

Short stature in children with respiratory allergy

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We evaluated the prevalence of short stature (SS) among children with respiratory allergic disease followed up in a specialised centre. These patients (N = 617; 8 months to 16 years) with respiratory allergy (asthma and/or rhinitis) were evaluated for SS (stature shorter than the 3rd percentile, NCHS pattern). The possible links between SS and gender; current age; type, severity, and duration of the allergic disease, treatment with corticosteroid and birth weight were also studied. To assess the influence of the socioeconomic level on SS frequency among atopics, 120 of these patients were compared to their non-atopics siblings. The overall prevalence of SS was 7.9%. Relationship between SS and gender type and severity of the allergic disease and treatment with corticosteroids were not observed. A significant higher frequency of SS occurred among patients with longer period of disease and birth weight less than 2,500 gr. Analysis of the pairs of brothers showed significant higher frequency of SS between allergics (12.5% x 4.2%) showing influence of allergic disease *per se*. Longitudinal studies for long periods of time are required to properly establish the relation between atopic disease and SS.

**Celso Avelar Sant'Anna,
Dirceu Solé,
Charles Kirov Naspitz**

Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Universidade Federal de São Paulo-Escola Paulista de Medicina, São Paulo, SP, Brazil

Dirceu Solé, Av. Paes de Barros nº 844, ap. 61, 03114-000, São Paulo, SP, Brasil

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Though failure to thrive is usually associated to genetic, hormonal and nutritional disorders, some chronic diseases, mainly asthma, are considered as causes of short stature (SS) in children. The prevalence of SS among patients with atopic disease varies from 2% to 10% (1–15) against the 2% to 3% in the global population.

The association between asthma and SS (stature shorter than 2.5 percentile) was first described by Cohen and Abram studying five allergic children from nine to 17 years of age. They observed significant delayed growth, with initial manifestation of weight loss, associated to suppression of stature growth and slowed skeletal maturation. In another study, comparing allergic children with non-allergic controls, they conclude that active allergy was the cause of this delay and its control was capable of establishing the normal rate of growth (16). Most of these children had asthma.

Several early studies documented delayed growth in children with moderate respiratory allergy, many without asthma. Following these studies, other investigations were made trying to establish the poss-

ible factors or mechanisms responsible for this association.

Treatment with corticosteroids (systemic or inhaled), duration of the disease, age of onset of the disease, anatomical changes induced by the disease (barrel chest due to chronic hyperinflation), and other factors mainly associated with severe asthma (intensity, chronic hypoxemia, chronic or recurrent infections, inadequate nutrition) are some of the main factors pointed out by several researchers as responsible for delayed growth (1–5, 7, 8–19). Nevertheless, so far a sole mechanism was not defined. In addition to the above-mentioned factors, related to the allergic disease *per se*, the socioeconomic level of the population under study should also be considered. In our environment, proteic-caloric malnutrition is relevant as a cause of SS.

We decided to evaluate the prevalence of SS in children with respiratory allergy in relation to the following variables: gender; present age; birth weight; diagnosis, severity and duration of atopic disease; therapy with corticosteroids, and influence of socioeconomic factors.

Casuistics and method

Six hundred and seventeen children, regularly followed up at the Division of Allergy, Clinical Immunology and Rheumatology of the Department of Pediatrics of the Federal University of São Paulo (Escola Paulista de Medicina) were evaluated at admission in the Division. Three hundred and fifty-seven (57.9%) were male, and 260 (42.1%) were female, with ages from 6 months to 16 years. They were divided in age ranges for comparison. The only group that had a smaller number of patients was the group < 2 years, since it is more difficult to establish the diagnosis of atopic respiratory disease in this age period.

