UPDATING

Linear growth in asthmatic children*

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Asthma is the most frequent chronic inflammatory disease in childhood, and its prevalence has increased remarkably over the last decades. Therefore, the scientific community became interested in studying the growth of the affected children. The relationship between asthma and growth suffers the influence of the clinical picture, of therapeutics, but the different study methods make it difficult to distinguish the factors responsible for the growth retardation detected by some authors. This review has the purpose of providing an overall outlook on this matter. *(**J Pneumol** 2003;29(1):36-42)*

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INTRODUCTION

Asthma is a chronic disease, and its prevalence in childhood has been growing remarkably.

In 1940, Cohen *et al.*[(1)] observed that there was an association between asthma and growth inhibition, and that the persistence of allergic symptoms caused a retardation in stature and bone maturation.

Since then, many studies about the relationship between asthma and growth were carried out, and it is now known that, regardless of treatment, moderate and severe asthma cause a delay in the puberty stretch, which is caught up later on regarding adult height [(2-4)].

Growth is a complex mechanism involving the multiplication of cells in various specialized tissues and systems, at different paces. It is an attribute of young living beings, with individual characteristics, and, in humans, height is a trait that has been observed and linked to physical strength from early days. In the 20th century, systematic studies on growth began to be performed [(5,6)]. Growth is completed around the age of 20 years, and its end signals the beginning of adult age [(8,9)]. It is influenced by genetic, biological and environmental factors, and the harmony between them determines its more or less satisfactory conclusion [(6-8)].

The role of environment in the nutritional status and the growth process of population groups has been the object of studies focusing mainly on food, infectious diseases, basic sanitation conditions, social layers and their determinants [(9-13)].

Morbid processes also interfere with growth. Acute illnesses can cause its temporary arrest, and its posterior recovery will depend on how favorable the environmental, nutritional and socioeconomic conditions will be [6,9]. As for chronic diseases, depending on the affected organs and systems, on the severity and duration of the disease, recovery may not occur at all [14,15].

INFLUENCE OF ASTHMA ON GROWTH

About 60 years ago, Cohen *et al.*[1] noted that a number of allergic children presented a growth arrest, manifested initially by weight loss, and that, if the symptoms persisted, their height and bone maturity could be affected. Eight years later, the same authors confirmed their findings in a group of mostly asthmatic children, and concluded that active allergy was the cause of their growth retardation, but that this could be normalized by controlling the allergy [16].

Early onset, duration and severity of the disease, chest deformity, hypoxemia, chronic anorexia, use of corticosteroids, and socioeconomic level are factors under study as potentially responsible for growth retardation, but the results have been conflicting [16-26].

Dawson *et al.*[26] studied a relatively stable population of 2,743 school children and detected asthma in 121 (4.8%) of them, with ages ranging between 10 and 15 years; their weight and height tended towards being below average for gender and age in those who had had the first crisis before the age of five years.

McNicol and Williams[21] conducted a longitudinal study on 315 children and adolescents and 82 controls at the ages of 7, 10, and 14 years, and observed that there was damage to height in patients with a severer disease who were 10 years old or more, the difference being more remarkable in the group of 14-years-olds. One of the characteristics considered to define severe asthma was early onset, which, in these cases, was before the age of 3 years.

Murray *et al.*[22] performed a transversal study on 183 young Canadians, aged from 7 to 20 years, where they also found an association between early onset of the disease (before the age of 3 years) and growth retardation.

With the purpose of studying the influence of age at the onset of asthma on weight and height, Wittig *et al.*[27] studied 380 male and 219 female patients with chronic asthma from a training hospital in Florida, aged between 4 and 20 years, who had not been under prolonged steroid treatment. They concluded that the early onset of asthma influenced the growth deficit, being more significant in males. However, this was not found by Falliers *et al.*[28], who studied 302 patients with untreatable asthma from a reference center and 103 children from private health care services.

In Brazil, studies on atopic children are scarce. Grumach *et al.*[29] conducted a transversal study on 323 children and adolescents with severe or moderate asthma from the city of São Paulo, aged from 2 years and 4 months to 17 years, of different socioeconomic levels. They analyzed their growth and found no evidence indicating that the age of asthma onset might be related to poorer growth, as opposed to socioeconomic conditions.

