

## CURRENT TOPIC

## Asthma and growth

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Although recent interest in the growth of asthmatic children has centred on growth failure as a potential side effect of inhaled corticosteroid treatment,<sup>1</sup> it has long been recognised that asthma itself can impair growth. It is now over a hundred years since Hyde Salter,<sup>2</sup> describing the appearance of the asthmatic patient, commented that, 'if the asthma has come on young, he is *generally* below the average height. Some asthmatics, however ... have nothing whatever the matter with their appearance, and would be taken for perfectly healthy people.' In 1940 Cohen *et al* extended Hyde Salter's observations on asthma to encompass the entire spectrum of allergic disorders in childhood and emphasised the importance of recording height, weight, and physical maturity in assessing the progress of allergic children.<sup>3</sup> They reported a spectrum of adverse effects on growth, the height being unaffected in milder cases but, with increasing severity of the allergic disease, there was impaired growth and finally delayed sexual maturation. In a later paper Cohen and Abram compared the growth of 150 allergic children with that of 102 age matched non-allergic controls and confirmed the association of uncontrolled allergy with growth impairment and found that satisfactory control of the allergic disease was associated with improved energy intake as well as satisfactory growth.<sup>4</sup>

Since then, although it has been widely accepted that asthma might impair growth, the published evidence has been scanty and often difficult to find, much of the data appearing as background information in papers dealing with other aspects of asthma and its management. My own interest in the subject was aroused while investigating the effects of inhaled corticosteroids on growth,<sup>5</sup> in the course of which I had difficulty in finding documentary support for my long held belief that asthma impaired growth. This paper reviews the literature on the association between growth impairment and asthma, but does not reopen the controversy on the effects of asthma treatment on growth.

**Review of literature**

Comments on the growth of asthmatic children can be found in three main types of paper:

## (1) INFORMATION CONTAINED IN REPORTS ON ASTHMA TREATMENT

After the introduction of corticosteroids for the management of asthma, it soon became

apparent that these drugs produced stunting of growth and several authors, reviewing their experience of this new treatment, included data on the growth of their patients. At the Hospital for Sick Children at Great Ormond Street, Norman reported that, even before his 33 patients had started on steroid treatment, the heights of 27% lay below the 10th centile and 15% lay below the 5th centile.<sup>6</sup> In Birmingham, Morrison Smith<sup>7</sup> found that the height lay below the 10th centile in 43% of 65 patients who were to receive steroid treatment and, in a later series of 145 children who had not yet received steroid steroids,<sup>8</sup> 26% had heights below the 10th centile for age. It is also worth pointing out that it was by no means universally agreed at that time that asthma impaired growth. Contributing to the debate on the use of continuous oral steroids in childhood asthma, Jacoby reported that his patients 'usually showed no reduction in height either before or after treatment'<sup>9</sup> and Walsh and Grant found that the mean height of 27 asthmatic children about to receive steroid treatment was only 2 cm less than that of comparable controls.<sup>10</sup>

More recently, Nassif *et al* reported that the mean height of patients before starting steroid treatment was at the 35th centile, compared with the 50th centile for both controls and children with milder asthma not requiring maintenance steroid treatment.<sup>11</sup> Oberger *et al* also reported on the growth velocity of children about to receive systemic corticosteroids or corticotrophin (ACTH).<sup>12</sup> During the year before treatment was started, growth velocity was well below the normal mean for age in both treatment groups, the mean height SD score ranging from -0.52 in the group who were to receive ACTH to -1.04 in the group who were to receive prednisolone. These patients had of course received modern asthma treatments, albeit unsuccessfully, before starting on systemic corticosteroids.

Using knemometry,<sup>13</sup> MacKenzie and Wales recorded mean lower leg growth rates of 0.38 mm per week in patients before starting inhaled steroid treatment.<sup>14</sup> Much higher growth rates were observed by Wolthers and Pedersen who examined the growth of children before starting treatment with inhaled steroids.<sup>15</sup> During run-in and run-out, they recorded mean lower leg growth rates of 0.63 and 0.64 mm per week respectively. MacKenzie and Wales speculated that these differences might have been explained by their

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patients having had more severe asthma than those studied by Wolthers and Pedersen. In our own study, patients who had not yet received treatment with inhaled corticosteroids showed impaired growth only during periods when their asthma control was poor,<sup>5</sup> lending further support to the suggestion that growth impairment is related to the severity of the asthma.

#### (2) REPORTS ON SELECTED POPULATIONS OF CHILDREN WITH SEVERE ASTHMA

Several papers have described the rather unusual population of asthmatic children admitted to the rehabilitation programme at the Children's Asthma Research Institute and Hospital (CARIH) in Denver, Colorado. Falliers *et al*, in a paper subtitled 'how to interfere with a child's growth without really trying,' found that in 49 patients admitted to CARIH who had never had steroids, 77% had heights below the normal age related mean, with 30% lying more than 1 SD below the mean and 8% more than 2 SD below the mean.<sup>16</sup>

As in the studies related to chronic systemic steroid treatment, these children were highly selected, with severe intractable asthma justifying uprooting them from their homes and, although their growth was clearly impaired, it was by no means as severely restricted as that of children who had had previous steroid treatment – of patients in whom intermittent steroid treatment had been given, 15% had heights more than 2 SD below the predicted mean and, when steroids had been given continuously, 33% had heights more than 2 SD below the mean (fig 1).

