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Does puberty interfere with asthma?

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Abstract — This study reviews whether, to date, scientific evidence exists that puberty interferes with the occurrence of asthma. This question was triggered by three points: (a) clinical experience with asthma as a relatively benign disease that children often 'grow out of'; (b) observations implying that asthma can change during fluctuations of sexual steroid hormones; and (c) knowledge that puberty is an age of deep hormonal changes. No scientific evidence was found that pubertal changes interfere with the occurrence of asthma. Nevertheless, there is a general agreement about the influence of age and sex on its outcome. The overall occurrence of the disease, which is highest in childhood, declines with age. In the wane phenomena, puberty does not seem to be more important than previous ages. Furthermore, the pattern of occurrence is different in the two sexes. Boys have more asthma before 10 years of age or the mid-teens. Girls then overtake boys and have more asthma up to the years of sexual maturity. During the fifth or sixth decade, asthma again seems to become slightly more prevalent in men than women, or at least the difference between the sexes disappears. It is concluded that the risk of asthma is not influenced by puberty. Age and sex seem to be more important factors, although the reason for this is unknown.

Introduction

Asthma is the most common chronic disease in children. An understanding of its natural history is essential to counsel parents and patients and to assess treatment. Many clinicians and investigators have experimented, for many years, with the idea that asthma is a relatively benign disease that children often 'grow out of' (1–3). Some evidence shows that asthma can change during fluctuations of sexual steroid hormones (4–8). It is well known that the teenage years are characterized by deep hormonal changes from pubertal development until sexual maturity (9,10).

Starting from these observations, we can hypothesize that the phenomena of puberty interfere with the occurrence of asthma; hence we investigated whether, to date, scientific evidence exists that this is true.

To review this problem, a comprehensive literature search for English language studies conducted from January 1966 to 31 May 1995 was performed using the MEDLINE database. The search strategy was developed by linking the following key words: [*asthma* and *epidemiology*] and [*testosterone* or *progesterone* or *estradiol* or *sex steroid hormones* or *luteinizing hormone* or *follicle stimulating hormone* or *gonadotrophins* or *dihydroepiandrosterone* or *puberty or sexual development* or *aging or sex*].

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A total of 467 papers was found. Review articles, letters and comments were eliminated, thus narrowing the references to 428. From these 428, all cross-sectional, prospective and retrospective studies were selected for review. Inclusion criteria were: (a) paper published in listed journals by the 1993 Science Citation Index (11); and (b) age of subjects in samples large enough to cover a period before and after puberty (i.e. childhood and adulthood). Studies that did not go beyond puberty (both before and after) were excluded (as they could give a false impression of the true natural history of asthma), unless specific hormonal or morphological changes, associated with the disease occurrence, were included in the study design.

From a biological point of view, puberty is the stage of physical maturation in which an individual becomes physiologically capable of sexual reproduction (9). It is reported that 95% of girls enter puberty at a mean age of 10.5 years and boys at 11.5 years, that sexual development is completed in a mean of 4.2 years for girls and 3.5 years for boys (10) and that puberty maturation should be considered delayed if more than five years have elapsed between the first sign of puberty and the onset of menarche in girls or completion of genital growth in boys (9). Thus it seemed reasonable to choose the cut-off points of 10 and 16 years to define puberty age (9,10).

Thirteen studies meeting the inclusion criteria were selected: three were cross-sectional, six prospective and four retrospective. The studies enrolled a total of 548 680 subjects ranging in age from 0 to 95 years with a mean age of about 29 years (Table).

None of these studies had included, in the experimental design, the detection of hormonal or morphological changes typical of puberty in association with the disease occurrence. None considered a specific definition of the age in which puberty should be ranged. Therefore, regarding the aim of our review, only two points could be concluded.

The first point is that in both sexes, the occurrence of asthma was found to be higher in childhood than in other ages (12–24). Nevertheless, the disease appeared to decline with age: the years of puberty (i.e. 10–16 years) (9,10) do not seem to be more important than the previous period. This pattern, present in all selected studies (12–24), was shown very clearly by a graphic presentation of data taken from papers of Schachter and Higgins (14), Crawford and Beedham (15) and Yunginger et al (23), as reported in the Figure.

The second point is that a switch in the occurrence of the disease between the sexes is seen throughout the years. Two main switches can be observed: the first happens in the second decade of life; the second during the fifth or the sixth decade, according to different workers. In other words, several workers (Table) reported that boys have asthma more frequently before the age of 10 or the mid-teens (14,15, 18–21,23) then girls overtake boys and have more disease up to the years of sexual maturity (13,15,16, 18,20,21). After the fifth or the sixth decade, men again become slightly more affected (16,18), or, at least, the difference between sexes disappears (14, 15). This phenomenon can best be understood from the Figure.

