

Childhood asthma and puberty

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SUMMARY Thirty eight, chronic, perennial asthmatic children were prospectively examined every six months for a mean 8.9 years to clarify the relation between clinical asthma and puberty. Improvement in the disease occurred independent of puberty but the rate of improvement was appreciably greater during puberty. This led to speculation that improvement in childhood asthma could be associated with an immunological process capable of receiving a powerful stimulus from hormones active during puberty.

In addition, children whose illness improved before any sign of puberty had developed could be confidently predicted to 'grow out' of their disease. Conversely, if no improvement was seen by the onset of puberty, a much more guarded prognosis was needed.

It is common practice for a physician to comfort the parents of an asthmatic patient with the assurance that most children 'grow out' of their illness by puberty. This favourable prognosis has become generally accepted despite the sceptics who believe, as Levison *et al*,¹ that they merely outgrow their paediatricians. A review of 23 retrospective studies reported between 1929 and 1972² showed that of 6737 patients with childhood asthma, 47% became asymptomatic by the end of puberty and a further 37% had sustained a 'marked improvement'. This clearly indicated a tendency towards recovery even if the process was not always complete.

The timing of puberty varies, however, from one child to another. In boys, puberty may begin between 9.5 and 13.5 years and end between 13.5 and 17 years.³ In girls, the equivalent times are 8 to 13 years and 13 to 18 years. Furthermore, the interval between the first sign of puberty and complete maturity varies from 1.5 to 6 years.⁴ This means that retrospective studies, although showing that an improvement in asthma does occur in most patients, are unable to answer the question whether this improvement is directly related to puberty. Nor has the timing of puberty in subjects been noted in four prospective studies.⁵⁻⁸

This study was undertaken to clarify the relation between clinical asthma and puberty. A group of well documented, chronic, perennial asthmatic children was followed up every six months to record the progress of their disease and to relate it to puberty.

Subjects

In 1972, 53 children with chronic, perennial asthma, inadequately controlled by bronchodilators alone, completed a 12 month, double blind trial of sodium cromoglycate.⁹ Although 15 of these children were lost in the process of organising this long term study, it has been possible to follow up the remaining 38 children for an average period of 8.9 years (3.3 to 11.8 years). Their mean age of entry to the study was 7.6 years (3.9 to 12.3 years) and their mean age at the end was 16.5 years (11.3 to 19.9 years).

The 38 children fell into three groups (Fig. 1).

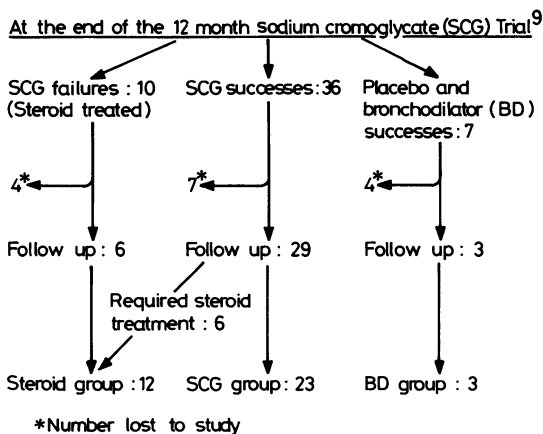


Fig. 1 Origin and composition of the three main patient groups in the study.

Twelve children whose condition was not controlled by sodium cromoglycate comprised the steroid group: six of the 12 children were from the original trial and six had deteriorated during the first three years and had to be put onto corticosteroids. Twenty three children successfully controlled by sodium cromoglycate formed the sodium cromoglycate group. Two of these children were observed for 8.2 and 4.7 years; both were lost to follow up before puberty but not before their condition was seen to have improved. The third, bronchodilator group comprised three children whose asthma was successfully controlled with bronchodilators.

Methods

Six monthly assessment of the severity of asthma.

The children in this study were seen by the author every six months as outpatients. At each visit a questionnaire was completed. An estimate of the severity of attacks was based on the number of admissions to hospital, the time off school or indoors, and the number of times a doctor had been consulted because of asthma. The frequency of milder symptoms, whether weekly, monthly, or 6 monthly, was gauged on further close questioning of the patient and parents. Drug treatment was recorded. The effects of exercise, schooling, and temperament were noted. Other illnesses and problems that had developed in the previous six months and the parents' overall assessment were recorded. The patient was then examined, taking particular note of any pubertal changes,¹⁰ and the following respiratory function tests were performed: peak respiratory flow rate (Wright Peak Flow Meter, Airmed) spirometry for forced vital capacity, forced expiratory volume in one second, and a standard exercise test.¹¹

Assessment of puberty. The classification of puberty into five stages by Tanner¹⁰ has been adopted in this study. Genital development in boys and breast development in girls were rated on a scale from 1 to 5. Pubic hair was rated separately on the same scale, and being similar in both sexes, forms a link allowing direct comparison throughout puberty.

