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Impaired Growth Parameters of Children Due to Affection with Chronic Asthma and its Drug Therapy

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Abstract: The World Health Organization (WHO) includes asthma as a worldwide public health priority, with a steadily increased morbidity rates reaching an epidemic pattern. Poor weight gain and growth retardation are commonly seen in patients with asthma. This study was conducted to detect the impact of chronic asthma and its drug therapy on growth rates of children.A case control study was conducted in pediatric outpatient clinic at El-Hussein university hospital where a group of 60 asthmatic children aged 5-10 years were matched with another group of 60 healthy children at the same age as a control group. Both groups were selected according to selection criteria and submitted to comprehensive medical examination including evaluation of anthropometric measurements as weight, height etc. Results revealed that there was a highly significant decrease in most growth measurements including weight, height, Wt /age, Ht/age percentiles, sitting height, sub-ischeal leg length (SLL) and delayed bone age among asthmatic children compared to control group. It was also found that the more severity of the diseases, the less growth measurements among the asthmatic children. Examining the effect of treatment received among asthmatic children showed that those who inhaled corticosteroids showed the lowest values of mean ±SD as regards Wt/age %, Ht/age % with the highest percentage of delayed bone age compared to other cases and controls. In conclusion and recommendation: There was a clear association between affection with asthma and development of growth impairment in children. The impaired growth may be related to the disease itself or its related treatment, as well as to a combination of both and this requires healthcare planners to consider growth evaluation as one of the main tasks in the regular follow up of these populations at high risk.The study recommended also enhancing preventive measures to lessen the morbidity rates of bronchial asthma, conducting further studies to confirm the association between asthma and growth retardation and adopting new and more safer strategies for treatments.

Key words: Growth parameters · Chronic asthma · Drug therapy

INTRODUCTION

Asthma is a chronic inflammatory condition of the lung airways resulting in a reversible episodic airflow obstruction [1].

It represents the most frequent chronic inflammatory disease in childhood. The World Health Organization (WHO) included asthma among the major chronic disorders, representing a worldwide public health priority. The CDC National Surveillance for asthma revealed that its prevalence in children has risen from 3.5% to 7.5% over a period ranging from 2001 to 2003. As many as 10-15% of boys and 7-10% of girls may have asthma during childhood [2].

In Egypt, it was estimated that more than one fifth of wheezy infants were affected with asthma, while the incidence of asthma among children at the school age was around 10% [3].

In U.S.A. asthma leads to 2 million emergency room visits and accounts for 14 million missed school days in the year 2000. As regards mortality, it leads to 5000 deaths yearly and there had been substantial increase in asthma mortality periodically in recent decades [4].

Medications for asthma range from quick relief medicines which give rapid and short term treatment for acute attacks (as short acting inhaled B-agonists) and long term controllers taken every day, over long periods of time as a prophylactic treatment to prevent asthma

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attacks e.g. inhaled corticosteroids (ICSs) (as budesonide and flutacasone) and non steroidal anti-inflammatory agents(as cromolyn and nedocromil) [5].

Inhaled corticosteroids (ICSs) are the most effective treatment of persistent asthma as they act locally to reduce inflammation in airways and prevent blood vessels from leaking fluids into airways passages, so minimizing the side effects of other systemic medications, however the best way to prevent asthma attacks is to identify and avoid indoor and outdoor allergens and pollutants [6].

Normal growth occurs only if the individual is healthy. Acute illness doesn't impair growth significantly but chronic ones including any organ can lead to marked changes in growth rate. Poor weight gain and growth retardation are seen commonly in patients with asthma [7].

During childhood and adolescence, the longitudinal growth of bones represents one of the most relevant changes of the body composition. These events are directly influenced by the interaction between genetic and acquired factors including environmental as socio-economic …etc. However, several other factors and especially chronic diseases, might also strongly modulate these complex mechanisms.Treatment adopted in several chronic diseases, mainly chronic corticosteroid treatment, may strongly affect bone metabolism and consequently exert negative effects on growth of children and adolescents [8].

Duration, severity and activity of the disease as well as poor nutrition and reduced physical activity represent the main determinants of growth impairment in chronic diseases in children and adolescents [9].

