

Association between Bronchial Asthma and Pubertal Delay in Pediatric Patients

Abdullah Khalid A Dakhel, Fahad Abdullah R Alqeaed , Fahad Mohammed A Alkhuzayyim
Qassim College of Medicine

ABSTRACT

Background: asthma is a chronic inflammatory disease with a considerable prevalence and unfavorable impacts on various body systems. The natural history of asthma has been extensively investigated in terms of the varied effects on age and gender. **Aim of the study:** this study aims to achieve a better understanding of the unclear relationship between bronchial asthma and pubertal delay in the pediatric age group. **Methods:** we reviewed the scientific literature concerned with studying the effect of asthma and its treatment on the growth of children and the onset of puberty using some international medical databases (Medline, Google scholar, EMBASE). **Conclusion:** Although there have been some community-based surveys and studies based on young children which failed to find an association between asthma and growth, others revealed that asthma can cause growth retardation through different mechanisms, including hypoxia, impaired lung functions, or endocrine malfunctions. Pubertal delay is also observed in untreated asthmatic boys and girls. In addition, inhaled corticosteroids, the best available treatment of asthma, were found also to have an effect on pubertal delay and this effect is dependent on the dose, duration and the outcome of therapy. When concentrating on pubertal delay, it seems that more longitudinal studies are required to comprehensively investigate the effects of asthma and its treatment on this vital stage of life.

Keywords: asthma, puberty, delayed puberty, pediatric growth.

INTRODUCTION

Being one of the commonest disorders of childhood, bronchial asthma has been acquiring the attention of medical researchers as it produces severe symptoms enough to be a real threatening condition. The prevalence of childhood asthma has been increasingly reported over the last three decades in developed countries, however, it has been reported that the prevalence decreased in adolescents in Western countries ⁽¹⁾. Setting an accurate definition of asthma is apparently difficult particularly in infants. For older children, a clear definition can be established for asthma as an airway inflammation with airflow limitation leading to suffering from cough and wheezes. In such cases, there is a predominance of eosinophils and mast cells with an association of an increased responsiveness of bronchi ⁽²⁾.

The actual mechanism by which the development of airway inflammation takes place in asthma has been well documented ⁽³⁾. Several steps are involved starting initially with a primary sensitization followed by the occurrence of an immune response of allergic phenotype. The sensitized cells can be subsequently activated by the following exposures resulting in releasing inflammatory mediators.

The natural history of bronchial asthma has been extensively investigated in terms of the varied effects on age and gender. Furthermore, it has been noticed that there is an apparent sexual variation in children with asthma and their respiratory system

development, with males having a tendency to develop asthma while females would have a subsequent relative deterioration in lung function ' such findings were evidenced by studies observing multiple changes in asthma taking place with the fluctuations of sexual steroid hormones observed during pubertal development until complete maturity ⁽⁴⁾. Considering the overall growth pattern during childhood up to the age of puberty, there have been many conflicting perspectives concerning the effects of asthma on growth. In this review, it is now our opportunity to demonstrate the relevant literature related to the relationship between asthma severity and its therapeutic approaches and their impact on the growth and developmental processes as well as the possible consequences leading to a pubertal delay.

The study was done according to the ethical board of King Abdulaziz university.

An overview of delayed puberty

Considering both sex and ethnic origin of an individual, the puberty can be delayed when there is a lack of normal pubertal development at an age of 2 SD above the mean age, which could be observed in boys at an age of 14 years with a testicular volume less than 4 ml and in girls at 13 years of age with a lack of the larche. Generally, the proposed cutoffs for the puberty age could be between 10 and 16 years of age ⁽⁵⁾. The chief causes of pubertal delay are broadly classified as genetic

or idiopathic factors, where a constitutional delay of both the growth and puberty takes place, or secondary to primary factors related to a chronic pathology. For the latter factors, several chronic illnesses can result in delayed puberty such as malnutrition and diseases of gastrointestinal (malabsorption and inflammatory bowel diseases), renal (nephrotic syndrome and chronic renal failure), hematological (leukemia and chronic leukemia), endocrine (hypogonadism and growth hormone deficiency), or respiratory origins (chronic asthma and cystic fibrosis)⁽⁶⁾.