In this study a child was assessed as reaching stage 2 of puberty at the first sign of a secondary sexual characteristic. This was either the initial enlargement of the genitalia in boys, a breast bud in girls, or pubic hair in both. The age at which this occurred was accepted as the beginning of puberty. The 3rd, 4th, and 5th stages of puberty were recorded when both pubic hair and the genitalia or breast were observed to have reached the appropriate phase in development. Stage 5 was not difficult to assess as it

Table *Treatment grading used to assess clinical progress over the period of follow up*

Grade	Treatment
8	Regular oral steroid treatment.
7	High dosage beclomethasone dipropionate treatment (over 400 µg/day) or regular, alternate day oral steroid treatment before availability of steroid aerosol (1972).
6	Low dose beclomethasone dipropionate treatment (50–400 µg/day).
5	Regular sodium cromoglycate treatment plus an occasional short course of oral steroids.
4	Regular sodium cromoglycate treatment.
3	Regular bronchodilator treatment plus an occasional short course of oral steroids.
2	Regular bronchodilator treatment.
1	Occasional use of bronchodilator treatment.
0	No treatment (ie symptom free).

depended on observing when both secondary sexual characteristics were finally adult in type. Stages 3 and 4 were less precise as the rate of development of the genitalia and breasts compared with the pubic hair often varied. Even so, a reasonable compromise always seemed possible, and as the same investigator made all the assessments, they should be comparable. The two important measurements for this study, however, the beginning (stage 2) and the end (stage 5) of puberty, were observed with an accepted accuracy to within six months.

Assessment of clinical progress. As each six monthly clinical assessment was directly related to the treatment required, the grading system set out in the Table has been used to assess the severity of the illness at each stage of this study.

Improvement in the disease was indicated by a reduction in treatment grade while worsening was signified by a rise. To simplify plotting of the clinical progress of the disease over the many years of follow up, the six monthly treatment grades have been combined into a single yearly one reflecting the overall trend, up to the onset of puberty. During puberty, however, the final treatment grading assessment was related directly to the stages 2 to 5. Those children followed beyond puberty then reverted to being assessed yearly.

Results

Clinical asthma and puberty. There was a clear overall improvement in the severity of asthma during puberty (Fig. 2), preceded by a tendency to improve three years before its onset. In the more severely affected steroid group, improvement was first noted at puberty, while in the less affected bronchodilator group all the children had begun to improve before puberty (Fig. 3). The sodium

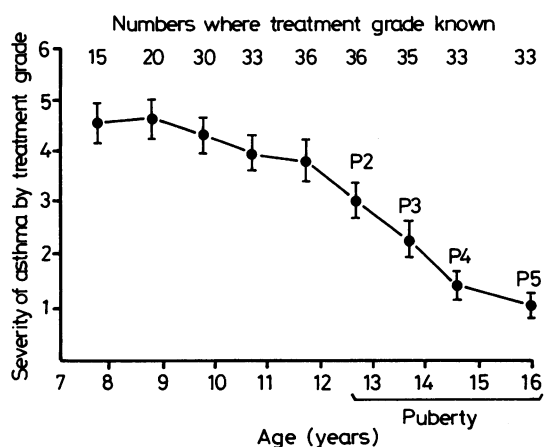


Fig. 2 Severity of asthma in 36 children who reached puberty, assessed by the mean values (SE) of their treatment grades, at the mean age of each stage of puberty and each year before puberty.

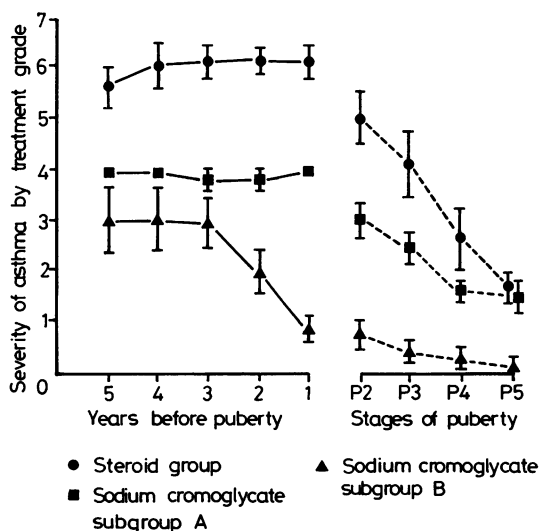


Fig. 4 Comparison of the severity of asthma in three groups (steroid and sodium cromoglycate subgroups A and B) assessed by the mean values (SE) of their treatment grades at each stage of puberty (irrespective of their mean age) and each year before puberty.