Up to now, one of the most important factors implicated in the impaired growth of asthmatic children and adolescents is corticosteroids treatment. Inhaled corticosteroids (ICSs) represent the cornerstone for the treatment of asthma. However, many side effects were already known, including its effect on growth. Of note, also (ICSs) are known to inhibit many key mediators involved in growth: secretion and action of growth hormone, the action of insulin-like growth factors, collagen synthesis and adrenal androgen production can all be reduced by glucocorticoids [10].

However, up to now, the effects of (ICSs) on linear growth and final adult height still remain controversial. In fact, there are several bias related to the effects of (ICSs) on growth during long-term follow up: severity of the disease, seasonal variation in growth rate, pubertal status and socioeconomic factors that might influence growth in subjects with asthma [11].

Aim of the Work: To detect the impact of chronic asthma and its drug therapy on growth measurements of children.

MATERIALS AND METHODS

- A case control study was conducted in pediatric outpatient clinic at El-Hussein university hospital in the period from February-May 2014.
- A sample of 60 asthmatic children aged 5-10 years were chosen by simple random sample (according to selection criteria) among all asthmatic children attending the clinic to represent the case group which was divided into two subgroups as follows:
- Subgroup (1):30 children with chronic controlled asthma depending mainly on inhaled corticosteroids(ICSs) as a treatment.
- Subgroup(2):30 children with chronic asthma using non steroidal therapy.
- Another Group of 60 non-asthmatic children of the same age chosen by simple random sample (according to selection criteria) to be matched with the case group as a control group.

In Choosing the Case Group, the Inclusion & Exclusion Criteria Were Considered:

Inclusion Criteria: Every child 5-10 years old suffering from chronic asthma, treated at least for 2 years & not suffering from any other chronic health problem.

Exclusion Criteria: Children of the following conditions were excluded from being chosen:

- Short stature.
- Chronic renal problems such as Cushing syndrome…..etc.
- Chronic rheumatic disease receiving corticosteroids.
- Leukemics and other blood dyscrasis children who were receiving steroids.
- The case group was subjected to a comprehensive medical examination including the following items:

History Taking: Including family history, past and present history of attacks, socio-demographic data including age, sex and social score [12], frequency and severity of attacks, type and duration of treatment received.

Complete Physical Examination: Including general examination and strict local one (with special attention to presence of chest deformity, using accessory muscles, audible wheezes,distress...).

- Control children were also subjected to a comprehensive medical examination so as to ensure that the selected children were free from any chronic health problems either asthma or others and attending the pediatric outpatient clinic for acute illnesses or minor operations as diarrhea or upper respiratory tract infections….etc.
- Both case & control groups were subjected to evaluation of the anthropometric measurements including:

Weight (Wt) in Kg & height (Ht) in cm

- Wt/age, Ht/age, Wt/Ht percentiles, where weight and height percentiles of the National Center for Health Statistics [13] were used for comparison.
- Sitting height (SH).
- Sub-ischeal leg length(SLL).
- Height standard deviation score (HSDS)=measured height minus mean height for age divided by standard deviation of height for age.

Plain X-ray: to assess the bone age or the degree of maturation of the child bone, where single A.P view was taken to different body bones and seen by a radiologist.

Statistical Analysis: Including the following statistical parameters and tests:
Range, median, mean ±SD, student t- test, x^2 test, F test(ANOVA), Mann whitney(Mw) test (non parametric test used for small sized samples or comparing data of groups not normally distributed).p value <0.05 was considered significant result and P< 0.01 was considered very significant.

- Administrative and ethical issues were considered including permission from the hospital administration beside autonomy, oral consent and confidentiality.

RESULTS

Table (1): showed that the mean± SD of weight &height of asthmatic children were lower than those of controls as follows: weight (22.7±4.5 vs 26.4±4.4 kg respectively) & height (110.9±11.7 vs 120.5±11.4 cm respectively).These differences were statistically very significant, while variations regarding age,sex and social class between cases and controls were not statistically significant.