Falliers *et al* also compared the heights of CARIH children with those of 103 children seen in routine consulting practice before the advent of steroid therapy; they too showed growth retardation, with 73% of the heights lying below the normal mean for age, and 30% more than 2 SD below the normal mean.

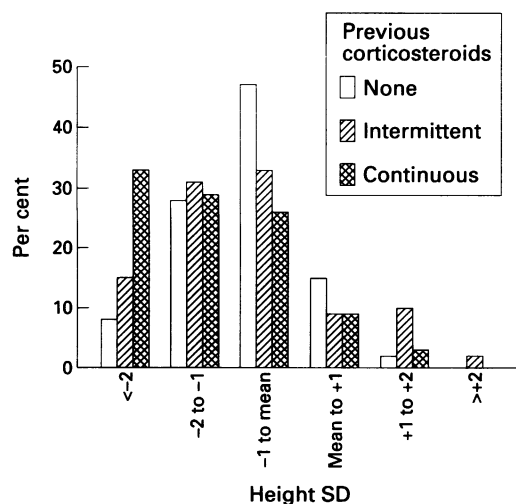


Figure 1 Height distribution of children entering CARIH. (Modified from Falliers *et al*, *Am J Dis Child* 1963; 105: 127-137.<sup>16</sup> Copyright 1963, American Medical Association.)

It is clear from these observations that growth retardation can occur in asthmatic children who have never been treated with corticosteroids, and that growth may be affected even in children with relatively mild asthma.

#### (3) CHILDREN ATTENDING HOSPITAL ALLERGY AND ASTHMA CLINICS

Given in high prevalence of asthma, and the large numbers of paediatricians and general practitioners who run asthma clinics, it might be imagined that the literature would be inundated with reports describing the growth and development of asthmatic children with varying degrees of affliction. Such, alas, is not the case and reports of this type are surprisingly few and far between.

Snyder *et al* compared the growth of 91 children with asthma with that of children with other allergies and of healthy controls.<sup>17</sup> In 74% of the asthmatics, the height was less than the 50th centile, and in 27% it was less than the 10th centile. In contrast, the height distribution of children in the other two groups was much more symmetrically distributed around the 50th centile. However, they also observed that the growth impairment of the asthmatic children was associated with delay in bone maturation and, therefore, with a good prognosis for ultimate adult height.

Murray *et al* reported that, of children attending their clinic and who had never received corticosteroids, 37% had a height below the 25th centile, and 7% had a height below the 3rd centile<sup>18</sup>; in other words, the proportion of small children was about twice as great as in the normal population. They adduced evidence that the important factors related to growth retardation were (a) onset of asthma before the age of 3 years; (b) chronic hypoxaemia; and (c) poor appetite and low milk intake. There was no association between growth retardation and low birth weight, frequency of respiratory tract infections, or frequency of fevers.

In a subsequent paper from the same group, the authors confirmed, in a large series of 598 children, the association between allergic respiratory tract disease (both asthma and allergic rhinitis) and short stature, with twice the predicted number of children falling below the 3rd centile for height.<sup>19</sup> They also confirmed the presence of delayed bone age, adding support to the view that growth retardation in asthma is a maturational phenomenon, and the long term prognosis is good. Their findings also supported the view that the growth retardation reflects the atopic state in general and is not specific to asthma.

They also found raised triiodothyronine concentrations in seven of 16 asthmatic children with growth retardation, apparently providing a metabolic explanation for at least some cases of growth impairment, although this feature has never been reported again and Solé *et al* found no evidence of triiodothyronine toxicosis in their patients.<sup>20</sup>

In contrast, Spock studied 200 children with bronchial asthma seen at the Duke University

Medical Center during a 10 year period and found that the height distribution was entirely normal.<sup>21</sup> He attributed his failure to confirm the results of Falliers *et al* to the fact that the Denver children represented 'an especially severely afflicted asthmatic population'.

Kuzemko reported that, in the absence of steroid treatment, the height of asthmatic children is normal, although many are relatively light for their height.<sup>22</sup> He also pointed out that many children with asthma have delayed puberty, a view later supported by Balfour-Lynn who performed a detailed long term prospective study of 66 children with chronic perennial asthma attending the Hammersmith Hospital in London.<sup>23</sup> He found that prepubertal growth was normal but in later childhood about half the children showed deceleration of growth associated with delayed puberty. This delayed maturation was not related to the severity of the asthma, nor to its treatment and, as so often occurs with the combination of short stature and delayed maturation, eventual adult height was well within the range predicted by parental height.

