Cough, airway inflammation, and mild asthma exacerbation

A B Chang, V A Harrhy, J Simpson, I B Masters, P G Gibson

Background: Prospective data on the temporal relation between cough, asthma symptoms, and airway inflammation in childhood asthma is unavailable.

Aims and methods: Using several clinical (diary, quality of life), lung function (FEV1, FEV1 variability, airway hyperresponsiveness), cough (diary, cough receptor sensitivity [CRS]), and inflammatory markers (sputum interleukin 8, eosinophilic cationic protein [ECP], myeloperoxidase; and serum ECP) of asthma severity, we prospectively described the course of these markers in children with asthma during a non-acute, acute, and resolution phase. A total of 21 children with asthma underwent these baseline tests; 11 were retested during days 1, 3, 7, and 28 of an exacerbation.

Results: Asthma exacerbations were characterised by increased asthma and cough symptoms and eosinophilic inflammation. Sputum ECP showed the largest increase and peaked later than clinical scores. Asthma scores consistently related to cough score only early in the exacerbation. Neither CRS nor cough scores related to any inflammatory marker.

Conclusion: In mild asthma exacerbations, eosinophilic inflammation is dominant. In asthmatic children who cough as a dominant symptom, cough heralds the onset of an exacerbation and increased eosinophilic inflammation, but cough scores and CRS do not reflect eosinophilic airway inflammation.

The severity of asthma can be categorised using several methods, such as assessment of clinical symptoms, pulmonary lung function indices (forced expiratory volume in one second [FEV1] or its variability), degree of airway hyperresponsiveness (AHR), quality of life (QOL), and sputum and serum inflammatory markers. The relation between asthma symptoms and lung function variables can be poor. Airway inflammation has recently been recognised as a determinant of asthma symptoms and physiology, and some have advocated sputum rather than clinical indices as the outcome measure.

Airway inflammation is a characteristic feature of acute exacerbations in asthmatic children where there is evidence of both eosinophilic and neutrophilic inflammation. Serum eosinophilic cationic protein (ECP) levels have been shown to correlate with clinical symptoms and FEV1 in children, and some groups have advocated the use of serum and sputum ECP in disease monitoring. In a prospective study of exacerbations in adults, sputum markers changed before clinical variables. However, there are no prospective data on the course and relation between these variable clinical and non-clinical markers of severity during a non-acute, acute, and resolution phase of childhood asthma. Childhood asthma differs from adult asthma in many distinctive ways, although they also share some common features. Understanding the course of the various markers of childhood asthma severity in mild and severe asthma exacerbations is important, as increasingly arguments are made for adequate anti-inflammatory treatment based on airway inflammation rather than on surrogates such as symptoms and spirometry. Studying mild asthma exacerbations is arguably more relevant as more children with asthma have such episodes rather than severe episodes requiring emergency attendance or hospitalisation.

Cough as a sole symptom has been equated to asthma, and included in asthma severity scales. Recent literature has questioned this approach, and contemporary asthma diary scores have removed isolated cough. It has been established that in human airways, the pathways for cough and broncho-constriction are distinctly different. Nevertheless, clinically it is well known that in some children, cough heralds the onset of an asthma exacerbation and alterations in cough receptor sensitivity (CRS) have been shown in those who cough with their asthma episodes. Furthermore, cough can be the sole manifestation of eosinophilic airway inflammation in adults with cough variant asthma and eosinophilic bronchitis. The relation between CRS, subjective cough scores, and airway inflammation is unknown in childhood asthma. In particular, to the authors’ knowledge, there is no published study that has prospectively defined the temporal relation between cough, asthma symptoms, and airway inflammation in a group of children with classical clinical asthma. The aims of this study were: (1) to examine and relate common asthma indices (QOL, AHR, lung function, asthma diary) with cough scores (CRS, cough diary) and markers of eosinophilic and neutrophilic inflammation (serum ECP, sputum ECP interleukin 8 [IL-8], myeloperoxidase [MPO]) in children with asthma during a non-acute, acute, and resolution phase of asthma; and (2) to determine if baseline markers’ clinical or inflammatory parameters could predict future asthma exacerbation. We hypothesised that the time sequence of airway inflammation would differ from asthma and cough symptoms.

