Relationship of exercise-induced asthma to clinical asthma in childhood

LIONEL BALFOUR-LYNN, MARIAN TOOLEY, AND SIMON GODFREY

Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital

SUMMARY Thirty-three asthmatics were followed up for a mean of 8.5 years in a prospective study in order to observe the clinical course of the disease. The severity of asthma was graded according to the treatment each required to keep him in reasonable health. Regular exercise tests were performed so that a comparison could be made between the degree of exercise-induced asthma and the severity of the disease. In this group of severe perennial childhood asthmatics profound exercise-induced asthma was found to exist throughout the entire clinical spectrum of the disease with no appreciable difference until the patient became symptom-free. Exercise-induced asthma then disappeared only to return if clinical asthma recurred. This study showed that exercise-induced asthma is a sensitive indicator of clinical asthma but has no prognostic significance in the symptom-free patient.

A relationship between exercise-induced asthma (EIA) and the long-term prognosis of the clinical disease in children was first suggested by Jones and Jones and supported by Blackhall. They noted that a considerable number of asthmatics had become symptom-free by the end of puberty, but that some of them relapsed later. They related these events by attempting to show that EIA varied little in ex-asthmatic subjects over several years, and that the patients who continued to exhibit EIA were the ones most likely to relapse if exposed to the appropriate trigger. In a one-year prospective study of asthmatic children, this contention was supported by Silverman and Anderson who suggested that EIA was a persistent feature of asthma and was independent of variations in clinical state.

During the course of a long-term prospective follow-up of childhood asthmatics during which clinical progress was observed throughout childhood and adolescence, regular exercise tests were performed. These are now reviewed to find out if any relationship exists between EIA and clinical asthma, and whether EIA has any value in predicting future asthmatic episodes.

**Methods**

At each clinic visit a detailed history was taken particularly noting the drug requirements of the preceding 6 months. Each patient had a complete physical examination, and a diary card recorded daily asthmatic symptoms for the previous month, spirometry (forced vital capacity and forced expiratory volume at one second), and peak expiratory flow rate (PEFR), using a Wright's peak flow meter, were measured. From this assessment, the treatment for the next 6 months was prescribed, the aim being to keep the child well enough to lead a normal life on the least treatment.

When the clinical assessment had been completed, an exercise test was performed as described by Silverman and Anderson. The child had to run continuously for 6 minutes on a treadmill, set at a speed and slope calculated to produce a final heart rate of about 170/min. PEFR (the best of three attempts on each occasion) was recorded before, during, and intermittently for 20 minutes after exercise. Pulse rate was counted at the end of the exercise. The lowest post-exercise fall in PEFR was

**Subjects**

Fifty-three children were observed in a one-year, double-blind trial of sodium cromoglycate (SCG) for severe perennial childhood asthma. It was possible to follow up 33 of these 53 children for a mean of 8.5 years: 2 for 6·0–6·9, 4 for 7·0–7·9, 16 for 8·0–8·9, 10 for 9·0–9·9, and 1 for 10 years. The mean age on entry to the study was 7·4 years, and the mean age at the end of follow-up was 15·9 years. Each was seen by one of us (L B-L) every 6 months as part of a prospective study to follow the course of the disease throughout childhood and puberty.
then compared with the pre-exercise PEFR as follows:
(pre-exercise PEFR—lowest PEFR after exercise) \( \times 100 / \text{pre-exercise PEFR} \).

Treatment with steroids was not stopped the day of the visit to the clinic as steroids have been shown not to influence the severity of EIA.\(^\text{14}\) However, children were asked not to take any bronchodilator or SCG to avoid affecting the results of the exercise tests. Although they were not always able to comply with this request, it was possible to carry out exercise tests on all the children in this study at least once a year.

As 98\% of normal children have a post-exercise fall in PEFR of less than 15\%,\(^\text{15-16}\) in this paper EIA means a post-exercise fall in PEFR greater than 15\%.

Unpaired \( t \) tests have been used in assessing the significance of group difference.

**Classification.** Treatment consisted of three basic regimens:

1. Treatment with bronchodilator could mean either full regular medication with salbutamol or orciprenaline orally or by inhalation, or occasional use. Theophylline was not prescribed for any patient as it had not been included in the initial SCG trial.

2. Treatment with SCG meant the inhalation of one capsule 4 times a day. If the patient’s condition improved, this was sometimes reduced to two capsules, but fewer than this was not considered to be SCG therapy.