Regarding the severity of the disease, most studies show an association or a trend towards growth decrease in children with severe asthma. Falliers *et al.*[28] and Dawson *et al.*[26] observed that children with severe asthma had weight and height below normal. McNicol *et al.*[20] followed up 276 patients and 94 controls in a longitudinal study on asthmatic children from Australia, and noted a trend towards a weight decrease in the group with severer asthma. Soon after this observation, the same authors studied 56 patients of 10 to 11 years of age and 36 controls matched for gender, age, and socioeconomic level. The patients had the following characteristics: onset of asthma crises at 3 years of age or earlier, persistent or frequent crises, chest deformity or alteration on pulmonary function test. The authors observed growth retardation particularly with regard to weight, while height was affected only in the most extremely severe cases of the disease [19]. In a national study started in 1972 in England and Scotland, Rona and Florey[30] monitored the growth of 7,411 elementary school children aged between 5 and 11 years, and observed the association between the severity of asthma and growth. In a prospective study on 342 randomly selected patients aged from 7 to 21 years, Martin *et al.*[31] also observed a growth suppression in the group aged from 10 to 14 years and with severe asthma. In a transversal analysis of the measurements of 699 children aged 3 years and 6 months, 5 years, 7 years, 9 years, 11, and 14 years, grouped according to their medication, Neville *et al.*[32] concluded that those with severe asthma who received high doses of inhaled corticosteroids were significantly shorter. Chest deformity, more specifically a barrel-shaped chest, which can be indicative of severity, associated to airway obstruction with altered ventilation tests, is indicated as a relevant factor in the association between growth and asthma. McNicol *et al.*[20] observed a trend towards low weight in the group of patients with asthma, chest deformity and airway obstruction. Gillam *et al.*[19] noted that weight was decreased in children with chest deformities, and that height was also affected in cases with severe chest deformities.

On the other hand, in a transversal study on 598 children and adolescents diagnosed with asthma or allergic rhinitis, Ferguson *et al.*[17] identified 66 patients aged from 18 months to 17 years who had a short stature. They concluded, however, that short stature is more common than expected in atopic children, but did not detect any difference regarding asthma severity. In the city of São Paulo, Brazil, Solé *et al.*[18] compared 397 patients aged from 8 months to 14 years and 7 months with allergic processes (asthma, atopic dermatitis, allergic rhinitis, and hives) with a group of 1,723 atopic patients, matched for age, but of a higher socioeconomic level. They found no association between growth deficit and the severity of the atopy. Similar results were found by Sant'Anna *et al.*[33] in their study on 617 children from the city of São Paulo.

SOCIOECONOMIC CHARACTERISTICS AND GROWTH OF PATIENTS WITH ASTHMA

Growth deficiencies, mainly in developing countries, are mostly related to deficient nutrition, and are directly linked to the socioeconomic level of the population. Some studies have attempted to determine the impact of the socioeconomic level on the growth of asthma patients.

In their previously mentioned study on elementary school children, Rona and Florey[30] observed a higher incidence of short stature among asthmatic children of a lower socioeconomic level; the association between other respiratory symptoms and short stature was marginal.

Some Brazilian studies have analyzed the association between the socioeconomic level and the growth of children with asthma. Grumach *et al.*[29] observed that the relationship between socioeconomic level and asthma severity was highly significant. Solé *et al.*[18], in their study on allergic children from two health care services (one public and the other private), noted that the disease had caused short stature only when associated with lower socioeconomic level. When Sant'Anna *et al.*[33] compared 120 atopic patients with their non-atopic siblings (120), they observed a significantly higher frequency of short stature among the atopic subjects, therefore concluding that, in that population, atopy alone was capable of causing a growth deficit.

INHALED CORTICOSTEROIDS AND GROWTH

The understanding of asthma as a disease where one of the main involved mechanisms is inflammatory was decisive for its therapeutic handling. Among the drugs used, corticosteroids are the only ones which expressively reduce inflammation of the airways.

From 1949, when the use of cortisone was first described in the treatment of rheumatoid arthritis, up to the 1970s, cortisone products were widely used, although its many side effects were already known, including its effect on the growth of children with asthma[28,34,35]. Since 1970, the inhaled corticosteroids have redefined the development of the disease, for they are both potent drugs and have fewer side effects [36,37].

Inhaled corticosteroids are lipophilic substances with a complex mechanism of action, which enter the cell cytoplasm, bond to the steroid receptor molecules and reach the cell nucleus, where they interact with the DNA, modifying gene transcription. The new RNA molecules return to the cytoplasm, where they encode new proteins (lipocortine-1, endonucleases, neutral endopeptidase, and β-adrenergic receptors) and reduce the production of other mediators, including cytocines, thus diminishing the inflammatory response. So, they act by reducing the number of inflammatory response cells and its mediators, thereby reducing inflammation and bronchial hyper-reactivity [38-41].

Investigations on the systemic side effects have focused on four conditions: the development of glaucoma and cataract, suppression of the hypothalamus-hypophysis-adrenal cortex axis, bone metabolism, and children's growth [39,42-45].

Regarding the suppression of the hypothalamus-hypophysis-adrenal cortex axis, there is no sound evidence of this adverse effect in children [40,41,46].

As for bone metabolism, there are studies showing a decrease in bone density, but no association between an increased risk for fractures and high doses of inhaled corticosteroids was observed. It should be pointed out that the patients studied were also users of oral corticosteroids, which are known to cause changes in bone metabolism (40,41,44,45).

Concerning the growth retardation, no consensus was reached so far, and the different methods used in different studies make a comparison between them difficult. Drug dose and type have been associated to growth retardation (40,43,47).

Glucocorticoids are known as potent inhibitors of growth hormone secretion and action, of IGF-1, of collagen synthesis, and of suprarenal androgen production; the most important factor of growth arrest or delay is, however, still uncertain [45-51].