METHODS

Children with classical clinical asthma (recurrent airways obstruction manifested by wheeze and dyspnoea relieved by bronchodilator therapy) aged 5.5–16 years were recruited.

Abbreviations: AHR, airway hyperresponsiveness; CRS, cough receptor sensitivity; ECP, eosinophilic cationic protein; ETS, environmental tobacco smoke; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HS, hypertonic saline; IL, interleukin; IQR, interquartile range; MPO, myeloperoxidase; QOL, quality of life
from the outpatient department. Children with any chronic disease (other than asthma) were excluded. The children were tested when well (no respiratory tract infection or exacerbation of asthma for at least four weeks) during baseline. A clinical history was obtained and a repeatable question of cough dominant asthma was utilised.\(^4\) At baseline, the children underwent: venipuncture for ECP (serum ECP), skin prick test, spirometry, capsaicin CRS test,\(^5\) hypertonic saline (HS) test, induced sputum, and FEV\(_1\) measured twice a day on a pocket digital spirometer (Vitalograph 2110 Electronic Diary, Buckingham, UK) for a week. The children and parents also kept separate daily daytime diaries for cough and asthma symptoms. The validated cough scale utilised a verbal descriptive score. Children and parents completed the child and carer’s component of their asthma symptoms in the asthma diary (cannot perform most usual daytime activity because of severe symptoms). The validated cough scale utilised a verbal descriptive score of daytime coughs, ranging from 0 (no cough) to 5 (cannot perform most usual daytime activity because of severe coughing).\(^6\) The asthma score was the average of four questions,\(^7\) and the children and parents excluded the cough component of their asthma symptoms in the asthma diary score. Children and parents completed the child and carer’s QOL questionnaire respectively.\(^8\) History of environmental tobacco smoke (ETS) exposure was obtained; urine cotinine levels were measured using gas chromatography with deuterated cotinine as an internal standard.

Subjects were retested on days 1 (D1), 3 (D3), 7 (D7), and 28 (D28) of an asthma exacerbation (increased wheeze, chest tightness, and requirement for additional bronchodilator medications for more than eight hours). The study was carried out between February 1999 and January 2000. During repeat visits, all tests except the skin prick test were repeated. D1 tests were done before any additional steroids were taken. Exacerbation surveillance was done on diary cards and telephone reminders. On a monthly basis, new diary cards were sent, and the preceding month’s diary card returned. Written consent was obtained from the parent(s) and the study was approved by the local hospital’s Ethics Committee for Human Research.

### Statistical analysis

Statistical software package SPSS version 7.5 (Chicago, USA) was utilised. For continuous variables, the Mann–Whitney test was used for unpaired data and the Wilcoxon test for paired data. When repeated measurements were made, the Friedman and Kruskal–Wallis tests were utilised for paired and unpaired data respectively. Spearman correlation (\(r_s\)) was used for correlation. A two tailed \(p\) value of \(\leq 0.05\) was considered significant. Logistic regression was utilised for prediction of the development of an asthma exacerbation within the follow up period.

### RESULTS

Twenty one children were recruited (16 boys, five girls; median age 10.8 years, interquartile range (IQR) 3.9). Only 11 of the 21 children had an exacerbation of their asthma during the observation period of 175 person months. The median age of these 11 children (nine boys, two girls) was 10.53 years (IQR 3.9). All but one were atopic, nine were on regular inhaled corticosteroids, three on cromolyn, and four on long acting \(\beta_2\) relievers.

