Original articles

Growth and childhood asthma

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SUMMARY Height and weight were measured every six months in a long term prospective study of 66 children with chronic perennial asthma for a mean 13.1 years. There was no evidence of growth retardation on entry into the study. Growth developed along normal lines in all 66 children until about 10 years, and in 35 of these children growth continued along normal lines throughout the whole period of follow up. Thirty children showed the physiological decelerating growth velocity pattern seen in children with delay in the onset of puberty, and one child had an early menarche. The tendency for delay in the onset of puberty was significant for both boys and girls and was noted to be independent of severity of asthma. Once puberty finally began in these children, complete catch up growth resulted in the attainment of the predicted adult height. Long term prophylactic inhalation of beclomethasone dipropionate in 26 children in a dosage up to 600 mcg/day before puberty and 400 mcg/day during puberty was shown not to affect growth.

It is concluded that asthma had no direct influence on growth in height but was associated with delay in the onset of puberty. The pre-adolescent physiological deceleration of growth velocity that occurs in these children gives the impression of growth retardation.

Since growth retardation in childhood asthma was first described by Cohen *et al* in 1940¹ there have been many conflicting views concerning its occurrence. Some workers have noted growth retardation only in those children treated with corticosteroids,^{2,3} while others have related it to the severity of asthma.^{4,5} The observation that bone age was retarded to the same extent as height suggested that the short stature was associated with developmental delay and led to the prediction that these children would ultimately grow to normal heights.^{6,7} This was supported by Ferguson *et al*, who also noted that short stature was three times more prevalent in children with allergic respiratory disease than the general population.⁸ They emphasised, however, that it was *not* related to the severity of asthma and was equally apparent in children suffering from allergic rhinitis only.

It is not disputed that growth retardation develops in children with asthma treated with regular oral corticosteroids,^{9,10} and it was an important advance in this form of treatment when it was shown that if given as a single dose on alternative days adequate control of asthma was possible without growth impairment.¹¹ Recently, the use of aerosol steroids in children has been shown to be effective and safe, while allowing children to grow along expected

lines,¹² although this too has been questioned.¹³

To clarify the effect that the disease and treatment has on growth, the opportunity has been taken during a long term prospective follow up study of children with chronic perennial asthma¹⁴ to observe the growth pattern throughout childhood and adolescence of 29 children treated with corticosteroids and 37 children who never received treatment with steroids.

Subjects

Thirty eight children with chronic perennial asthma were seen at six monthly intervals for a mean of 8.9 years in a prospective study designed to observe the relation between childhood asthma and puberty.¹⁴ Recently, 32 of these patients have been traced and their final adult heights and the heights of their parents obtained. Of the remaining six patients, one had died aged 13.7 years in an acute attack of asthma and the other five could not be found.

A further 28 patients who attended the Paediatric Asthma Clinic at the Hammersmith Hospital have been added to the original group. All 28 parental heights were known and all were seen at least every six months by the author from middle childhood, through puberty until reaching their final adult

heights. In many it has been possible to review their clinic records from an early age, giving a consistent follow up of their growth and progress for nearly 20 years. Thus mean age of entry to this study for all 66 children was 7.5 years (1.9–12.1 years) and mean age when last reviewed was 20.6 years (12.8–25.9 years), giving a mean period of follow up of 13.1 years.

The 66 children were grouped as previously;¹⁴ 29 children who could not be controlled by sodium cromoglycate and needed treatment with steroids; 33 children who could not be controlled by bronchodilators alone and were successfully treated with sodium cromoglycate; and four children successfully controlled by bronchodilators alone. The group successfully treated with sodium cromoglycate were further subdivided into 19 children who showed no improvement in their asthma before the onset of puberty (subgroup A) and 14 children who improved before the onset of puberty (subgroup B). As the group treated with bronchodilator consisted of only four children and has been shown previously to have a similar prognosis to subgroup B of the group treated with sodium cromoglycate,¹⁴ these two groups have been combined when comparing the severity of asthma.

Methods

Anthropometry. Height was measured standing with heels and back in contact with the vertical measuring column. Gentle pressure was applied beneath the mastoid process and the head was held so that the lower border of the eye socket was in the same horizontal plane as the external auditory meatus.

Weight was measured without coat and shoes.

Estimation of growth. Height and weight were recorded on longitudinal growth and developmental charts prepared by J M Tanner and R H Whitehouse for the Hospital for Sick Children, London. They were measured at each six monthly visit. The pattern of growth corresponding to the height and weight centile was apparent for each child (Fig. 1), and by extrapolation it was possible to predict the expected height and weight of each child at the end of the study. The effect that severity of asthma, treatment, and delayed puberty had on growth could be seen by noting any deviation from the established centile pattern. By comparing the predicted heights and weights of the children with the actual heights and weights finally attained, the effect of childhood asthma on growth could be directly observed.