Table (2): revealed that the mean ±SD of most anthropometric measures of asthmatic children were lower than those of controls as follows: Wt/ age percentile was

Table 1: Personal characteristics of the studied case and control groups

Item	Case group (n=60)	Control group (n=60)	Statistical tests
Age			
Range	5-10	5-10	T=1.6
Mean±SD	5.9±1.2	6.3±1.3	P=0.10
Sex			
Male	32(53.4%)	29(48.4%)	X^2=0.49
Female	28(46.6%)	31(51.6%)	P=0.91
Social score*			
Lower	24(35.0%)	20(33.3%)	X^2=1.8
Intermediate	26(53.4%)	28(46.7%)	P=0.71
High	10(11.6%)	12(20.0%)	
Weight (kg)			
Range	12-38	15.5-32.5	T = 2 . 9
Mean ±SD	22.7±4.5	26.4±4.4	P=0.004
Height (cm)			
Range	92.5-138	97-140	T=3.2
Mean±SD	110.9±11.7	120.5±11.4	P=0.001

Social score*: Modified from Fahmy & El-Sherbini [12]

Table 2: Comparing anthropometric measurements of case group with controls.

Item	Case group (n=60)	Control group (n=60)	Statistical tests
Weight /age%			
Range	<5-97	22-90	T=2.9
Mean±SD	33.2±25.7	54.3±23.3	P=0.009
Median	27	60	Mw=12.06
			P=0.006
Height /age%			
Range	<5-82	7-80	T=3.1
Mean±SD	29.2±23.9	51.1±25.4	P=0.002
Median	26	61	Mw=11.6
			P=0.005
Weight /height %			
Range	<5-97	8-91	T=2.1
Mean ±SD	47.6±26.2	59.6±20.3	P=0.07
Median	49	60	Mw=3.1
			P=0.060
Sitting Ht(cm)			
Range	48.6-66.8	50.7-71.3	T=3.7
Mean±SD	57.2±4.2	60.5±6.1	P=0.003
Median	55	62	Mw=6.7
			P=0.007
SLL (cm)			
Range	36-68	48.5-66.5	T=3.5
Mean±SD	50.6±4.5	57.9±5.7	P=0.023
Median	49.2	56	Mw=6.1
			P=0.018
HSDS			
Range	2.9-11	4-11.7	T=1.37
Mean±SD	5.1±1.3	5.8±1.9	P=0.28
Median	5	6	Mw=1.1
			P=0.4
Delayed bone age:			X=4.1
no.& (%)	11(18.3%)	0(0.0%)	P=0.014

Table 3: Comparison between the two case subgroups and the control one as regards weight & height measurements.

Item	Cases: Subgroup 1: Cases with inhaled corticosteroids (ICSs)(n=30)	Cases: Subgroup 2: Cases with non steroidal therapy (n=30)	Controls (n=60)	Statistical tests
Weight (Kg)				F=2.6
Mean±SD	23.3±5.5	20.1±6.3	27.4±5.6	P=0.031
Height (cm)				F=1.7
Mean±SD	117.9±8.3	111.9±12.08	122.5±10.4	P=0.087
Wt /age %				F=3.4
Mean±SD	36.4±24.1	40.1±29.9	61.3±27.9	P=0.001
Ht/ age %				F=3.1
Mean±SD	17±26.0	37.8±22.0	52.1±24.0	P=0.004

Table 4: Comparison between the two case subgroups and control one as regards other anthropometric measurements.

Item	Cases: Subgroup 1: Cases with inhaled corticosteroids (ICSs)(n=30)	Cases: Subgroup 2: Cases with non steroidal therapy (n=30)	Controls (n=60)	Statistical tests
Wt /Ht %				F=1.9
Mean±SD	56.9±23.8	43.4±32.5	64.6±23.3	P=0.058
Sitting Ht				F=1.7
Mean±SD	62.5±4.4	54.4±5.2	66.3±5.6	P=0.10
Subischeal leg length				F=1.9
Mean±SD	55.4±4.03	50.9±6.3	57.9±4.8	P=0.071
Height standard deviation score (HSDS)				F=0.84
Mean±SD	5.16±0.52	5.34±1.78	5.62±1.73	P=0.24
Bone age				
Normal	23 (76.7%)	26 (86.6%)	60 (100%)	X^2=4.1
Delayed	7 (23.3%)	4 (13.4%)	0 (0%)	P=0.02

Table 5: Severity of the disease Vs some anthropometric measurements of the asthmatic children.