The criteria for diagnosis and severity of asthma was the one of the International Consensus Report on Diagnosis and Treatment of Asthma (20). Those with allergic rhinitis were defined considering the presence of rhinorrhea, sneezing, episodic or persistent nasal obstruction, and pruritus. Of the 617 patients, 82 had only asthma, 103 only rhinitis and 432 had both rhinitis and asthma. The previous use of corticosteroids was evaluated by "recall inquiry method" in which the intake of corticosteroids was spontaneously reported or after interrogation during at least 7 days.

The exclusion conditions were: phenotypical deviations, clear changes in body proportions, other chronic diseases, rash and/or atopic dermatitis.

Height was obtained by one measurement with a stadiometer performed by a single trained individual (C.A.S.).

The values obtained for height and weight were registered in centimeters and in kilograms and compared with the expected values for age and gender, according to the "National Center of Health Statistics" (NHCS) patterns (21). Children shorter than the third percentile for gender and age were defined as of SS.

All patients were submitted to skin prick tests using a standard set of allergens (Ifidesa Aristegui): excipient, histamine solution (1mg/ml), *D. pteronyssinus* indoor dust, fungi mixture (*Penicillium sp*, *Alternaria alternata*, *Cladosporium sp*, *Aspergillus fumigatus*), feathers, dog epithelium, cat epithelium, and pollen mixture (*Lolium perenne*, *Phleum pratense*, *Ambrosia artemisiifolia*, *Parietaria judaica*).

Of the 617 patients, 120 had non-allergic siblings (negative skin prick tests, aged from 1 year and 2 months to 15 years and 9 months) that were considered as the control group (C).

The results were analyzed by the Chi-square test, and the Fisher's Exact test and Relative Risk calculation. For each test the rejection level of the null hypothesis was set at 5.0% ($\alpha < 0.05$), and the significant values were marked with an asterisk.

Table 1. Children with respiratory allergy (%) according to gender, present age, birth weight and stature percentile upon admission

	Stature percentile*		Total	Chi square χ^2 calculated
	<3	≥3		
Gender				
Male	33 (8.9)	325 (91.1)	357	1.865
Female	17 (6.5)	243 (93.5)	260	
Present Age				
<2y	1 (2.8)	35 (97.2)	36	8.022
2-6y	12 (5.7)	197 (94.3)	209	
6-10y	19 (7.7)	227 (92.3)	246	
10-16y	17 (13.5)	109 (86.5)	126	
Birth Weight				
<2500g	12 (19.7)	49 (80.3)	61	7.630**
≥2500g	48 (8.6)	508 (91.4)	556	

*NHCS ** $p < 0.05$

Results

In the different age periods there were no significant differences between the number of children below or above the third percentile (Table 1). Although the frequency of SS has been higher among boys in comparison to girls (8.9% × 6.5%), the difference was not significant (Table 1). In relation to birth weight, a significant higher frequency of SS (19.7%) was observed among children weighing less than 2,500 grams (Table 1).

According to the allergic disease, 82 children had asthma only, 103 isolated rhinitis, and the others had asthma and rhinitis. No significant differences among all those patients were observed (Table 2). Severe asthmatics showed a non significant increase in SS (Table 2). In contrast we found a significant higher frequency of SS among those with long time evolu-

Table 2. Children with respiratory allergy (%) according to type and severity of disease, and stature percentile upon admission

	Stature percentile*		Total	Chi square χ^2 calculated
	<3	≥3		
Allergic disease				
Isolated				
Asthma	8 (9.7)	74 (90.3)	82	0.00
Rhinitis	10 (5.4)	93 (64.6)	103	
Rhinitis				
Isolated	10 (9.7)	93 (90.3)	103	1.174
Associated	29 (6.6)	408 (93.4)		
Asthma				
Mild	12 (5.7)	199 (94.3)	211	3.105
Moderate	12 (10.7)	142 (89.3)	154	
Severe	16 (10.7)	133 (89.3)	149	

*NHCS

Table 3. Children with respiratory allergy (%) according to period of disease, corticotherapy and stature percentile upon admission