3. Treatment with steroids consisted of regular aerosol inhalation of beclomethasone dipropionate in a dosage varying between 1 and 16 puffs (50-800 \( \mu \)g) a day. Early in the study, before this form of treatment was available, alternate-day oral prednisolone was used. Occasionally it was required later if treatment with beclomethasone dipropionate failed temporarily.

In both the SCG and steroid regimens, additional treatment with bronchodilators was encouraged if required, and any sudden acute exacerbation was treated with a short course of prednisolone, 1-2 mg/kg daily for 2-3 days until relieved, followed by rapid reduction during the next 3 or 4 days. However, if there were frequent exacerbations the regimen was changed. Patients inadequately controlled on bronchodilators were changed to SCG and if this failed too, they were prescribed regular treatment with aerosol steroids.

As each 6-monthly clinical assessment was directly related to the treatment required, a simple grading was used to assess the severity of the illness throughout the long period of follow-up. In decreasing severity, these grades were regular steroids, regular SCG, regular bronchodilator, occasional bronchodilator, no treatment.

**Progress**

Thirty-two of the 33 children had all initially been on SCG. They had either started with SCG or had been treatment failures on the placebo and had changed to SCG. Twenty of these 32 children were successfully treated with SCG, but 12 were not and had to be given steroids. The one remaining patient (Case 1) had been placed in the placebo group on entering the trial and was successfully managed on placebo with additional bronchodilators. He will be described later.

The 20 children successfully treated by SCG (Table 1) remained on this for a mean of 4.2 years. All were eventually able to stop the drug, 13 being controlled satisfactorily on regular bronchodilators, and 7 needing occasional bronchodilators only. Of the 13 children on regular bronchodilators, 5 still continue to need them. Of the remaining 8, one soon became symptom-free and required no therapy, and 7 reduced their need for bronchodilator to occasional use only. Thus, 14 children reached this stage and of them, 6 still require bronchodilators occasionally, and 8 are now well without treatment, so that 9 children are now symptom-free.

The 12 children who required treatment with steroids (Table 2) can be placed in 3 categories: 4 who took regular steroids throughout the period of follow-up, 5 who stopped taking regular steroids after a mean of 5-4 years as the condition of each appreciably improved; and 3 who had regular steroids for less than a year. As the last group had been given steroids because SCG had failed to control their asthma, SCG was not tried again when their condition improved.\(^\text{17-18}\)

<table>
<thead>
<tr>
<th>Clinical grading</th>
<th>Progress of children</th>
<th>Number of children in each grade</th>
<th>Who had exercise tests at end of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium cromoglycate</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>13</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Regular</td>
<td>7</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Occasional</td>
<td>5</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>No treatment</td>
<td>5</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>
The 5 children on prolonged steroid therapy were eventually satisfactorily controlled on bronchodilators, 4 taking them regularly, and one taking them occasionally. Of the 4 on regular bronchodilators, one still takes them regularly and 3 were able to reduce this to occasional use only. One of them no longer requires treatment. The one child who stopped taking steroids and was well enough to need only occasional bronchodilators, then became symptom-free for 18 months, but now has reverted to needing bronchodilators occasionally.

The 3 children who required steroids for less than a year still need to take regular bronchodilators. One of them did not have an exercise test during the period he was on steroids.

Results

The results on 32 children studied for a mean of 8.4 years are shown in Table 3. They are divided into two groups: group 1 (n = 20), children treated successfully with SCG; group 2 (n = 12), children with more severe asthma who needed steroids. The progress of the disease, as assessed by the treatment required to maintain reasonable health, is shown with the number of exercise tests each child performed. The degree of EIA in each grade is expressed as the mean post-exercise fall in PEFR. These results are also shown in Fig. 1. In both groups the mean post-exercise fall in PEFR was remarkably similar for children requiring SCG, steroids, or regular bronchodilators. For the children who had recovered sufficiently from the disease to require only an occasional bronchodilator, a stage when many would dismiss the disease as being negligible, the mean severity of EIA appeared to have diminished, particularly in the group taking steroids. However, this difference was not statistically significant. When patients in both groups finally became symptom-free and no longer required treatment, the degree of EIA fell significantly to within the normal range (P < 0.001).

Discussion

This prospective study of a hospital-controlled group of childhood asthmatics shows that profound EIA is present throughout the entire clinical course of the disease. The degree of EIA did not appear to
differ in patients requiring steroids, SCG, or regular treatment with bronchodilators to control their disease. Even when the illness became so slight that only the occasional use of a bronchodilator aerosol was required, the EIA had not appreciably altered. However, the disappearance of EIA in those patients who finally became symptom-free, was striking.