In general, few data are available to obtain a detailed knowledge related to the association between delayed puberty and chronic diseases. It is possibly due to such delay may be a normal variant or a known consequence of the pathology and it could not be an important player in disease pathogenesis. Nonetheless, it is basically imperative to investigate pubertal delay because it would have a negative impact on several aspects of the child including the final height, total bone mass and the psychological patterns⁽⁷⁾. Usually, pubertal delay secondary to a chronic illness is characterized by a delay in growth for one or more years as well as a smaller pubertal growth spurt. It has been noticed that if the chronic illness took place earlier in life or in a severe pattern, the effects on growth and pubertal growth would have been greater.

The actual pathophysiological mechanism by which the delayed puberty occurs in association with a chronic illness is mainly dependent on some accompanied basic alterations in the body as a consequence of the disease. Malnutrition, increased protein degradation rate, toxic substance accumulation, stress, or emotional disturbance may all be involved in the development of pubertal delay. Malnutrition is thought to be integrated into the most of the pathological changes resulting in a delay in puberty onset. It may be related to reduced food intake, increased nutritional losses or an increase in body requirements⁽⁶⁾.

Childhood asthma

Asthma is considered as a chronic inflammatory process takes its place in the airway in which there is a group of involved cells and cellular elements. Asthma is affected by several risk factors particularly during the early years of life. Of these, nonspecific bronchial hyper responsiveness (BHR) and atopy are of great impact. The latter is an IgE-mediated allergic response to the environmental allergens and is thought to be closely linked to asthma while the former is also clinically linked to asthmatic children even in asymptomatic ones⁽⁸⁾.

Together with BHR, chronic inflammation of the airway lead to recurrent episodes of wheezing, cough, and chest tightness. Although the resultant symptoms are the most acceptable marker of disease activity, they frequently don't reflect the actual severity of BHR or airway inflammation. Indeed, BHR, itself, is a useful tool in the diagnosis, severity identification, and management of asthma. Furthermore, BHR is associated with a more prominent reduction in lung function and an increase in the possibility of persistence of wheezes with development⁽⁹⁾.

The interaction between genetic and environmental factors, such as air allergens, outdoor and indoor air pollution, and respiratory tract infection, seems to be an important determinant of the clinical picture of the disease. It has been supposed that both the environmental exposure and genetic predisposition are required to produce asthma symptoms. Another aspect of this notion is that the environmental triggering factor could have an increased risk of asthma development not in all individuals, but rather only in those with the susceptible genotype⁽¹⁰⁾. Inhaled corticosteroids are important therapeutic approaches for children with persistent asthma associated with abnormalities of lung function. Considering evidence-based conditions, asthma treatment should be based on β_2 agonists and inhaled corticosteroids. Additionally, oral medications can help achieve high compliance rates. Both theophylline and leukotriene antagonists have anti-inflammatory and bronchodilator effects⁽¹¹⁾. Finally, for children with infrequent asthmatic episodes and normal lung function between them, inhaled β_2 agonists are necessary for the symptoms associated with exercise.

Patterns of asthma prevalence with development:

The relationship between asthma and gender is continually a source of enriched debates. Up to the age of puberty, males usually experience asthma prevalence almost twice as in females with a peak incidence up to 5 years of age, This finding is also supported by the observation that over 60% of all asthmatic cases before puberty are males⁽¹²⁾. However, the exact factors that have been responsible for such increased risk in males are still unclear. The skin reactivity to aeroallergens in boys seems to be increased when compared to females⁽¹²⁾. Another possible contributing factor is airway size. The maximal expiratory volume at given lung volumes is significantly lower in males than females in infants and the same is applied

during the prepubertal period ⁽¹³⁾. As a consequence, both the respiratory and immunological factors are possibly important players during this period.

The aforementioned asthmatic pattern would then be changed markedly among boys and girls during puberty. The general scheme would be switched, as demonstrated by the fact that new asthma cases during puberty are more observed in girls than in boys, although the actual interpretation of this notable change could not be accomplished, it may be related to the rapid increase in airway size, relative to lung size in boys than in girls during puberty ⁽¹⁴⁾.

Another remarkable factor in determining the prevalence of asthma in girls during adolescence is the preexistence of obesity. For those girls who become obese during prepubertal years, it has been observed that there is an increased incidence of asthma which was additionally supported by the fact that prepubertal obese girls are more likely to have early menarche. Therefore, this dual mechanism possibly contributes to developing asthma symptoms due to both an early menarche ⁽¹⁵⁾ on one hand and obesity on the other one. The onset of menarche is determined according to the hormonal balance which may be changed in obese girls, and this also may be involved in predisposing girls to experience asthmatic symptoms. A study conducted by Varraso R *et al.* aimed at assessing this hypothesis which has in fact revealed a stronger association between body mass index and asthma severity in women with early menarche than those without early menarche ⁽¹⁵⁾. In general, during puberty, girls seem to have a complicated interaction of factors related to obesity, asthma, and hormonal balance, a matter which may require further careful investigations.

