated IgE at their first episode of wheezing (not significant). At follow-up, one patient in each group had developed atopic dermatitis. Two of ten children with RSV bronchiolitis and six of 13 with bronchiolitis caused by other agents had developed asthma.

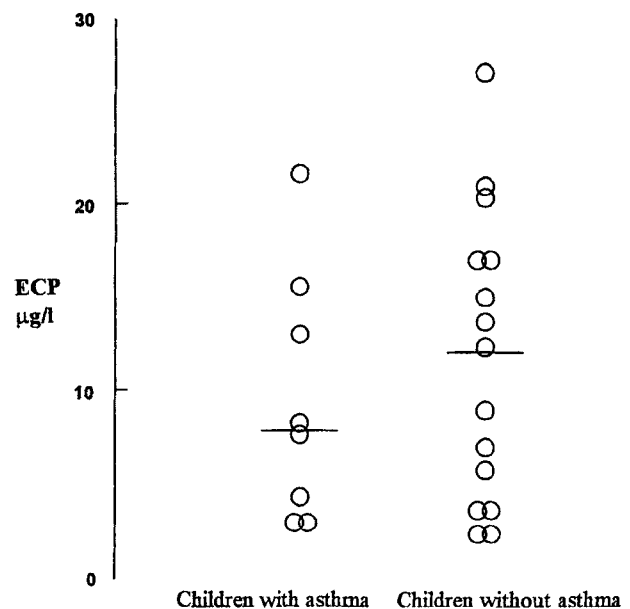


Fig. 1. The serum concentrations of ECP at admission in eight children with bronchiolitis who subsequently developed asthma (8.0 µg/l; 3.6–14.2) (median, quartiles) and in 15 children who did not (12 µg/l; 4.5–16.8). Lines indicate the median.

Serum concentrations of ECP and total eosinophil counts

The concentrations of serum ECP and total eosinophil counts at admission have been reported earlier (9). Briefly, the circulating levels of ECP were similar in patients with bronchiolitis (8.8 µg/l; 3.6 to 16.6) and controls (11.7 µg/l; 5.5 to 14.4). However, the children with RSV bronchiolitis had higher serum concentrations of ECP than those with bronchiolitis caused by other agents (15.2 µg/l; 10.4 to 17.3 and 5.5 µg/l; 3.2 to 10.9; $P < 0.05$). The values of serum ECP for those who subsequently developed asthma (8.0 µg/l; 3.6 to 14.2) were similar to those who did not (12 µg/l; 4.5 to 16.8) (Fig. 1).

At admission, the total eosinophil counts were significantly lower in children with RSV bronchiolitis ($0.07 \times 10^9/l$; 0.03 to 0.20) and in those with RSV negative disease ($0.09 \times 10^9/l$; 0.02 to 0.16) as compared to the controls ($0.26 \times 10^9/l$; 0.18 to 0.37) ($P < 0.05$ for both). However, the total eosinophil counts for those who subsequently developed asthma ($0.10 \times 10^9/l$; 0.04 to 0.20) were similar to those who did not ($0.09 \times 10^9/l$; 0.02 to 0.13) (Fig. 2).

Discussion

The aim of this study was to determine whether during bronchiolitis the serum concentration of ECP or the total eosinophil count at admission could indicate the subsequent development of asthma. It was not possible to predict, either from the serum con-