Sixty of the 66 children were followed into adult life until growth was complete. Comparison of their

Fig. 1 Height record on a Tanner and Whitehouse growth and development chart (10th, 50th, and 90th centile lines) for a child illustrating:

- (1) the established centile pattern from 7.7–12.3 years;
- (2) the physiological decelerating growth velocity pattern of delayed puberty;
- (3) the puberty growth spurt, resulting in the child regaining his original height centile.

The broken line represents the onset of puberty.

final heights with their predicted heights from the centile chart was supported by comparing their final heights with the heights of their parents. In addition, 24 of these 60 children had their left wrist and hand x rayed soon after entry into the study. Skeletal maturity and prediction of adult height by the TW2 method¹⁵ was assessed in the 24 children and compared with the actual adult height obtained.

The remaining six children who were lost to the study before their final adult height was known were followed up to a mean 8.3 years (6.3–14.6 years). Thus the effect of the illness on their pattern of growth was well observed and in four was supported by comparison of the chronological age with the bone age estimated from a radiograph of the left wrist before the onset of puberty.

Onset of puberty. A physical examination was performed at each visit. The beginning of puberty was defined as the first sign of a secondary sexual characteristic, either the initial enlargement of the genitalia in boys, a breast bud in girls, or pubic hair in both. The age at which this sign was noted was accepted as the age of onset of puberty and was accurate to within six months.

Analysis. The results were analysed by use of paired and unpaired Student's *t* tests.

Results

None of the 66 children on entering the study were below the 3rd centile and most (40/66) were above the 50th centile (Fig. 2). Distribution of the separate groups did not indicate an initial relation between severity of asthma and growth retardation with respect to height. On the contrary, it should be noted that on entering the trial 19 of the 29 children in the group treated with steroids had a height centile above the 50th centile.

From then until about 10 years of age all 66 children grew along their expected centile lines without appreciable deviation, irrespective of the severity of asthma or treatment. Thirty five of the 66 children continued to grow along their expected centile lines without appreciable deviation throughout the whole period of follow up, 30 showed the physiological decelerating growth velocity pattern seen in children with delay in the onset of puberty (Fig. 1), and one showed the rapid deceleration in growth that follows an early menarche. She was the only child in this study who failed to grow to within

five per cent of her expected height. Her height remained consistently on the 97th centile despite severe perennial asthma controlled by regular treatment with aerosol steroids for 4.4 years. Pronounced growth deceleration followed an early menarche, at which time she no longer took corticosteroids and had virtually recovered from her disease. In contrast, the 30 children with the delayed growth pattern were observed to catch up dramatically once puberty finally began.

In the 60 children whose final adult heights were known no significant difference was detected between the heights predicted from the extrapolated centile line and the final adult heights in either the 41 boys ($t=1.03$) or the 19 girls ($t=1.35$). Nor was any significant difference detected when comparing the three treatment groups: the group given steroids, the subgroup A given sodium cromoglycate, and the combined subgroup B given sodium cromoglycate and group given bronchodilator (Fig. 3). Both the boys and girls grew well in comparison to their parents (Table 1), and the mean parental heights were comparable with the accepted norms for this country.¹⁶ Moreover, the mean mid-parental

Fig. 2 Height centile of each child on entering the study, indicating group distribution. SG=group given steroids; SCSA=sodium cromoglycate subgroup A; SCSB=sodium cromoglycate subgroup B; BG=group given bronchodilator.

Fig. 3 Final adult height as a percentage of the height predicted from the extrapolated centile line in 60 children (●=boys, ▲=girls), and height last seen as a percentage of predicted centile height in six boys not seen as adults (○). Comparison between the group given steroids (SG), the sodium cromoglycate subgroup A (SCSA), and the sodium cromoglycate subgroup B + group given bronchodilator (the four open symbols) (SCSB+BG) was not significant in any pairing.