Considerations

Our comprehensive search through 30 years of publications to determine whether there is published evidence for an effect of puberty on the course of childhood asthma was not able to answer this question. Among 13 studies meeting the outlined criteria, none included in the experimental design the detection of hormonal or morphological changes typical of puberty in association with disease occurrence. None considered a specific definition of the age range in which puberty occurs.

Instead, two other phenomena clearly stood out. The first is that the incidence of the disease, mostly occurring in children, decreases with age; the second is that there are two switches in the sex prevalence of occurrence of the disease, the first in the second decade and the second during the fifth or sixth decade.

In other words, the overall occurrence of the disease is highest in childhood and declines with age. In the decline, the period of puberty seems to be no more affected than the previous years. A different occurrence emerges between the sexes. Boys more frequently have asthma before 10 years of age or their mid-teens. Then girls overtake boys and have more asthma up to the years of sexual maturity. During the fifth or the sixth decade, men again have a slightly greater prevalence; the difference between the sexes disappears. No scientific evidence could be found that the phenomena of puberty interfere with the described patterns (i.e. neither in the decline phenomena, nor in the sex switch phenomena). Age and sex themselves seem to be more important factors. How these factors work still remains unknown.

Age is known to be linked to a steady decline in IgE production. After reaching peak levels in the latter half of the first decade and at the beginning of the second decade of life, serum IgE levels, both in normal and in diseased subjects, decrease progressively to reach the lowest levels after 60 years of age (25,26). In parallel with the decrease, both the incidence and severity of the disease decrease (27).

Table Thirteen studies meeting selection criteria: MEDLINE database (January 1966 to 31 May 1995)

Study	Sample size	Age range (years)	Puberty interference assessment	Asthma epidemiology: main findings		
				Childhood age	Puberty age (10–16 years)	Adult age
Pearson (12)*	286	0–59	No	Highest occurrence Tendency to level out with age	No observation of specific pattern	—
Mantle & Pepys (13)*	216	1–70+	No	Highest occurrence up to 13 years	No observation of specific Pattern	Higher occurrence in girls/women from 13 to 39 years
Schachter & Higgins (14)*	9226	0–75+	No	Highest occurrence, boys more than girls Tendency to level out with age	No observation of specific pattern	—
Crawford & Beedhan (15)†	13 651	0–60+	No	Highest occurrence, boys more than girls Tendency to level out with age	No observation of specific pattern	Higher occurrence in girls by a progressive switch compared with boys at 14–20 years At 60 years: similar disease occurrence between sexes
Dogde & Burrows (16)*	13 435	0–70+	No	Highest occurrence Tendency to level out with age	No observation of specific pattern	Before 30 years: similar disease occurrence between sexes After 55 years: higher occurrence in men
Martin et al (17)*	331	7–21	No	Highest occurrence Tendency to level out with age	No observation of specific pattern	—
Pedersen & Weeke (18)*	456 160	0–80+	No	Highest occurrence from 5 to 14 years Boys more than girls up to teenage period	No observation of specific pattern	Higher occurrence in women up to 55 years with a progressive switch compared with men after 20 years. Then, again higher disease occurrence in men
Bezzaoucha (19)†	4677	0–25	No	Highest occurrence after 5 years in all age groups Boys more than girls	No observation of specific pattern	—
Skobeloff et al (20)‡	33 269	0–50+	No	Highest occurrence Boys more than girls before 10 years	No observation of specific pattern	After 20 years: women more than men, with a progressive switch with boys from 11 to 20 years
Anderson et al (21)*	7225	0–23	No	Highest occurrence Boys more than girls	No observation of specific pattern	After 16 years: women more than men
Campbell et al (22)‡	4083	0–60+	No	Highest occurrence up to mid-teens	No observation of specific pattern	After mid-teens: tendency to level out with age
Yunginger et al (23)‡	3622	0–50+	No	Highest occurrence Boys more than girls up to 14 years Tendency to level out with age	No observation of specific pattern	—
Silverstein et al (24)‡	2499	0–95+	No	Highest occurrence before 5 years Tendency to level out with age	No observation of specific pattern	—