Effects of childhood asthma on growth and puberty

The first study which revealed an impact of childhood asthma on growth was established by Cohen *et al.* in 1940 ⁽¹⁶⁾. The authors have observed a remarkable growth retardation associated with asthma in their cohort providing an important locus for subsequent investigations. Since then, supporting these findings, a longitudinal study ⁽¹⁷⁾ has been conducted on 315 children and adolescents and 82 controls with ages ranged between 7-14 years. The authors have shown marked reductions of heights in their subjects with severe asthma. Recently, the results of a retrospective study ⁽¹⁸⁾ showed a significant reduction in growth rates in children with moderate

or severe asthma and this association is more apparent in those with a co-morbid rhinitis, indicating an important connection between such two conditions.

Thus, it is imperative to conclude the mechanism by which severe asthma can cause a reduction in growth rate. Indeed, growth retardation in asthma is associated with hypoxemia, impaired pulmonary functions and the adverse clinical scores. Another hypothesis is the endocrine instability represented as raised triiodothyronine concentration in nearly half of asthmatic children with short stature as per results of Ferguson *e al.* ⁽¹⁹⁾. Nonetheless, this finding could not be further confirmed. Another endocrine malfunction is the impaired nocturnal secretion of growth hormone due to sleep disturbances in children having severe night symptoms. However, Morris and colleagues ⁽²⁰⁾ have found that the administration of growth hormone did not yield an impact on the growth of children having asthma. Since this finding was observed in children receiving corticosteroid treatment, it is important to study growth hormone effect in asthmatic children without treatment.

Focusing on delayed bone maturation in asthmatic children and its role in growth retardation, several studies have shown that there was a marked delay in maturation associated with prolonged prepubertal growth nadir ⁽¹⁹⁾.

Again, this proposed growth-retarding mechanism would finally have no influence on the ultimate adult height as demonstrated by the satisfactory estimate of maturity obtained by X-ray findings, It is therefore clear that the children with untreated moderate to severe asthma usually have slow prepubertal growth rate explained by a pubertal delay for 1.3 years, delayed bone age and a reduction in the growth spurt ⁽²¹⁾. However, they would eventually reach the normal adult height.

This assumption was studied by Balfour-Lynn ⁽²²⁾ in a long-term prospective study on 66 children suffering from asthma without any initial evidence of growth abnormalities. The author claimed that there was a deceleration in growth pattern during the prepubertal period (after 10 years of age in about half of the children) and this was within the physiological limits. However, this finding was associated with a significant delay of puberty in both boys ($P < 0.001$) and girls ($P < 0.001$). Additionally, the severity of asthma had no contributing role in all of the above findings as observed in children receiving prophylactic doses of beclomethasone by inhalation without changes in growth. Surprisingly, this study showed that the delay in puberty onset was subsequently followed

by a growth catch up leading to achieving the expected adult height. Since this study was established for a long period, (starting with children at a mean age of 7.5 years, and ending at a mean age of 20.6 years), the author suggested that growth retardation was observed in other studies employing old children (10-15 years old), while those investigating younger children (below 10 years old) would ultimately find no growth abnormalities.

For a cross-sectional study⁽²³⁾ of 531 boys with an age range between 2 and 20 years, the subjects with asthma were significantly older in reaching the stage of Tanner pubic hair if their values were compared to both British and Dutch values. As a consequence, there was a delay by 1.3 years of their peak height velocity, indicating short statures during adolescence in asthmatic boys. When comparing children with graded asthma symptoms to normal controls, those with the severest form of asthma experienced short statures at age 14 years, while their heights at 21 years were not different to those with mild and moderate symptoms or even normal controls.