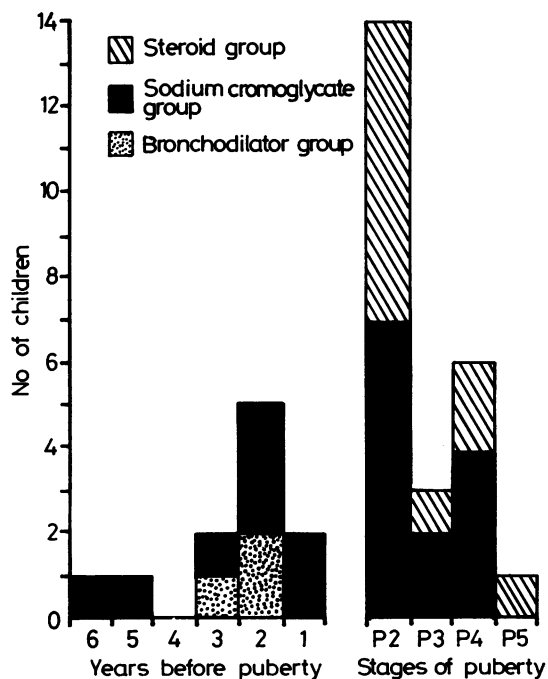


Fig. 3 The first consistent improvement observed in 35 asthmatic children related to puberty.

The children are separated into the three main groups—steroid, sodium cromoglycate, and bronchodilator, and plotted against the year before puberty or the stage of puberty that the first consistent drop in treatment grade was detected.

Three remaining children in the study are omitted: two improved before the onset of puberty but were lost to follow up before it began and one became worse during puberty and died in stage 3.

cromoglycate group fell between these two extremes with 13 children not improving until the onset of puberty (subgroup A) and 10 children improving before (subgroup B).

There was a close similarity in the progress of the disease between the sodium cromoglycate subgroup A and the steroid group (Fig. 4). In this combined group of 25 children, none of whom had shown any improvement before the onset of puberty, 15 children improved immediately on reaching pubertal stage 2, and all, except one child who died during a severe exacerbation, had improved by stage 5. Three children were then symptom free, nine children were grade 1, seven children grade 2, and four children grade 3.

As the bronchodilator group consisted of only three children, it was not included in Fig. 4, but a close similarity in the progress of the disease was also noted between the children in this group and those in the sodium cromoglycate group who improved before puberty (subgroup B). In this combined group of 13 children, recovery began three years before the onset of puberty and three children became symptom free and seven virtually so (grade 1) without any pubertal influence. Further improvement occurred during puberty and by stage 5, 11 children were known to be symptom free and two children virtually so (grade 1). The number symp-

tom free was probably 100% as the two children recorded as grade 1 were lost to follow up before the end of puberty, and the usual reason for failure to attend the clinic was loss of all symptoms.

Follow up after puberty. Seventeen of the 38 children were observed from 1 to 5 years (mean 2.2 years) after reaching stage 5 of puberty. Six patients continued to improve; four became symptom free and two improved from grade 3 to grade 1. Seven patients remained unchanged. One patient, well controlled on regular bronchodilators, needed a short course of steroids for an exacerbation, and three patients who had been symptom free for sometime (one, three, and four years) relapsed. Apparently 'cured' asthmatics have been noted to relapse in the past,⁸ and it was of interest that in all three in this study, relapse occurred after puberty was completed. Two had moderate wheezing episodes, one during a hay fever season and the other due to an upper respiratory tract infection. The third had a much more severe asthmatic attack requiring his first short course of steroid treatment.

Discussion

The 38 children in this prospective study originated from a group of chronic, perennial asthmatic children admitted to a 12 month trial of sodium cromoglycate.⁹ As such they represent moderately severe hospital treated asthmatics; yet, when last seen, their final assessment showed that 42% were symptom free, a figure similar to the 47% estimated from the 23 retrospective studies on 6737 children. Moreover, by separating the children in this study into a severe group treated with steroids and a moderate to mild group treated with sodium cromoglycate or bronchodilators, or both, a close similarity can be seen with the results of the prospective study of a randomly selected group of wheezy children carried out by McNicol and Williams⁶ and completed by Martin *et al.*⁷ At the end of this present study, 17% of the severe group and 54% of the moderate to mild group had become symptom free compared with 13% and 55% of patients reported by Martin *et al.* Despite originating as a hospital sample, the natural history of childhood asthma in the 38 children in this present study was similar to that based on whole population samples. This would suggest that the results in this study are generally applicable.

