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Sex differences in asthma and immunological response: an overview

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Summary. Gender differences in asthma incidence, prevalence and clinical phenotypes have been extensively reported worldwide. A number of studies have shown that respiratory allergy, and especially asthma, is prevalent in males during childhood, whereas it becomes more frequent and severe in females between adolescence and adulthood, suggesting that sex hormones play a role as important modulators of immune response. The mechanisms underlying these differences between females and males are most likely the effects on the immune and inflammatory responses of female hormones and the result of the activity of various cells and cytokines. Understanding gender differences in respiratory allergies and asthma is important for providing effective education and personalized management plans for patients throughout their lives.

Key words. Gender differences, bronchial asthma, immune response, pregnancy, menopause.

Differenze sessuali nell'asma e nella risposta immunologica: una panoramica

Riassunto. Le differenze di genere nell'incidenza di asma, nella prevalenza e nei fenotipi clinici sono state ampiamente riportate in tutto il mondo. Numerosi studi hanno dimostrato che l'allergia respiratoria, e in particolare l'asma, è prevalente nei maschi durante l'infanzia, mentre diventa più frequente e grave nelle donne dall'adolescenza all'età adulta, suggerendo un ruolo per gli ormoni sessuali come importanti modulatori delle risposte immunitarie. I meccanismi alla base di queste differenze tra femmine e maschi sono probabilmente gli effetti sulle risposte immunitarie e infiammatorie degli ormoni femminili e il risultato dell'attività di varie cellule e citochine. Comprendere le differenze di genere nelle allergie respiratorie e nell'asma è importante per fornire un'educazione efficace e piani di gestione personalizzati per i pazienti nel corso della vita.

Parole chiave. Differenze di genere, asma bronchiale, risposta immunitaria, gestazione, menopausa.

Introduction

Nearly 40 million people in the Unites States are diagnosed with asthma[1]. This chronic inflammatory airway disease results in a cost to society of ~$50 billion per year, in addition to the significant loss of productivity of individuals who suffer from asthma[1,2].

In recent decades, international literature on sex differences in human diseases has grown steadily, but immunology ranked the lowest of 10 biological disciplines for reporting on the sex of animals or human subjects in published papers[3]. In a recent review, Klein and Flanagan emphasized that sex is a biological variable that should be considered in immunological studies[4]. There is, on the other hand, abundant literature on the role of sex factors in respiratory allergy, including allergic rhinitis (AR) and especially asthma, which is the most studied disease and was found to be different in females in terms of both prevalence and clinical severity[5].

Epidemiological data show that overall asthma prevalence, severity, exacerbation rate, hospitalizations and mortality are higher amongst women than men; however, asthma-related office and emergency room visits and hospitalizations are higher among boys than girls in the 0 to 14 years age range[6,7].

The reasons for this gender difference are unknown, but have been linked to immunological and hormonal factors, and/or to differences in gender-specific responses to environmental or occupational exposure[8].

The purpose of this concise review is to better identify and understand gender differences in asthma and respiratory allergy conditions, in order to provide more appropriate and personalized management plans for these patients. Figure 1 summarizes the potential factors contributing to the gender difference in respiratory allergies and asthma.

Sex differences in immune response

Males and females differ in the strength of immune response and these effects have been verified in humans and other animals. Sex hormones act as important modulators of immune response; the male sex hormone testosterone is generally immunosuppressive, whereas the female sex hormone estrogen tends to be immunoenhancing. Different sets of T-helper cells (Th) play important roles in adaptive immunity, e.g. Th1 cells trigger type 1 responses that are primarily cell-mediated, and Th2

cells trigger type 2 responses that are primarily humoral responses[9]. Reviewing the literature, it is apparent that in females estrogen (at periovulatory to pregnancy levels) and progesterone enhance type 2 and suppress type 1 responses, whereas in males testosterone suppresses type 2 responses and shows an inconsistent pattern for type 1 responses. Thus, the sex differences in immune response should be particularly strong in immune functions associated with type 2 responses, and less pronounced with type 1 responses. In general, the hormone-mediated sex differences in immune response may lead to genetic sexual conflicts on immunity. Finally, behavioral and ecological contexts can play a role in sex hormone-induced effects on immune response, considering the social mating system, sexual selection, geographical distribution of hosts, and parasite abundance[9].

In experimental animal models of asthma, female mice have increased airway hyper-responsiveness, eosinophilic influx, and increased production of type 2 cytokines (i.e. interleukin [IL]-4, IL-5, and IL-13) in the lungs after allergen challenge compared to males. Although $CD4^+$ TH2 cells are known to produce type 2 cytokines, type 2 innate lymphoid cells (ILC2s) have been described as producing far larger quantities of IL-5 and IL-13 than TH2 cells[10].