This is in sharp contrast to the conclusions of Jones and Jones and of Blackhall. Jones and Jones studied 8 young adults, with a mean age of 22 years, who had suffered from asthma in childhood but had been symptom-free for about 6 years, and carried out exercise tests to show they had a mean lability index of 38. Blackhall studied an older group of 12 men, with a mean age of 26 years, who had been free of asthma for about 10-6 years, and found an increased lability index in 7. When these papers were published, the upper limit of normal for the lability index was considered to be 15 with a few normal subjects being in the 15-20 range. However, the more extensive studies of Anderson extended the normal range of the lability index to 29-4 and if Blackhall had used this value all her patients would have been within the normal range. But this would not be so for the cases studied by Jones and Jones as their patients had a mean lability index of 38. Nevertheless it is reasonable to speculate that these cases, taken at random, might not have been entirely symptom-free. Most adults tend to ignore slight occasional tightness in the chest and adjust their life to avoid precipitating factors. They may be equivalent to the 'occasional bronchodilator' group in our classification. The mean fall in FEV1 of 31-4% after exercise, calculated from the data of Jones and Jones is close to the value found in the group taking bronchodilators occasionally in our study.

By demonstrating EIA in apparently normal adult ex-asthmatics, Jones and Jones and Blackhall envisaged a continuous state of abnormal bronchial lability somehow 'lying dormant' during a latent phase, waiting to be triggered off by an appropriate stimulus. This, they argued, could explain the relapses described by many investigators. Yet our study suggests that if clinical asthma disappears, so does EIA, and the bronchial lability returns to normal. However, if a relapse does occur, so too will the EIA, and rather than being a separate entity within the spectrum of asthma, it is merely a highly sensitive indicator of the presence of the clinical disease. This is particularly well shown by Case 1 (Fig. 2) a boy who had been followed up continuously for 9-2 years. In the original SCG trial he was placed in the placebo group and managed to remain well on regular bronchodilators only. He continued on this treatment for a further 3 years after which he appeared to recover, requiring occasional bronchodilators for 18 months and then being entirely symptom-free for 3 years during which period his original severe EIA dropped to the norm.

He then returned to the clinic with a severe asthmatic episode which had been steadily getting worse during the previous 2 months despite regular bronchodilators. This attack coincided with the introduction of a cat into the house. He was subsequently shown to be extremely sensitive to cat fur by prick testing. He responded to a short course of steroids but since then has continued to need intermittent bronchodilators and his EIA has again become profound.

Recently it has been shown that an increase in airways hyper-reactivity can occur in normal subjects after an influenza A infection of the upper respiratory tract and that the airways may remain labile for up to 7 weeks after resolution of the illness. The results of the present study could be explained by a similar alteration in airways reactivity, perhaps more prolonged and occurring in response to a wide variety of precipitating factors. Thus one can envisage a persistent state of increased airways lability brought about by the repeated assaults of a number of agents, the extent of the lability varying according to the prevailing challenge. EIA may be a
measure of this lability, reflecting changes in airways reactivity from time to time. With the development of immunity in later childhood and adolescence, resistance to major stimuli (for example, viral respiratory tract infections) may be associated with a fall in airways reactivity and hence with EIA. If finally the subject no longer has clinical asthma, this study would suggest that EIA can no longer be provoked thus indicating that the bronchi have lost their abnormal lability. However, if in the future a further challenge should cause the illness to recur, the bronchi can again be shown to be abnormally labile by a return of EIA.

The concept of EIA being merely part of the general syndrome of clinical asthma is much easier to accept than the current hypothesis of a separately inherited manifestation of a constant state of abnormal bronchial lability present throughout life, sometimes complicated by the disease and at other times not. Clinical experience has never supported this hypothesis as it is not uncommon to find the seasonal asthmatic actively engaged in sport when symptom-free, only to be affected during the asthma season. The mild perennial asthmatic may have been the cause of confusion in the past. EIA would seem to be such a sensitive indicator of abnormal bronchial lability that it can be easily demonstrated in these patients even though they may dismiss their symptoms as trivial. It is only in the truly symptom-free patient that EIA ultimately disappears. Even so, the disappearance is not necessarily synonymous with 'cure' as relapse may occur.

Conclusion

It would appear from this study that EIA is a highly sensitive indicator of clinical asthma in children; it disappears when the patient is truly symptom-free, but it has no prognostic significance as to the final outcome of the disease or the likelihood of relapse.

References


Correspondence to Dr L Balfour-Lynn, Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, Du Cane Road, London W12 0HS.

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