The 38 children had twice yearly clinical and physiological assessments for a mean of 8.9 years. In such a variable disease, physical examination and respiratory function tests were only of value in checking the condition on the day of the visit and

these assessments relied heavily on the history of the illness over the previous six months, a short enough period of time for both the children and parents to recall. Careful questioning on drug intake provided an efficient cross check on their memory of events. Bronchodilator usage was a useful guide to the extent of the general disability and effectiveness of prophylactic sodium cromoglycate or steroid treatment. The severity of exacerbations could be measured by the degree and duration of administration of the treatment used to combat it. Even failure to take the prophylactic treatment was helpful in assessment. If the illness became worse it emphasised the importance of continuing with regular administration, and if not, would suggest the drugs were no longer required. To give prophylactic treatment for longer than necessary to children with few symptoms could have led to serious errors in a grading system based on drug intake. These were minimised by a deliberate policy of reducing the level of treatment if the patient reported a satisfactory six month period, with the proviso that the parents were at liberty to increase it again if they felt it was necessary.

In this study the children were grouped by their initial treatment into a severe group requiring steroids, a moderate group treated with sodium cromoglycate, and a mild group needing bronchodilators only. It seemed reasonable to classify children whose asthma was not controlled by treatment other than steroids as the most severe cases and those requiring bronchodilators only as milder. It is less certain, however, whether children treated satisfactorily with sodium cromoglycate constitute an intermediate group. More recently it has been shown that theophylline, a bronchodilator drug, used regularly in optimum dosage is as effective as sodium cromoglycate.¹² Even so, the natural history of the disease in this study would support the grouping used. The children admitted to the original 12 month sodium cromoglycate trial were selected because their asthma was inadequately controlled by bronchodilators, and the sodium cromoglycate group consisted of those children who were successfully treated with this drug. In time all were able to dispense with sodium cromoglycate and could then be satisfactorily controlled with bronchodilators alone.

On reviewing the children in the sodium cromoglycate group, however, it was apparent that they could be further divided into two groups; those who did not improve before puberty (subgroup A) showing a close similarity to the steroid group, and those who did (subgroup B) showing a close similarity to the bronchodilator group. In the 25 children who did not improve before the onset of

puberty (sodium cromoglycate subgroup A + steroid group) only three were symptom free by stage 5 of puberty. Whereas in the 13 children who had already shown improvement before puberty (sodium cromoglycate subgroup B + bronchodilator group) 11 children were known to be symptom free and the other two virtually so when lost to follow up, a good prognosis in 100%. This would suggest an important prognostic indicator. Parents of children who have shown improvement in their asthma before any sign of puberty has developed may be told confidently that their child should 'grow out' of the disease, but those who show no improvement by puberty need a much more guarded prognosis.

It has been shown that a dramatic improvement in the disease is associated with the onset and duration of puberty. Yet a third of the children in this study (sodium cromoglycate subgroup B + bronchodilator group) actually improved *before* puberty began: three children became symptom free and seven virtually so (grade 1), an excellent result in 10 children, before any pubertal influence had developed. Moreover, it has also been observed that improvement can still progress after puberty has finished. Thus it would seem that the potential for improvement in childhood asthma exists irrespective of puberty and is a totally separate mechanism. Yet, whatever mechanism is involved in improvement in childhood asthma, this study would suggest it receives a powerful stimulus during puberty, which in some cases actually seems to 'switch on' the process for the first time, and in almost every case accelerates it, sometimes to the extent of complete cessation of symptoms. The fact that one child deteriorated and died during puberty shows that the common mode of progression is not universal.¹³

An analogy exists with the growth spurt during puberty. The slow, steady growth present before puberty will continue at the same pace if puberty is prevented from occurring, and the final height may eventually be even greater than if it had taken place.^{14 15} The growth mechanism, however, receives a tremendous stimulus during puberty and the whole process is dramatically accelerated, with the result that the final height achieved is much more rapidly attained.

The stimulus to growth during puberty is directly related to complex hormone interplay and it does not seem unreasonable to postulate that hormonal influences stimulate similarly the mechanism responsible for improvement in asthma. Unfortunately, the nature of that mechanism is unknown, although it has been suggested that it is immunological.^{16 17} An association between endocrine function and immunity has often been found in the

past 60 years,¹⁸ and it is tempting to speculate from the results in this study that the improvement in childhood asthma could be related to a slow progressive immunological process which receives an equally dramatic stimulus during puberty from the increase in endocrine activity.

I thank Professor Simon Godfrey and Dr Michael Silverman for their constant support, encouragement, and advice over the many years of this study; Miss Marian Tooley for her technical assistance; and Mrs Jane Fallows for the medical illustrations.

This study was supported in part by the Asthma Research Council.

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Received 16 November 1984