The studies which attempted to assess the influence of inhaled corticosteroids on growth have used two methods: measurement of a body segment (*Knemometry*: leg length measurement), and measurement of the patient's height.

Knemometry was described by Valk *et al.*[52], and is used over short periods of time, to evaluate the endochondral growth of the leg bones. Measurements are usually made once a week, allowing to demonstrate and quantify the influence of a given drug on growth. This method, however, does not allow to make a prognosis about adult height [52-54].

Studies aimed at evaluating the impact of inhaled corticosteroid use on the growth of children and adolescents by using *knemometry* show divergent results.

Wolthers and Pedersen[55] conducted a double-blind study using budesonide and placebo on 15 patients with mild asthma aged from 6 to 13 years, and observed that growth suppression was dose-dependent. In another study [56], comprising 43 youngsters with mild asthma and ages between 7 and 14 years, the same authors observed that only the use of 800µg/day of budesonide caused a decrease in leg growth. In a third study[57], they compared the use of 200µg/day of fluticasone with beclometasone dipropionate at doses of 400 e 800µg/day, in 19 children and adolescents aged from 7 to 14 years. They concluded that a statistically significant decrease in growth occurred with beclometasone dipropionate used at the above mentioned doses.

In a controlled prospective study, Agertoft and Pedersen[58] made height and *knemometry* measurements of 47 asthma patients during one year, using 300 e 600µg/day doses of budesonide and placebo. They concluded that the variations detected by leg length measurements were not predictive of long-term height.

In spite of these studies, the traditional growth evaluation methods are still the most frequently used. However, there is no consensus regarding the results either.

Some works suggest that the use of low doses of inhaled corticosteroids, as well as of oral corticosteroids given on alternate days, might minimize a possible negative effect on growth [22,28,59].

Several authors who evaluated asthma patients of different age groups, using different inhaled corticosteroids, and various ways of administration, did not observe a negative impact of these drugs on growth [23,60-74]. In Brazil, Kovalhuk *et al.*[59] did not observe growth retardation either, during the study period, in patients on prednisone given on alternate days or BDP.

On the other hand, growth retardation associated with the use of inhaled corticosteroids was documented by other authors[75-86]. So, there is evidence that inhaled corticosteroids can reduce growth speed, mainly when given in high doses.

Allen *et al.*[87] performed the first meta-analysis study found in the literature. They analyzed 95 works, selected 21 of them comprising a total of 810 asthma patients, and concluded that inhaled corticosteroids can be considered safe. Lipworth[88] did not find evidence of an effect of inhaled corticosteroids on growth in his review and meta-analysis either.

There are many studies carried out with the objective of evaluating the mean- and long-term impact of corticosteroids on growth, but the different age brackets involved, the lack of definition of puberal development, the lack of a control group, the different disease severity classifications, the different drugs and ways of administration, do not allow drawing consensual conclusions [89].

More recent studies have shown that asthma patients, whether treated with corticosteroids or not, have an adult height within expectations [74,83,90,91], pointing out the lack of association between growth speed observed during a given period of time and the adult height of such patients. On the other hand, Norjavaara *et al.*[92] analyzed the height of Swedish men drafted for military service, and observed that those with severe asthma had a lower mean height than the others. In a second study [93], they observed that girls with moderate or severe asthma who did not use inhaled corticosteroids had a statistically significant decrease in their adult height, but this was not clinically relevant.

Intervention studies, such as randomized clinical trials, are the most indicated to establish a cause-effect relationship (93). However, they are limited by the ethical issue, since, in the case of asthma, the benefits of these drugs are unquestionable (95).

Conclusions

Patients with asthma, regardless of its severity, may have a growth delay with posterior catching-up; severe asthmatics are the most susceptible to present such alterations.

In order to prevent children using an inhaled corticosteroid from having growth alterations and other side effects, the chemical formulation with the best cost/benefit rate should be selected. These medications should be used at the lowest possible dose and for the shortest time possible (Table 1), with extension devices, and avoiding ultrasound nebulizers. In children over 5 years of age, the use of a mouthpiece rather than of a facial mask is beneficial, but a well adjusted mask can prevent the medication spray from spreading over eyes and face. Patients should always be advised to wash their face and the apparatus after its use, besides washing their mouth and spitting out (42,96-98).

TABLE 1
Doses of inhaled corticosteroids (mcg/ 24 hours) recommended for individuals under the age of 12 years

Steroid	Low dose	Mean dose	High dose
Beclometasone	200-400		400-800
> 800			
Budesonide	100-200	200-400	> 400
Triamcinolone	400-800	800-1,200	> 1,200
Fluticasone	100-200	200-400	> 400
Flunisolide	500-750	750-1,250	> 1,250

Final Considerations

Inhaled corticosteroids are the therapy of choice in school children, adolescents and adults with moderate and severe asthma. The studies show few side effects, high effectiveness and safety, and a favorable cost/benefit rate.

Systematic identification and monitoring of risk groups for growth deficiencies, mainly patients with severe asthma, allow making adequate adaptations in the management of the disease, resulting in a better quality of life for the patients.

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