### Table 1: Spirometer indices, AHR, and clinical markers during baseline and an exacerbation of asthma

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=11)</th>
<th>Day 1 (n=11)</th>
<th>Day 3 (n=11)</th>
<th>Day 7 (n=11)</th>
<th>Day 28 (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(child recorded)</td>
<td>0.2 (0.89)</td>
<td>1.75 (0.75, 5)</td>
<td>1.5 (0.25, 2.75)</td>
<td>0 (0.75)</td>
<td>0.87 (0)</td>
</tr>
<tr>
<td>(parent recorded)</td>
<td>0.2 (0.88)</td>
<td>1.75 (1.25, 4.5)</td>
<td>1 (0.25, 3.75)</td>
<td>0 (0.25)</td>
<td>0.21 (0)</td>
</tr>
<tr>
<td><strong>Cough score</strong></td>
<td>0.66 (0.22, 1.44)</td>
<td>3.5 (2.4)</td>
<td>2 (1.75, 1.4)</td>
<td>1 (0.1)</td>
<td>0.72 (0)</td>
</tr>
<tr>
<td>(child recorded)</td>
<td>0.71 (0.14)</td>
<td>3 (2.4)</td>
<td>2 (2.4)</td>
<td>1 (0)</td>
<td>0.51 (0)</td>
</tr>
<tr>
<td><strong>Child’s QOL</strong></td>
<td>6.7 (5.7)</td>
<td>5.5 (5.1, 6.3)</td>
<td>5.6 (5.1, 6.1)</td>
<td>6.1 (5.5, 6.3)</td>
<td>7 (6.7, 7)</td>
</tr>
<tr>
<td><strong>Parents’ QOL</strong></td>
<td>6 (4.9, 6.7)</td>
<td>5.6 (4.7, 6)</td>
<td>5.5 (4.1, 5.9)</td>
<td>5.8 (5.2, 6.6)</td>
<td>4.4 (5.8, 7)</td>
</tr>
<tr>
<td><strong>FEV(_1) % predicted</strong></td>
<td>88 (76, 100)</td>
<td>85.5 (71, 92)</td>
<td>85.5 (62, 92)</td>
<td>87.4 (83, 98)</td>
<td>87.4 (76, 90)</td>
</tr>
<tr>
<td><strong>FVC % predicted</strong></td>
<td>94.5 (85, 106)</td>
<td>90.7 (83, 97)</td>
<td>89.5 (75, 105)</td>
<td>95.4 (89, 113)</td>
<td>95.4 (88, 108)</td>
</tr>
<tr>
<td><strong>FEV(_1) variability %</strong></td>
<td>7.4 (3, 11.3)</td>
<td>14.5 (4.3, 23.7)</td>
<td>4.6 (2.7, 17.1)</td>
<td>8.5 (5.2, 27)</td>
<td>4.6 (2.4, 9.9)</td>
</tr>
<tr>
<td><strong>AHR positive, n (%)</strong></td>
<td>2 (18%)</td>
<td>3 (30%)</td>
<td>3 (30%)</td>
<td>1 (10%)</td>
<td>4 (40%)</td>
</tr>
</tbody>
</table>

Results expressed as median (quartiles).  
*Wilcoxon test between baseline and day 1 data; †Wilcoxon test between baseline and day 3 data; ‡Wilcoxon test between baseline and day 7 data; §Friedman test for baseline, day 1, day 3, and day 7 data.
A strong correlation between cough and asthma score, as assessed at baseline, D1, D3, D7, and D28. At baseline and D1, there was an increase in sputum ECP, serum eosinophils, sputum eosinophils, and sputum neutrophils. There was no significant difference in the length of time from baseline to D1 for both child and parent scores when compared to baseline. These peaks were concurrent with the exacerbation and resolution state. Mild exacerbations were characterised by an increase in symptoms and airway inflammation, with non-significant changes in lung function. Only sputum ECP showed a significant increase during the exacerbation, and peaked later than clinical scores. Asthma scores consistently related to cough score only in the very early stages of the exacerbation. We have also shown that neither CRS nor cough scores relate to any of the inflammatory markers measured, and that spirometry, AHR, and FEV, variability were insensitive markers of mild asthma exacerbations. Lastly, baseline measurements could not predict the development of an exacerbation within the follow up time of 175 person months.