Table 1 Final adult height in relation to parental height in 60 children with asthma. Values are mean (SD)

Sex	n=	Height (cm)			
		Final	Paternal	Maternal	Mid-parental
Boys	41	177.7 (6.0)	174.4 (5.9)	160.8 (5.7)	167.6 (4.5)
Girls	19	164.3 (7.1)	175.3 (9.3)	161.1 (5.8)	168.2 (6.7)

Table 2 Final adult height in relation to height predicted from prepubertal bone age in 24 children with asthma with information on bone age. Values are mean (SD)

Sex	n=	Height (cm)		p Value
		Final	Bone age predicted	
Boys	15	180.0 (5.4)	174.9 (6.2)	<0.005
Girls	9	163.1 (4.7)	161.3 (5.2)	Not significant

heights were extremely close to the value of 168 cm found in the Harpenden growth study.¹⁷

In the 24 children where it was possible to compare the predicted final height determined from the bone age measurement with the actual final adult height (Table 2) there was no significant difference for the girls. The boys' final adult height was, however, significantly greater than the final height predicted from bone age ($p<0.005$).

When last seen, the heights of the six children whose final adult heights were not obtained were either equal to or slightly greater than their heights predicted from the extrapolated centile line (Fig. 3). Four of these children had bone age assessments; three were equivalent to their chronological ages and one, a boy whose onset of puberty was delayed until 14.2 years, was retarded by 2.6 years.

Growth in weight generally followed the same pattern as height, but with much broader variations. Many of the children in their teens, especially the boys, gained an excessive amount of weight, while some of the girls were difficult to assess as they lost weight dieting, one developing anorexia nervosa. Comparison of the weight centile with the height centile on entering the study did show, however, that those children most severely affected by the disease, in the group given steroids, tended to be underweight (Table 3). To determine whether poor weight gain influenced the delay in the onset of puberty, the 35 children who were underweight on entering the trial were compared with the 31 children who were not. The mean (SD) age of onset of puberty for the boys was 13.5 (1.5) and 13.3 (1.3) years, respectively, and for the girls was 12.5 (1.2)

Table 3 Relation between height and weight in 66 children with asthma on entering the study

Group	n=	Height centile greater than weight centile	Height centile equal to weight centile	Height centile less than weight centile
Steroid	29	20	6	3
Sodium cromoglycate subgroup A	19	7	6	6
Sodium cromoglycate subgroup B + bronchodilator	18	8	3	7
Total	66	35	15	16

and 12.4 (1.0) years, respectively. The differences were not significant.

Group treated with steroids. The 29 children in this group divided into three children treated with intermittent courses of oral prednisolone and 26 children treated with prophylactic aerosol inhalation of beclomethasone dipropionate for a mean of 5.8 years (1.1–12.3 years).

The three children on intermittent treatment with steroids, six children whose dosage of beclomethasone dipropionate did not exceed 400 mcg, and nine children whose dosage of beclomethasone dipropionate reached 600 mcg, five for longer than two years, grew along expected lines unaffected by their treatment. Eleven children whose dosage of beclomethasone dipropionate exceeded 400 mcg did seem to show inhibition of height growth, but only during the immediate pre-adolescent period of delayed puberty when growth velocity naturally falls. All 11 children regained their predicted height during the subsequent growth spurt.

Delayed puberty. It became apparent while charting the growth of the children in this study that there was a considerable number whose growth rate followed the physiological decelerating velocity pattern seen with delayed puberty (Fig. 1). In 21 of the 47 boys and four of the 19 girls the onset of puberty was delayed beyond the 95% confidence limits of Marshall and Tanner^{18 19} (Fig. 4), and the mean age of onset of puberty was significantly delayed in both the boys ($p<0.001$) and the girls ($p<0.001$). There was no significant difference, however, between the treatment groups, showing that this delay in puberty was independent of the degree of severity of their illness.

Discussion

This long term follow up of 66 children with chronic perennial asthma has supported previous observations that weight gain tends to be reduced depending

Fig. 4 Age (in years) at which onset of puberty was first detected in 47 boys (mean 13.4 (SE 0.2)) and 19 girls (mean 12.6 (SE 0.3)) plotted against their respective groups.

The mean age and 2SD lines are shown indicating the first sign of puberty noted by Marshall and Tanner: Girls¹⁸=breast development (mean 11.2 (2SD 2.2) (SE 0.1)); Boys¹⁹=genital development (mean 11.6 (2SD 2.1) (SE 0.1)).

Comparison of the group given steroids (SG), sodium cromoglycate subgroup A (SCSA), and sodium cromoglycate subgroup B (SCSB) + group given bronchodilator (BG) in the boys showed no significant difference in any pairing, nor was any significant difference noted between the group given steroids and sodium cromoglycate subgroup A in the girls. There were too few in the remaining group for comparison.