Regarding girls, several clinical trials have shown variable results in terms of the effect of asthma on the onset of the first menstruation cycle in girls, aka menarche⁽²¹⁾. However, there may be a slight tendency toward an early menarche onset in asthmatic girls (17 months earlier) if compared to normal controls as per results of a prospective study conducted by Drosdzol and co-authors⁽²⁴⁾. Such study failed to reveal any significant difference in body weights and heights between both groups. Indeed, these findings are remarkable since asthma incidence did not disturb growth process but it did exert its effects on the course of sexual maturation with a notable association between disease severity and early menarche. Likewise, another study⁽²⁵⁾ has assessed the sexual maturation and somatic development of girls with asthma, and the authors found that the more asthma severity the much earlier first menstruation and, in contrast to the previous report, somatic development was significantly inhibited in girls with severe asthma.

Effects of asthma treatment on growth and puberty

First, it is noteworthy that systemic glucocorticoid therapy is well-known to cause growth suppression in non-asthmatic children. Corticosteroids interfere with various biological processes, including the endogenous secretion of growth hormone, bone and collagen formation, and nitrogen retention. As a whole, the final outcome

will be growth arrest and pubertal delay. Since the advent of inhaled corticosteroids, the relevant early reports focused on their therapeutic efficacy whereas their side effects remained negligible⁽²⁶⁾. It is thought that treatment of children with ICS with doses less than 400 µg/d during puberty period will have no impact on growth velocity or sexual maturation⁽²¹⁾. Therefore, it seems that the ICS have been shown to cause growth retardation which is dependent on the dose.

In order to compare the growth-retarding impact of prednisone, cortisone, betamethasone in asthmatic children, Falliers and other researchers⁽²⁷⁾ observed that there was a significant reduction in linear growth rates in children receiving prednisone daily doses of 6 mg/m² of body surface. Conversely, for cortisone, the children grew normally when receiving daily doses reached 50-70 mg/m² body surface area. Growth inhibition by betamethasone occurred when the daily doses exceeded 0.6 mg/m².

Short-term studies, performed for less than six months, are mainly dependent on knemometry as a mean of measuring the growth of lower leg length. Wolthers and Pedersen⁽²⁸⁾ found that oral prednisolone (2.5 or 5 mg) causes a complete inhibition of lower leg length in children with mild asthma. For budesonide, doses up to 400 µg/day did not affect lower leg growth, while there was a significant growth reduction in the majority of children receiving 800 µg/day. Nonetheless, short-term results may be unrepresentative of the real conditions because there may be some differences between the onset of starting each study, a matter which may affect the final outcome.

For studies involving a follow-up period of 6-24 months, beclomethasone dipropionate use at a dose of 400 µg/day results in a significant growth suppression if compared to theophylline, salmeterol, or placebo⁽²⁹⁾. Again, there were no growth abnormalities when the children received 200 µg/day. When comparing children groups treated with fluticasone propionate (FP) for 12 months at two different doses (100 and 200 µg/day) with a placebo-treated group, although there were differences in growth rates (6.15, 5.94, and 5.73 cm for the placebo, 100 µg/day FB, and 200 µg/day FB respectively), the overall difference between groups was insignificant⁽³⁰⁾. To conclude, beforementioned studies comparing beclomethasone dipropionate and FP showed a significant growth suppression in the beclomethasone-receiving group versus FP-treated one.

The most impactful long-term study has employed budesonide in 300 asthmatic children

over 14 years follow-up period ⁽³¹⁾. There was a significant growth suppression after one year and after two years while there was no difference in the following years when compared to controls. However, the subjects took about a mean of 9.2 years to reach adult weight with no significant difference to the control group.

CONCLUSION

It is apparently clear that community-based surveys usually fail to find an association between asthma and short stature since the children with severe asthma represent only a small number of the total cohorts under study. In addition, some studies performed on young children did not reveal any impact of asthma on growth. Therefore, although several studies have revealed a degree of growth retardation with childhood asthma irrespective of the therapy, the concept is still controversial with a degree of growth variation even for each single child. Growth retardation appears to be more prominent in older children (10 years old or more) with an approximate consensus on the association of pubertal delay.

In general, despite this delay in puberty onset, the final adult height would be ultimately attained. Pubertal delay may be due to several factors accompanied with asthma, including hypoxemia, increased energy demands due to increased work of breathing, endocrine malfunction, or malnutrition due to decreased appetite. For girls, it seems that asthma accelerates the menarche with delaying the final stage of sexual maturation. Inhaled corticosteroid drugs may also have an effect on pubertal delay and this effect is dependent on the dose, duration and the outcome of therapy. This temporary growth decelerations would be followed by a period of improved growth to compensate the shortage and eventually drive the affected children to reach the ideal parameters as their peers.

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