	Stature Percentile*			Chi Square χ^2 calculated
	<3	≥3	Total	
Period of disease				
<2y	(A) 6 (7.3)	76 (92.7)	82	22.869*
2-6y	(B) 17 (5.7)	280 (94.3)	297	ABC<D
6-10y	(C) 14 (7.3)	178 (92.7)	192	A=C
>10y	(D) 12 (26.1)	34 (73.9)	46	B=AC
Corticosteroid				
Systemic	10 (7.8)	118 (92.2)	128	0.352
Inhaled	3 (13.1)	20 (86.9)	23	
None	36 (7.7)	430 (92.3)	466	

* NCHS

tion of atopic disease (more than 10 years). This frequency (26.1%) was significantly higher than the other mentioned periods of disease (Table 3).

Treatment with corticosteroids (systemic or inhaled) was referred by 24.5% of children. However, there were no significant differences between patients treated or not treated with inhaled or systemic corticosteroids (Table 3).

The comparison of the 120 atopic children with their non-atopic siblings (n = 120) showed a highly significant difference in SS between both groups. SS was observed in 12.5% of the atopic children and only in 4.2% of their siblings (Table 4). Both groups had same birth weight.

Discussion

Several variables, acting directly or indirectly over the growth rate of atopic children, mainly the asthmatics, restrain the data comparison in several studies. Those variables are: age of onset of asthma, number, duration and severity of episodes, triggering and aggravating factors, therapeutic regimes used (class of corticosteroids, doses, period of use, systemic or inhaled), age period analyzed (before or after puberty), method used for growth evaluation, time and type of study section (transversal and longitudinal), besides the socioeconomic level of the population studied.

The effect of asthma over delayed growth continues to be a matter of controversy and constitutes a complex study in asthmatic children for many reasons. Most studies conducted seek to define the relations between the above mentioned variables and the normal growth rate of the patients. Similarly, we intended to study the respiratory allergic disease (allergic asthma and/or allergic rhinitis) as cause of SS and/or delayed growth in children and to evaluate the influence of some variables on them.

Table 4. Frequency of short stature in pairs of siblings: Atopics and non-Atopics (Controls)

	Stature Percentile*		Total	%<3
	<3	≥3		
Atopics	15	105	120	12.5*
Controls	5	115	120	4.2
Total	20	220	240	8.3

Fischer's Exact test p=0.0166* *NCHS

Relative Risk 3.286 (CI 95% - 1.154 - 9.356)

In this study we applied the NCHS curve, since it allows for comparison between several studies made in many places around the world (21).

To evaluate the nutritional status of children, the following anthropometric ratios were used: weight/stature and stature/weight. These ratios refer to different physiological and biological processes. A low weight/stature ratio shows wasting (difficulty in gaining weight or weight loss), and a low stature/age ratio indicates growth interruption (precarious overall economic conditions and/or repeated exposure to adverse conditions). In the short term, weight fluctuations can occur because of nutritional status changes, but the same is not true with stature. Stature does not change with short-term nutritional deprivation but there is no growth if the deprivation period extends for weeks and months. So, excluding genetic and constitutional causes, depression of stature against age is considered evidence of chronic malnutrition (22).

In spite of having the weight and height values for all children, we focused our study on height only. Evaluations of stature versus age provide an indicator capable of assessing the effect of chronic conditions such as atopic disease, diabetes, malnutrition etc. In this study, we evaluated the relation between chronic respiratory atopic diseases and growth.

Another factor to consider would be a section point below which we could consider a child of SS. There are three options commonly used: percentiles, Z-score and median percentage. Because they are easier to handle, percentiles are the most used. The critical points in anthropometric analysis are usually below percentile 10, 5, or 3. However, in evaluating an individual or a population subgroup the ideal section point is percentile 3. It shows more specificity, though with reduced sensitivity. Thus, we adopted percentile 3 of NCHS standard as section point accepting that only 3% of normal children will be accepted as with SS. This definition was established in order to undoubtedly detect children with SS.