We have previously shown that in acute severe asthma, airway inflammation is characterised by infiltration of both eosinophils and neutrophils. In the present study where mild exacerbations were studied, eosinophilic but not neutrophilic inflammation was present (evidenced by D1 sputum eosinophils >2.5%, increase in sputum ECP but not IL-8 or MPO). This raises the question of whether the more common occurrence of mild asthma exacerbations in childhood differs from the less common severe exacerbations. In adults, neutrophilic inflammation occurs in the more severe forms of asthma.

DISCUSSION
This study has described the course of various markers of cough and asthma, spirometry indices, and airway inflammation in childhood asthma, from baseline to an acute mild exacerbation and resolution state. The mild exacerbations were characterised by an increase in symptoms and airway inflammation, with non-significant changes in lung function. Only sputum ECP showed a significant increase during the exacerbation, and peaked later than clinical scores. Asthma scores consistently related to cough score only in the very early stages of the exacerbation. We have also shown that neither CRS nor cough scores relate to any of the inflammatory markers measured, and that spirometry, AHR, and FEV, variability were insensitive markers of mild asthma exacerbations. Lastly, baseline measurements could not predict the development of an exacerbation within the follow up time of 175 person months.

Table 2: Cough receptor sensitivity and inflammatory markers during baseline and an exacerbation of asthma

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=11)</th>
<th>Day 1 (n=11)</th>
<th>p*</th>
<th>Day 3 (n=11)</th>
<th>Day 7 (n=11)</th>
<th>Day 28 (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS</td>
<td>110 (9, 157)</td>
<td>78 (11, 122)</td>
<td>0.17</td>
<td>39 (11, 156)</td>
<td>78 (31, 322)</td>
<td>39 (11, 78)</td>
</tr>
<tr>
<td>% Sputum eosinophils</td>
<td>2.8 (1, 2)</td>
<td>6.42 (8, 10)</td>
<td>0.8</td>
<td>3.6 (8, 12)</td>
<td>7.5 (9, 3)</td>
<td>3.64 (9, 9)</td>
</tr>
<tr>
<td>% Sputum neutrophils</td>
<td>4.8 (23, 22)</td>
<td>28.3 (4, 56)</td>
<td>0.33</td>
<td>8.0 (9, 27)</td>
<td>36.8 (10, 60)</td>
<td>9.7 (10, 63)</td>
</tr>
<tr>
<td>Sputum ECP (ng/ml)</td>
<td>151 (33, 460)</td>
<td>457 (8, 233)</td>
<td>0.017</td>
<td>1154 (4, 129)</td>
<td>2886 (9, 45)</td>
<td>335 (10, 27)</td>
</tr>
<tr>
<td>IL-8 [ng/ml]</td>
<td>0.76 (0, 1.22)</td>
<td>1.69 (8, 0.79)</td>
<td>0.11</td>
<td>6.21 (8, 0.27)</td>
<td>1.39 (8, 0.6)</td>
<td>0.92 (10, 0.66)</td>
</tr>
<tr>
<td>MPO [mg/ml]</td>
<td>24.5 (9, 4.5)</td>
<td>53.6 (8, 9.1)</td>
<td>0.17</td>
<td>14.4 (7, 19.8)</td>
<td>14.4 (9, 14.1)</td>
<td>26.2 (10, 14.4)</td>
</tr>
<tr>
<td>Serum ECP [ng/l]</td>
<td>34.5 (10, 59.3)</td>
<td>45 (10, 15)</td>
<td>0.24</td>
<td>33 (10, 21)</td>
<td>2886 (9, 14.5)</td>
<td>335 (10, 19.5)</td>
</tr>
</tbody>
</table>

Results expressed as median (quartiles).
*Wilcoxon test between baseline and day 1 data; †Wilcoxon test between baseline and day 3 data; ‡Wilcoxon test between baseline and day 7 data; §Friedman test for baseline, day 1, day 3, and day 7 data.