Item	Severity of the disease: Mild (n=18)	Moderate (n=34)	Severe (n=8)	Statistical tests
Weight /age%				F=1.07
Mean±SD	34.1±24.1	33.2±18.2	31.9±20.6	P=0.09
Height /age%				F=1.8
Mean±SD	29.5±24.4	31.6±31.3	27.8±18.9	P=0.10
SLL				F=1.8
Mean±SD	54.6±4.7	53.4±4.2	51.6±3.8	P=0.10
HSDS				F=1.8
Mean±SD	5.1±1.1	5.4±1.4	5.6±1.6	P=0.13
Delayed bone age no. &(%)	2 (11.1%)	7 (20.6 %)	2 (25%)	X^2=4.9 P=0.016

(33.2±25.7 vs 54.3±23.3 respectivly) & Ht /age % as (29.2±23.9 vs 51.1±25.4 respectively),sitting height (57.2±4.2 vs 60.5±6.1 cm) and subischeal leg length SLL (50.6±4.5 vs 57.9±5.7 cm).Bone age was delayed in (18.3%) of case group vs (0%) of control children. All these differences were statistically significant.

Table (3): Detected that subgroup(1) of asthmatic children who used (ICSs)in their treatment showed the lowest values of mean±SD as regards Wt/age % and Ht/age % compared to other cases and controls with highly significant statistical differences, while subgroup (2)of asthmatic children who used non-steroidal therapy had the lowest values of mean ±SD as regards weight and height compared to other groups with significant statistical difference as regards the weight only.

Table (4): Revealed that subgroup (1) of asthmatic children who were using (ICSs) in their treatment showed the lowest value of Mean±SD as regards HSDS and the highest percentage of delayed bone age than other cases and controls with significant statistical difference regarding delayed bone age only, while asthmatic children of subgroup (2) had the lowest values of Mean±SD as regards Wt / Ht %, sitting height and subischeal leg length compared to other groups with non significant statistical differences.

Table (5): Revealed that the more severity of the diseases, the less growth measurements among the asthmatic children with only statistically significant difference regarding delayed bone age.

Table (6): Cases who were inhaling (ICSs) (subgroup 1) had non-significant a longer mean duration of treatment than (subgroup2) who used non steroid therapy.

Table 6: Comparison between the two asthmatic subgroups as regards duration of treatment

	Asthmatic children		
Duration of treatment (in years)	Subgroup (1) With (ICSs) inhalation	Subgroup (2) With non steroid therapy	Statistical test
Range	3-5	3-4	T=3.1
Mean ± SD	3.9±0.7	3.4±0.5	P=0.082

Table 7: Frequency of asthmatic attacks in contrast to the two asthmatic subgroups.

	Asthmatic children		
Frequency of attacks/month	Subgroup(1) With (ICSs) inhalation	Subgroup (2) With non steroid therapy	Statistics
Range	4-11	3-8	T=2.1
Mean ±SD	6.1± 3.4	4.4±2.3	P=0.036