Normal adult height was also reported by Martin *et al*<sup>24</sup> and by Shohat *et al*<sup>25</sup>; indeed, in the army recruits who were the subjects of the study of Shohat *et al*, adult height was actually significantly greater in individuals with asthma in remission and with mild intermittent asthma than in individuals without asthma although the difference, which amounted to about 0.5 cm, was of little clinical (or military!) importance.

### Discussion

It is easy to be critical of much of the literature cited above. Most of the studies looked at attained height at a single point rather than at growth over a period. Many studies have included children old enough for puberty (or delayed puberty) to have influenced growth patterns. Even when growth was monitored and pubertal influences discounted, most studies (including our own) were retrospective and unplanned.

Nevertheless, there is a substantial body of evidence supporting the existence of an association between asthma and poor growth, operating independently of any effect of treatments such as systemic or inhaled corticosteroids. There are several possible explanations for the association:

#### (1) DELAYED MATURATION

Asthma (and perhaps allergy in general) is associated with delayed maturation,<sup>3 17 19 22 23 26 27</sup> and hence with prolongation and deepening of the prepubertal growth nadir. Such an effect would not be expected to have any very great influence on final adult height, which is in accordance with the observed facts.<sup>22-26</sup>

#### (2) IMPAIRED GROWTH HORMONE SECRETION

It is tempting to speculate that asthmatic children, who commonly suffer from night

time symptoms with consequent sleep disturbance, might have impaired nocturnal growth hormone secretion. However, at the 1993 meeting of the British Paediatric Association, Professor Brook and his colleagues from the Middlesex Hospital presented the results of an analysis of the 24 hour growth hormone secretion profiles of asthmatic children, including children who were receiving no steroid treatment, and showed no evidence of reduced growth hormone secretion. Moreover, the administration of growth hormone has no effect on the growth of asthmatic children,<sup>28</sup> although this has yet to be evaluated in undergrown asthmatic children who have not had corticosteroid treatment.

#### (3) OTHER ENDOCRINE MALFUNCTION

Asthma may be associated with other endocrine malfunction. Ferguson *et al* reported that almost half their asthmatic children with short stature had raised triiodothyronine concentrations, although Solé *et al* could not confirm this finding.<sup>20</sup>

#### (4) THE SEVERITY OF THE ASTHMA

The severity of the asthma may influence growth,<sup>3-5</sup> a concept supported by the high incidence of growth retardation in series of highly selected asthmatic children<sup>6-9 12 16 29</sup> and the reported association of growth retardation with hypoxaemia<sup>18</sup>, adverse clinical scores (see fig 2), and impaired pulmonary function.<sup>5 19 30-32</sup> Children with severe asthma represent only a small proportion of the total which may well explain why community based surveys,<sup>33-35</sup> and studies of children attending routine hospital clinics have commonly failed to identify an association between asthma and short stature.<sup>21 22 36</sup>

#### (5) DECREASED APPETITE

Asthma, in common with most systemic disorders, may affect appetite<sup>3 18</sup> although Zeitlin *et al* found no evidence of decreased

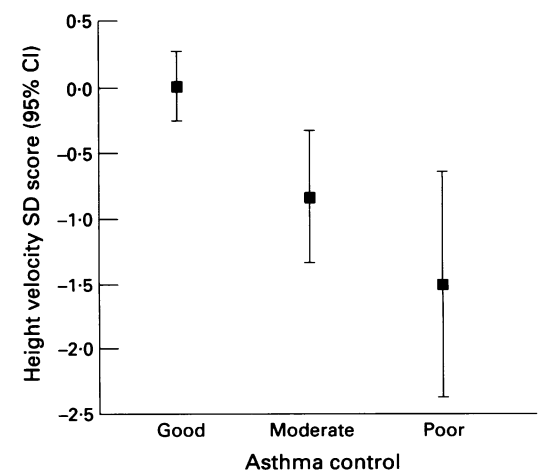


Figure 2 Relationship between asthma control and height velocity SD score in patients who had not yet received inhaled steroids; CI=confidence intervals (from Ninan and Russell<sup>5</sup>).

energy intake in a group of 34 children with perennial asthma,<sup>37</sup> and energy supplementation in asthmatic children has been shown to produce increased weight rather than height.<sup>38</sup>

#### (6) INCREASED ENERGY DEMANDS

It would not be surprising if the diversion of energy resources to maintain the enhanced metabolic demands of increased work of breathing were to result in growth impairment and Zeitlin *et al* found that the basal metabolic rate was significantly increased in children with perennial asthma, an increase that was balanced by a compensating increase in energy intake.<sup>37</sup> These findings are difficult to interpret, and Zeitlin *et al* speculated on causes other than asthma, including the possible effects of eczema on metabolism and the known effect of  $\beta_2$  agonists in raising metabolic rate.<sup>39</sup>

#### Conclusion

Whatever the reason for asthma related growth retardation, it is clear that a great deal of work remains to be done – far too little is known about the metabolic effects of asthma, and of atopy in general, to determine the relative contributions of the above explanations for asthma related growth retardation.

It is also important, in planning future studies of the effects of asthma treatment on growth, to take account of the potential of asthma itself to impair growth, and to document carefully the quality of asthma control before, during, and after treatment.

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