Then we analyzed the patients individually, seeking to evaluate the variables that could possibly influence, separately or not, on the frequency of SS.

We did not find differences related to gender and the total frequency of SS was 7.9%, lower than the frequency previously observed in our environment (6, 14). In these studies, the Brazilian curve was used instead of the NCHS standard.

The study of the age periods distribution showed no significant differences among them. However, from 10 years of age on the SS frequency increased, but not significantly, reaching up to twice the frequency observed in the prepubertal phase. Since this is a phase of rapid growth, inadequate treatment of the atopic disease or something else acting in this period, might cause growth delay.

Generally, birth weight has been considered as an important factor to ensure proper growth. Studies evaluating this relationship have reported a higher frequency of children with short stature among those born with less than 2,500 grams. Our findings were similar (Table 1).

There was no significant difference in the prevalence of SS among children with asthma and/or rhinitis, as previously reported (5, 14). Although the criteria used to classify asthma according to severity are variable, findings on the repercussion of severe conditions on growth have been consistent. Among others, the main justifications are: prolonged use of systemic corticosteroids, chest deformities, hypoxemia, chronic anorexia and repeated infections (2, 3, 8, 17).

Because the study was cross section we only had information from the parents on corticosteroid treatment. Thus, even using the recall inquiry method, the dosage and periods of such treatments could not be established. Therefore, it was not possible to discuss a possible relationship between the consumption of corticosteroids and SS. However, it should be noted that 151/617 patients underwent this treatment and 149 of them were severe asthmatics (Table 3). Several reports on the management of asthma are consistent in pointing out inhaled corticotherapy, as the best treatment for these patients (20, 24). However, this treatment was used by only 3.4% of our severe asthmatic patients, showing that they were not properly treated. This fact reinforces the hypothesis that poor asthma control can contribute to growth delay or suppression.

Generally, the longitudinal studies are the most adequate for the actual influence of the corticosteroid treatment on growth. Van Metre & Pinkerton (17) followed up on children with severe asthma submitted to different regimens of oral corticotherapy for six months, and observed delayed growth depending on the kind and dosage of corticosteroid used. Discontinuation of therapy provided the resumption of growth.

It is agreed that daily therapy or frequent "acute courses" of oral corticosteroids are accompanied by significant inhibition of linear growth (2, 16, 23).

The same is not true with an alternate-day regimen (15). However, in spite of evidence of the blocking action of chronic use of glucocorticosteroids, it is very difficult to isolate their participation since they are used in more severe conditions and are associated with other factors.

On the other hand, Fergusson et al. (5), studying delayed maturation and prevalence of SS in children with respiratory allergy, found 6% with short stature and none of them had received corticosteroids. Among patients with allergic rhinitis only, the value was 5.4%. According to the authors, the delayed growth observed in these patients was independent of its association with asthma and/or corticosteroid use. They believe that it results from atopic status, affecting growth regulation.

The precise way that corticosteroids reduce growth is controversial. The action over the releasing pulses of the growth hormone (GH) and the inhibition of the hepatic synthesis of the somatomedin are questionable. However, administration of GH in patients on continuous and prolonged corticotherapy did not present good results (25).

Hall (25) evaluated the serum concentration of somatomedin after intravenous injection of GH and verified the production of somatomedin between those who did not receive corticosteroids. This finding supported the idea that corticosteroids inhibit the action of GH on the liver, permitting only a peripheral action.

As for inhaled corticosteroids, several investigations were made to determine the degree of adrenal suppression and/or the repercussion over the growth rate of children when used mainly in the long term (1, 9, 18, 26-28).