Figures in parentheses indicate statistically significant differences.
and typically reflects an infective cause. Eosinophilic exacerbations can be triggered by allergen exposure or non-compliance with corticosteroid therapy. Poor agreement between clinical judgement (symptoms, spirometry) and airway inflammatory component assessed by sputum cell counts has been recently described in adults with asthma. We have also shown that asthma symptoms related poorly to most inflammatory markers in mild exacerbations of childhood asthma. The relation between sputum ECP and asthma was significant but negatively associated; as asthma exacerbation where neutrophilic airway inflammation occurs, poor to most inflammatory markers in mild exacerbations of childhood asthma with its various phenotypes are unlikely to predict the development of an asthma exacerbation within the follow up period. As viral infections are the commonest cause of asthma exacerbations in children, this finding is not surprising. However, this study is limited by small numbers and a relatively short follow up period. Martinez argues that in an individual patient (in contrast to research), single markers for childhood asthma with its various phenotypes are unlikely to be useful as they are context and time variant dependent. This study cannot answer the question of the usefulness of the various markers of asthma in an individual patient, but the data presented support the sensitivity of sputum ECP when compared to other indices of asthma severity.

Although cough features prominently in asthma management plans, whether the presence of cough does indeed herald the onset of an asthma exacerbation has never been shown prospectively. This study has shown this is indeed true in a selected group of children, whose parents had previously indicated that cough was a significant symptom with their asthma episodes. We were unable to compare coughers versus non-coughers because of the small sample size. Although we used a validated cough score chart, this finding is also limited by the lack of an objective cough monitor, as symptoms reflect perception, which is known to be dependent on the population studied. Nevertheless we found no relation between CRS and asthma inflammatory markers, again raising the question whether cough should be used as a marker of asthma severity in the non-acute asthma. The occurrence of cough without an increase in CRS may be related to an irritant effect or cough receptor activation by eosinophilic activates. The reduction in cough symptoms while sputum ECP was still raised could be a result of temporal adaptation to the cough stimulus. In this study CRS measures did not change, unlike our previous study which described increased cough sensitivity during the coughing period in hospitalised children with asthma. We postulate this difference relates to the different asthma exacerbations studied (mild versus severe exacerbation where neutrophilic airway inflammation occurs), and possibly to the small sample size.

Children with ETS exposure were more likely to have higher asthma and cough scores at baseline but not during an exacerbation. We did not find any difference in the inflammatory markers. A three hour ETS exposure did not change cellular and inflammatory markers (ECP, MPO, tryptase, prostanoids, and leukotrienes) in bronchoalveolar lavage fluid and FEV,

Table 3 Correlation between the different markers at baseline and day 1 of asthma exacerbation