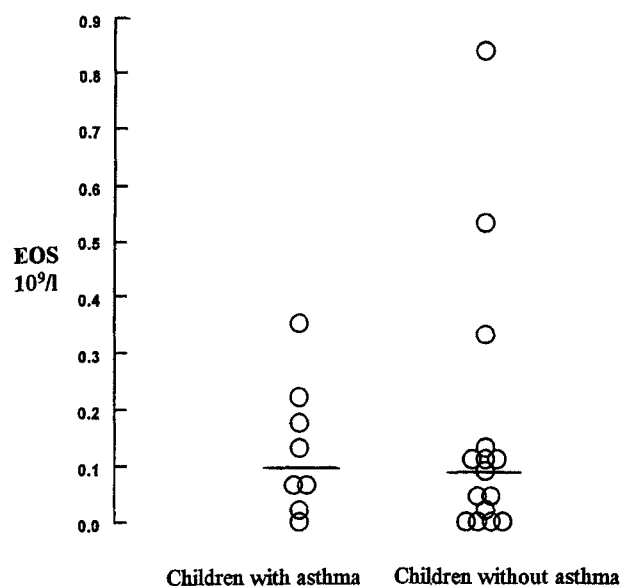


Fig. 2. The serum concentrations of the total eosinophil counts (EOS) at admission in eight children with bronchiolitis who subsequently developed asthma ($0.10 \times 10^9/l$; 0.04 – 0.20) (median; quartiles) and in 15 children who did not ($0.09 \times 10^9/l$; 0.02 – 0.13). Lines indicate the median.

centrations of ECP or the total eosinophil counts, who would develop asthma during the follow-up period of three years. Our study included a small number of patients with a risk of type II error – not to be able to show that the group which developed asthma had higher levels of serum ECP at admission for bronchiolitis. However, there is no tendency towards this in our results, on the contrary, the group who did not develop asthma tended to have higher levels of serum-ECP at admission. Further, seven out of eight patients who developed asthma had levels of serum ECP in the normal range, and five of 15 patients who did not develop asthma had serum ECP above the normal range. It is therefore not probable that including more patients would show that serum ECP would have high specificity or sensitivity in individual patients to predict asthma when measured at admission for bronchiolitis.

Increased levels of ECP have been demonstrated in serum and nasal secretion in children with wheezing, suggesting that the activation of eosinophils does play a role in the pathogenesis of the airway inflammation in these children (7, 8, 13, 14). In children with persisting wheezing, the concentration of ECP in nasal secretion may be elevated six (13) or even 24 months (7) after their first bronchiolitis. We observed the highest concentrations of serum ECP in children with RSV bronchiolitis (9), suggesting a more pronounced inflammatory response than that in wheezing episodes caused by other agents. However, in our study children with RSV bronchiolitis

did not develop asthma more frequently than those who were RSV negative, as reported by others (2, 15). Moreover, some of the highest serum concentrations of ECP were demonstrated in patients who experienced no further wheezing (Fig. 1). Hence, elevated serum concentrations of ECP in young children with bronchiolitis probably reflect the actual inflammatory activity rather than the onset of a process that induces asthma.

The results of our study are consistent with those of Sigurs, *et al.* (13) who in children with bronchiolitis found that the concentration of ECP in serum or nasal secretion had no predictive value as to the development of asthma during a follow-up period of two years. Koller, *et al.* (10) have recently demonstrated higher levels of serum ECP in a group of children who one year after their first episode of wheezing fulfilled the criteria for asthma than in children who did not develop asthma. However, those patients were only 19 months old at follow-up. A high proportion of children with recurrent wheeze at this age will outgrow their symptoms before the age of three (1, 3). Recently, Reijonen, *et al.* (11) demonstrated that high levels of serum ECP measured at admission for bronchiolitis had high specificity but low sensitivity to predict further wheezing. However, these children were only followed for 16 weeks. Hence, it is possible that elevated serum ECP in bronchiolitis may predict wheezing only in the subsequent months. The patients in our study were between three and four years of age at follow-up, an age group where individual symptoms seem to be the strongest predictors of asthma (3), and in this age group serum ECP does not appear to be a powerful clinical predictor of asthma.

In two earlier studies no increased risk has been reported as to the development of asthma in atopic children with bronchiolitis compared to non-atopics (13, 16). In our study there was a tendency towards a higher risk for subsequent asthma in children with IgE above the normal age range, but the numbers were too small to reach significance.

As this is a retrospective study, the results may be weakened by recall bias. However, in the group of non-asthmatic patients, the parents reported no symptoms of wheezing or chronic cough occurring the last year before answering the questionnaire and no children had received any anti-asthmatic treatment or had been given the diagnosis of bronchitis or asthma during the same period. Hence, it is unlikely any of these children suffered from undiagnosed asthma.

In conclusion, in 23 children experiencing their first episode of bronchiolitis, neither the serum concentration of ECP nor the total eosinophil count could predict asthma in later childhood. However,

larger studies need to be carried out to confirm these findings.

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