Table 4 Comparison of studies of growth retardation in children with asthma

Authors	Study	No of patients	Age range (yrs)	Mean age (yrs)
<i>Studies showing growth retardation</i>				
Cohen <i>et al</i> ¹	Longitudinal	5	9-17	?
Cohen <i>et al</i> ²¹	Longitudinal	150	?	?
Snyder <i>et al</i> ⁶	Cross sectional	91	1.5-15	7.6
Dawson <i>et al</i> ⁴	Cross sectional	121	10-15	12.1
McNicol and Williams ⁵	Longitudinal	314	7:10:14	Martin <i>et al</i> ²³ at 21
Murray <i>et al</i> ²²	Cross sectional	183	7-20	10.0
Hauspie <i>et al</i> ⁷	Mixed longitudinal	531	2-20	?
Chang <i>et al</i> ²⁴	Cross sectional	231	6.2-16.2	11.5
Ferguson <i>et al</i> ⁸	Cross sectional	598	3-17	?
<i>Studies showing no growth retardation</i>				
Van Metre <i>et al</i> ¹⁰	Longitudinal (10 months or more)	52	?	?
Falliers <i>et al</i> ²	Longitudinal (6 months or more)	270	5-16	?
Spock ³	Longitudinal (3 years or more)	200	4-12	7.0
Klein <i>et al</i> ²⁵	Cross sectional	20	4-15	?

and 12 years whose asthma was severe enough to cause chest deformity.²⁶ Yet when Martin *et al* reviewed all McNicol and Williams' cases at the age of 21 years, they noted that complete catch up growth had occurred, as observed in the present study.²³

Hauspie *et al* in their mixed longitudinal study also stated that height growth retardation was related to the degree of severity of asthma.⁷ They considered that the retarding effect on growth caused the delay in the onset of puberty, with the subsequent catch up growth apparently overcoming all previous effects of the disease. They speculated that the growth retardation could have been due to various factors suggested in the past: respiratory insufficiency with hypoxia,^{22 27} inadequate nutrition,^{28 29} chronic or recurrent infections,^{6 30} long term stress,⁷ and suppression of normal activity.²⁷ The opportunity for close long term observation in this study has made it possible to discount all these factors, particularly as all the children were given treatment specifically aimed at keeping them well enough to lead a normal life on a minimum of treatment.

The two studies by Cohen *et al* were also longitudinal, but the first consisted of only five cases,¹ two of whom had merely nasal allergy and only one of whom had moderately severe asthma. They made the interesting observation that 'active treatment', indicating desensitisation, soon cured the growth retardation. They emphasised this eight years later with a further 150 cases, but with no details of their age range.²¹ The importance of these studies was their description of growth retardation in children with mild respiratory allergy, many without asthma. This observation has been reported recently by Ferguson *et al*, who noted growth retardation independent of the severity of the disease and stated that the basic problem was the atopic state.⁸ Whereas that group of workers emphasised that it affected 'growth regulation', however, this present study would suggest the effect was primarily on the mechanism responsible for the 'switching on' of puberty itself. The regulation of height growth has been shown to be normal in all 66 children followed up. The only deviation from the established centile pattern has been the pre-adolescent deceleration in growth velocity seen in the children with delayed puberty, and this is physiological. Tanner has described this period as having the 'lowest growth velocity ever experienced' and talks about the immediate pre-adolescent velocity being so low that parents sometimes allege, mistakenly, that the child has actually stopped growing altogether for a year or more.³¹ It is the large number of children with asthma with delayed

puberty exhibiting this pattern that gives the impression of abnormal growth retardation.

It has been shown that effective treatment was possible with regular inhaled steroids without affecting growth.¹² These observations were supported in this study. Before the onset of puberty, dosage of beclomethasone dipropionate up to 600 mcg/day has been compatible with a normal growth velocity, and up to 400 mcg/day has been given during puberty without impairing the growth spurt. With the expected improvement in childhood asthma that has been shown to occur during puberty,¹⁴ it should rarely be necessary to exceed this dose on a regular basis. Thus it should be possible for all children with asthma to attain their normal predicted height.

Conclusion

In this prospective study of children with asthma all grew normally until about 10 years of age, and all ultimately reached their predicted adult height, showing that asthma had no effect on growth in terms of height. A considerable number, irrespective of the severity of asthma, had delay in the onset of puberty, and it is suggested that the pre-adolescent physiological deceleration of growth velocity that occurs in these children is the reason that asthma has previously been considered to cause growth retardation.

I thank Dr Michael Silverman and Professor Simon Godfrey for their help and advice over the many years of this study, Miss Margaret Rehahn for help with statistics, Mrs Jane Fallows for the medical illustrations, and Miss Karen Fox for typing the manuscript.

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Received 16 May 1986