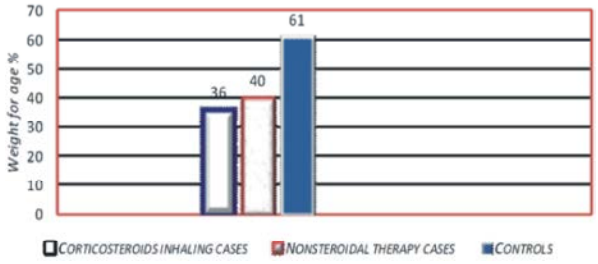

Fig. 1: Mean Weight for Age % among the Two Case Subgroups and Controls

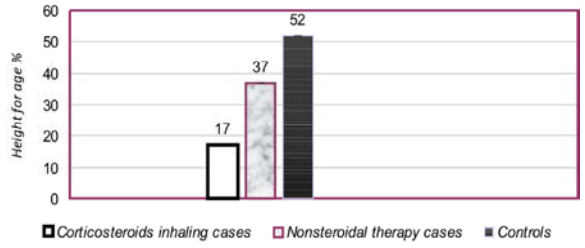

Fig. 2: Mean Heighjt for Age % among the Two Case Subgroups and Controls

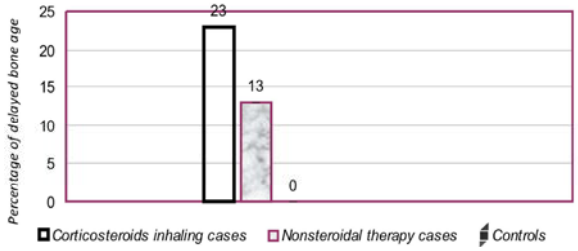

Fig. 3: Percentage of Delayed Bone Age among the Two Case Subgroups and Controls

Table (7): Comparing the two subgroups of asthmatic children regarding frequency of asthma attacks /month showed that children of subgroup (1)(who inhaled ICSs) had more frequent attacks per month than subgroup (2) (who used non steroids).The mean ±SD was 6.1±3.4 vs 4.4±2.3 respectively with statistically significant difference.

DISCUSSION

Asthma represents the most frequent chronic inflammatory disease in childhood. It affects approximately 100 million people worldwide and during the past few decades, this figure has been increased by 5-6% yearly reaching rates of 30-40% in many countries [14].

In another study of 2020 children aged 5-14 years by Cagney and MacIntyre [15] in Sydney, Australia revealed that 31% of them were asthmatics and asthma medication was used by 21% of them in the previous year.

The growth and development of children had been the subject of great interest by many investigators. A complete knowledge of the physiological events leading to growth alterations in children and adolescents with these chronic diseases is crucial in order to allow a growth as physiological as possible and attainment of expected final height [16].

Our study included 60 asthmatic and another group of 60 healthy non asthmatic children.There were no statistically significant variations as regards age, sex or social class between case and control groups. Socio-economic factor could be implicated in growth deficiency in children with asthma. Rona and Florey [17] observed that asthmatic children with lower socioeconomic level showed a higher incidence of short stature. Also, Grumach *et al.*[18] have analyzed the association between socioeconomic level and growth of asthmatic children, confirming that this link was highly significant.It was also found in our study that more boys than girls were asthmatics. Most studies reported a more prevalence of asthma in boys than girls with ratio of 1.3:1, but after the puberty the difference disappears [19].

The present study revealed that there was a highly significant decrease in most growth measurements including weight, height,Wt /age and Ht/age percentiles, sitting height, subischeal leg length (SLL) and delayed bone age among asthmatic children compared to control group.

The findings of our study were supported by many studies as Van der Voort *et al.* [20], who noticed that most growth measurements were decreased among asthmatic

children than non-asthmatic ones especially weight and height besides delayed bone formation indicating growth retardation.That was also supported by the negatively deviating growth curves in asthmatic boys aged 5-18 years as detected by Simon [21].

Asthma itself can impair growth through several mechanisms. Some of them are directly related to the disease and these include early disease onset, duration and severity of the disease, chest deformity, hypoxemia, impaired pulmonary function and enhanced metabolic demands due to increased work of breathing and allergic processes. However, up to now, the results on this topic are still conflicting [22].

In a population of 121 school-age children with asthma in Scotland, their weights and heights tended to be similar to those who had the first asthma episode before five years of age [23]. Similar results have been confirmed by Pike *et al.* [24] who conducted a study on 183 young Canadians, in which an association between early onset of the disease (before the age of 3 years) and growth retardation has been found.

Regarding the severity of asthma, it has been found that children with more severe asthma had more decreased weight and height below the normal range. In a longitudinal study, McNicol *et al*.[25] noted a trend towards weight decrease in the group with more severe asthma.

However, these data were not confirmed by other studies, where no association has been detected between growth defects and the severity of the atopy [26].

Interestingly, it has been largely speculated the role of asthma as a condition inducing growth hormone alterations. In fact, it has been hypothesized that asthmatic children who usually suffer from nighttime symptoms with sleep disturbance might have an impairment of growth hormone release. Nevertheless, these data have not been confirmed because several other studies demonstrated a normal growth hormone profile in asthmatic children [27].