<table>
<thead>
<tr>
<th></th>
<th>Asthma score (parent recorded)</th>
<th>Cough score (child recorded)</th>
<th>Cough score (parent recorded)</th>
<th>Child’s QOL (child recorded)</th>
<th>Parents’ QOL (parent recorded)</th>
<th>IL-8</th>
<th>Sputum ECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.93 (0.0001)</td>
<td>0.81 (0.002)</td>
<td>0.84 (0.001)</td>
<td>-0.91 (0.0001)</td>
<td>-0.76 (0.006)</td>
<td>0.1 (0.37)</td>
<td>0.32 (0.25)</td>
</tr>
<tr>
<td>Day 1</td>
<td>0.75 (0.008)</td>
<td>0.88 (0.001)</td>
<td>0.84 (0.001)</td>
<td>-0.014 (0.48)</td>
<td>0.24 (0.031)</td>
<td>-0.76 (0.01)</td>
<td>-0.83 (0.01)</td>
</tr>
<tr>
<td></td>
<td>0.75 (0.004)</td>
<td>0.78 (0.004)</td>
<td>0.78 (0.004)</td>
<td>-0.27 (0.43)</td>
<td>-0.22 (0.51)</td>
<td>-0.79 (0.02)</td>
<td>-0.76 (0.03)</td>
</tr>
<tr>
<td></td>
<td>0.97 (0.0001)</td>
<td>0.11 (0.76)</td>
<td>0.19 (0.6)</td>
<td>-0.43 (0.29)</td>
<td>-0.38 (0.13)</td>
<td>0.55 (0.13)</td>
<td>-0.58 (0.13)</td>
</tr>
<tr>
<td></td>
<td>-0.27 (0.43)</td>
<td>0.2 (0.56)</td>
<td>0.55 (0.16)</td>
<td>0.55 (0.16)</td>
<td>-0.58 (0.14)</td>
<td>0.17 (0.6)</td>
<td>0.17 (0.6)</td>
</tr>
<tr>
<td></td>
<td>0.51 (0.11)</td>
<td>0.29 (0.49)</td>
<td>0.29 (0.49)</td>
<td>-0.17 (0.49)</td>
<td>0.14 (0.69)</td>
<td>-0.14 (0.48)</td>
<td>0.14 (0.69)</td>
</tr>
<tr>
<td></td>
<td>0.43 (0.43)</td>
<td>0.43 (0.43)</td>
<td>0.43 (0.43)</td>
<td>0.43 (0.43)</td>
<td>0.43 (0.43)</td>
<td>0.43 (0.43)</td>
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</tbody>
</table>

Results expressed as Spearman correlation (two tailed p value).
but increased symptoms in adults with mild asthma.11 The lack of difference could be related to the small subject numbers or more likely, the appropriate inflammatory marker was not measured. In animal studies, ETS exposure primarily causes neurogenic inflammation,12 which is arguably important in the symptom perception of cough and chest tightness.13

We conclude that in mild asthma exacerbations in children, eosinophilic inflammation is dominant, and that the common used clinical indices of asthma, FEV1, FEV1 variability, and AHR are insensitive markers. These markers could not predict the development of an asthma exacerbation. In the subgroup of children with asthma (those with cough dominant asthma), the presence of cough heralds the onset of an exacerbation and increased eosinophilic inflammation, but cough scores and CRS do not reflect eosinophilic inflammation during the course of the exacerbation. Whether cough scores and CRS reflect neutrophilic airway inflammation in severe childhood asthma exacerbations is unknown.

### ACKNOWLEDGEMENTS

We thank Peter Dash (cytology department) for performing the cell differential counts and Dr Melissa Hubbard for her assistance in examining some children during their asthma exacerbation. The project was supported in part by The Sylvia and Charles Viertel Charitable Trust.

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Cough and asthma markers in acute asthma

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Screening for coeliac disease has benefits in Williams syndrome

Researchers in Italy have shown that coeliac disease coexists with Williams syndrome, a disorder resulting from a deletion on chromosome 7q11.23. Among other features of Williams syndrome are gastrointestinal symptoms. Feeding problems, colic, vomiting, constipation, and recurring abdominal pain are common in young children. Unusually, however, coeliac disease has been noted before only sporadically in Williams syndrome, given that its presence is high—around 4–13%—in other chromosomal disorders such as Down syndrome and Turner syndrome.

Gianotti et al screened a consecutive series of 63 children (mean age 11 years) with Williams syndrome confirmed by molecular techniques for concentrations of antigludin antibodies and antiendomysium antibodies—serological markers of coeliac disease. Coeliac disease was indicated in seven children in the series who tested positive for antigludin and antiendomysium antibodies, and was confirmed by characteristic histological findings of villous atrophy in six who had a jejunal biopsy. All patients with confirmed coeliac disease in the series responded well to a gluten free diet.

The prevalence of coeliac disease in the series (9.6%, 6/63) was significantly higher than a published general population estimate (0.54%, 1/184) obtained from a population of more than 17 000 Italians aged 6–15 years and fell within the prevalences noted for Down and Turner syndromes.

On this basis Gianotti et al recommend antibody screening for coeliac disease in patients with Williams syndrome.