†cross-sectional study; *prospective study; ‡retrospective study

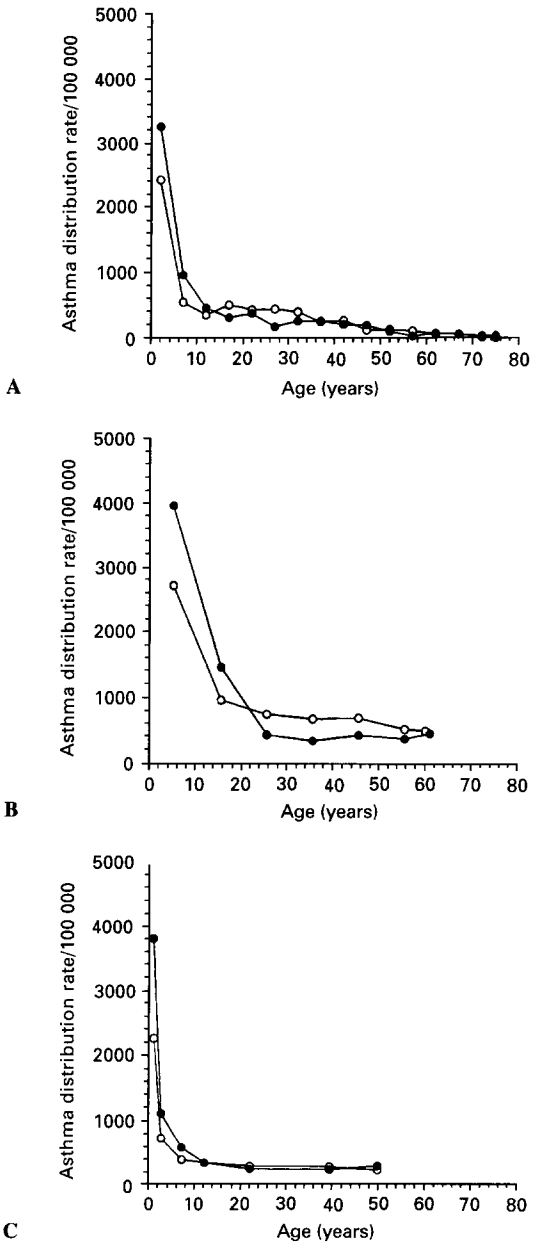

Figure Distribution of asthma occurrence from childhood to adult life in (●) boys/men and (○) girls/women (developed from references 14 (Part A) 15 (Part B) and 23 (Part C)). Note how the occurrence decreases strongly from childhood to adult life in both sexes and how age of puberty seems to be no more important in the phenomena than other ages. In contrast, among all the phenomena leading to the decrease, the most important factor appears to be the progression of age. Furthermore, note the sex switch phenomena: boys have more asthma before 10 years of age or their mid-teens. Girls overtake boys ana have more asthma up to the years of sexual maturity. Men then again become more prevalent or, at least, the difference between the sexes disappears.

It is known that IgE production by human peripheral blood mononuclear cells requires two signals. One signal is delivered by the cytokine interleukin-4 (IL-4) and the other by cognate as well as noncognate interactions between T and B cells (28,29). In elderly subjects the ability to release IL-4 has been found to be 50% less than in young subjects (30). Might a deficit of IL-4 release be responsible for the decrease of the disease with aging?

Furthermore, what causes a gender difference on the occurrence of the disease is, to date, completely unknown. A role for hormones related to sexual development has been long searched for.

Testosterone has been shown to be a powerful inhibitor of histamine and slow-reacting substance (8): because a difference in disease occurrence exists between the sexes and as boys have more asthma in childhood and also at the end of sexual maturity, it has been thought that testosterone could play some part in the occurrence of asthma, but this has never been demonstrated.

Sex hormones have important regulatory functions in both normal and pathological immune responses (31,32) and studies during the past few years have searched for a possible relationship between these hormones and the IgE levels, but without success.

In 1977, supposing that boys, gonadal dysgenetics and girls during the follicular phase represented convenient models with a base level of circulating progesterone and estradiol, whereas women during pregnancy or the luteal phase represented convenient models with increased levels of circulating hormones, Mathur et al (33) hypothesized that, if progesterone and estradiol influence plasma IgE levels, fluctuations would be expected in the various IgE model systems. However, they did not discern any such relationship, which thus suggests that sex steroid hormones have no effect on humoral IgE levels.

Furthermore, as menstrual rhythm has been documented as a cause of exacerbation of asthma in some subjects (34,35), several reports have suggested that airway responsiveness and clinical asthma severity could be associated with changes in serum progesterone, as it is known that progesterone can act on smooth muscle (6).

However, only Rubio et al (36) have reported that at least one of the levels of progesterone or estradiol was outside the normal range in 80% of women with asthma and concluded that 'bronchial asthma is associated in a high proportion with abnormalities in the production or metabolism of sex steroid hormones in women during their reproductive life'.

Pauli et al (37) found no correlation between sex hormones and airway function when assessing the influence of the menstrual cycle on airway function

in asthmatic and normal subjects. Furthermore, in spite of a significant increase in serum progesterone levels during pregnancy, Juniper et al (38) were unable to demonstrate a relationship between these levels and airway responsiveness.

Conclusions

Our study was unable to find any evidence of a possible interference of pubertal changes with the occurrence of asthma. However, two factors clearly emerged: the decrease of the disease with age in both sexes and the switch between the sexes regarding its occurrence during the first and second decades of life and during the fifth or sixth decades. No explanation for these phenomena has been given. The often hypothesized role of sexual hormones still remains to be demonstrated.

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