Up to now, one of the most important factors implicated in the impaired growth of asthmatic children and adolescents is corticosteroids (ICSs) treatment. Due to the inflammatory mechanisms implicated in the pathogenesis of asthma, corticosteroids represent the best way to reduce inflammation of the airways. Inhaled corticosteroids (ICSs) represent the cornerstone for the treatment of asthma. At present, all guidelines advocate the use of (ICSs) for persistent asthma because they have reduced asthma mortality and morbidity. In addition, they reduce asthma symptoms, improve lung function and reduce the severity of bronchial hyper-responsiveness and, probably most importantly, reduce the number of exacerbations. However, many side effects were already known, including its effect on growth [28].

Of note, also (ICSs) are known to inhibit many key mediators involved in growth: secretion and action of growth hormone, the action of insulin-like growth factors, collagen synthesis and adrenal androgen production can all be reduced by glucocorticoids.Treatment regimes represent a key factor associated with adrenal suppression in children and adolescents with asthma [29]. In a previous study by Guilbert,*et al*.[30], a high-dose inhaled corticosteroids had been shown to induce adrenal suppression in children with asthma. However, not only high but also low corticosteroids doses (100 mg twice daily) have been shown to have similar effects on adrenal function [31].

However, up to now, the effects of (ICSs) on linear growth and final adult height still remain controversial. In fact, there are several bias related to the effects of (ICSs) on growth during long-term follow up: severity of the disease, seasonal variation in growth rate, pubertal status and socioeconomic factors that might influence growth in subjects with asthma [32].

In pre-pubertal children, the use of (ICSs) has been shown to reduce growth velocity, resulting in a linear growth reduction of 0.5 to 3.0 cm (approximately 1 cm on average) during the first few years of therapy. Although growth velocity returns to normal values within few years after the initiation of (ICSs) therapy, the long-term effect of the initial decrease in growth velocity on attainment of adult height is still unclear [33].

In a prospective study compared treatment with budesonide (ICSs) up to 600 µg with sodium cromoglycate (non steroidal anti-inflammatory agent), it has been found that (ICSs) did not affect either growth velocity up to 10 years of age or expected final adult height. Interestingly, the incidence of delayed puberty was significantly increased in both groups suggesting that asthma itself and not (ICSs) per se, has a potential direct influence on growth and onset of puberty [34].

According to Childhood Asthma Management Program (CAMP)[35], there was a study, conducted to assess the influence of (ICSs) on growth in a randomized controlled manner. In that study, children were randomly assigned to receive 200 µg budesonide (ICSs), 8 mg of nedocromil (non steroidal agent), or placebo twice daily. This study demonstrated in those subjects treated with budesonide a mean increase in height of 1.1 cm less than the mean increase in the placebo group. However, height

was still within the normal range based on parental height. In contrast, no difference was documented in terms of height increase between the nedocromil and placebo group. The difference in growth velocity was mainly documented during the first year of treatment and did not increase afterwards.

The available data evaluating the relationship between asthma and growth suffer from the influence of the clinical picture, treatment options and different study methods that are unable to firmly distinguish those factors which might be responsible for the growth retardation in children and adolescents with asthma. Therefore, further well-designed longitudinal studies are needed to clarify the role of asthma or (ICSs) itself in directly influencing growth and puberty [36].

CONCLUSION

There was a significant association between childhood asthma and occurrence of impaired growth parameters of the studied children. This may be due to the disease itself or its related treatment, as well as to a combination of both. Progress in the understanding of the complex mechanisms related to growth impairment in these chronic diseases has improved the prognosis of growth in these high risk populations.

Recommendations:

- The peculiar onset of several chronic diseases, mainly asthma during childhood requires enhancing preventive measures to lessen the morbidity rates of these diseases.Healthcare planners have to consider growth evaluation as a main task in the regular follow up of these populations at high risk.
- Further studies should be done to confirm the association between asthma and growth retardation.
- Inhaled corticosteroids should only be used when justified by severity of asthma attacks with the choice of the safest ingredients. Controlling growth alterations by adopting new and specific treatments is now a possible option in these clinical conditions.

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