In children, inhaled dosages of beclomethasone dipropionate (BDP) up to 400 mcg/day rarely have a suppressor effect on the hypothalamus-hypophysis-adrenal (HHA) axis (29). However dosages higher than those can be followed by a decrease in cortisol secretion and inadequate response of the HHA. In spite of this, a suppressive action over the growth of children who were administered dosages from 200 mcg/day to 800 mcg/day of BDP (6, 9, 18) is not frequently found.

Two recent studies evaluating children in chronic use (at least 6 months) of BDP (400 mcg/day) showed decrease in the growth rate in comparison to the control group (19, 29). However, one of them showed that discontinuation of treatment was not accompanied by resuming the growth rate (30).

In a study with the use of inhaled BDP the apparent suppression of growth can be explained by delay at the beginning of puberty associated to asthma. In another study some deceleration was observed in six of 50 children receiving high dosages of inhaled corticosteroid from 750 to 1,500 mcg/day (15).

Evaluating asthmatic children, Murray et al. (12) observed a positive relation between early onset of asthma and greater repercussion on growth. Intercurrent conditions during the phase of life in which the growth is rapid and intense would be the explanation for this finding. In addition, the duration of atopic disease has been considered as an important factor in the delayed growth genesis. In this study we observed a significant relation between the period of disease and short stature (Table 3). Patients with more than ten years of illness presented SS frequency significantly higher when compared to others.

Unfavorable socioeconomic conditions, with less access to health care and specialised medical treatment, generally late in relation to the onset of the disease - a common situation found among us - can contribute in a way to justify the significant association between duration of allergic disease and SS in our results (4, 6, 13). However, Hauspie et al. (7), studying matching pairs of asthmatics and normal controls as for the socioeconomic level, found a higher frequency of delayed growth between asthmatics.

In another study we found a higher frequency of SS among children with allergic diseases treated at specialised centers (12.7%) compared to children treated at the general pediatrics division of the same institute (8.8%), and children treated at private allergic clinics (3.3%) and private pediatric clinics (1.9%). At that time the fundamental role of the socioeconomic level seemed clear to us (14). However, although we were evaluating populations assisted at the same health care institute, this was not an indication that they had the same socioeconomic situation.

In order to evaluate the influence of the socioeconomic factor on SS frequency in children with respiratory allergy, we compared our patients with the group formed by their non-atopic siblings. Because they belonged to the same family, if nutritional factors were a relevant cause for SS, this would act more or less consistently among brothers and sisters. The significantly higher values among atopics made us believe that the allergic disease is, by itself, capable of promoting delayed growth.

Balfour Lynn (1), in a longitudinal prospective study, involving 66 asthmatic children, from 13.1 to 20 years of age, proposes that the contradictory results over the association of asthma and delayed growth could perhaps be explained according to the age period under study. The analysis of asthmatic children of 10 years of age and under showed that there was not a clear association between asthma and delayed growth. On the other hand, in investigations involving children from 10 to 15 years of age that association was clear. In this case, the delay would occur in the beginning of puberty (observed

in the pre-adolescent phase of several asthmatic children), resulting in physiologic decrease in the speed pattern of growth, which in turn, would give a false impression of delayed growth. However, once puberty began, the normal growth rate normalised and the final stature expected for adult age, observed in evolution studies, would be within the normal limits.

In a prospective study, Martin et al. (10) followed the growth of 342 asthmatic children, from seven to 21 years of age. Suppression of growth was first observed at 10 years of age and was evident at 14 years of age. However, at 21 years of age all groups studied presented stature and weight not differing significantly from the controls.

The main goal of this study was the analysis of respiratory allergic disease (asthma and/or allergic rhinitis) as cause of SS and/or delayed growth in children, and to study the socioeconomic variable that follows the allergic disease mainly in countries like ours, marked by profound inequalities of income distribution. Future evaluations, in the long term, comparing asthmatic children in different percentiles of growth, comprising the pubertal and post-pubertal phases would be helpful for the evaluation of the exact moment the growth rate is resumed and consequently to propose a more adequate therapy.

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