Moreover, estrogens contribute to the sex differences in immunity by regulating dendritic cell (DC) subsets, which express estrogen receptors and act as ligand-dependent transcription factors[11]. Laffont et al. showed, in an experimental study, that group 2 innate lymphoid cells (ILC2s), which are key regulators of type 2 inflammatory responses, are negatively influenced by male sex hormones. Indeed, male mice had fewer ILC2 progenitors and mature ILC2s in peripheral tissues than female mice. This resulted in reduced susceptibility to allergic airway inflammation in response to environmental allergens in males and less severe interleukin (IL)-33-driven lung inflammation[12]. Interestingly, orchiectomy, but not ovariectomy, abolished the sex differences in ILC2 development and reinstated IL-33-mediated lung inflammation[12].

Estrogen's influences on immune cells favor the allergic response, promoting Th2 polarization, encouraging class switching of B cells to IgE production and prompting mast cell and basophil degranulation[13].

Sex differences in genetics

As regards genetics, other studies used experimental models to analyze the potential mechanisms involved in the sexual dimorphism of asthma. The gender difference in the expression profiles of histamine receptors (HR) was explored, making it possible to observe that H2R and H3R expression was higher in female rats than in males and was down-regulated in ovariectomized females, whereas H1R expression was equal across both sexes[14].

Genetic polymorphisms are also influenced by gender. Immunoglobulin E (IgE) levels and asthma have been associated with single nucleotide polymorphisms (SNPs) in thymic stromal lymphopoietin (TSLP), a cytokine that is known to play an important role in the maturation of T cells through the activation of antigen-presenting cells. In humans, there are increased

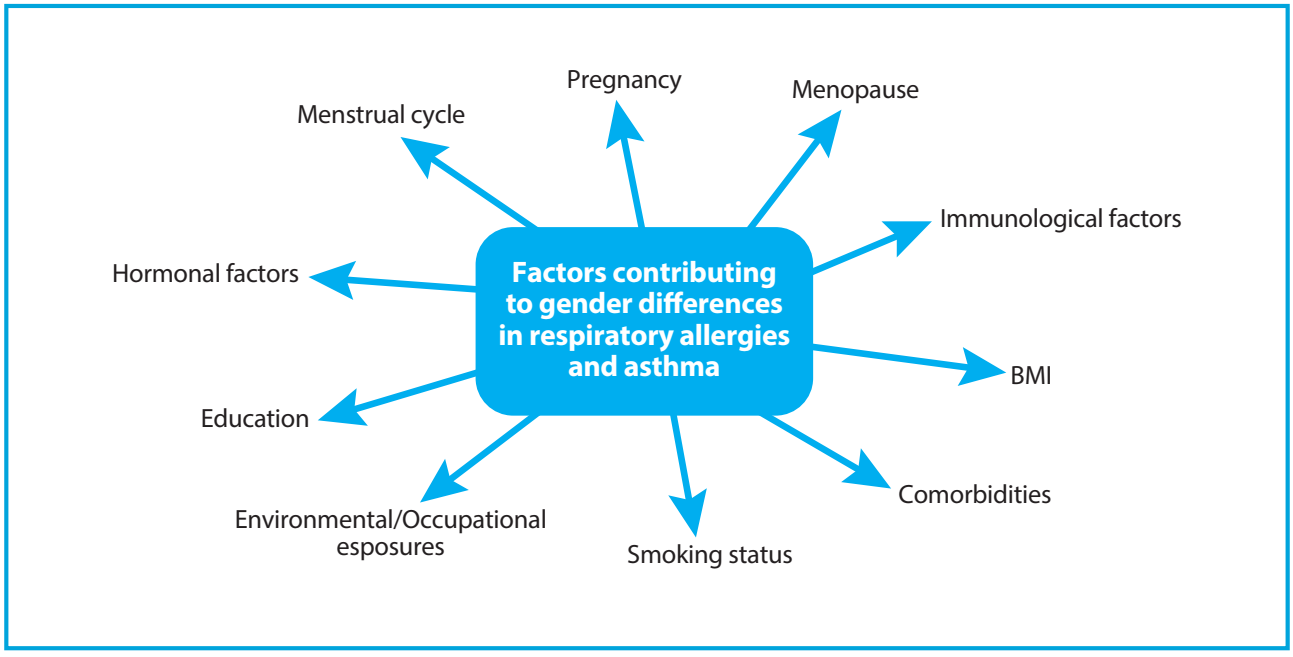

Figure 1. The potential factors contributing to gender difference in respiratory allergies and asthma.

numbers of TSLP mRNA+ bronchial epithelial cells in asthmatics vs. controls, and this correlates with the degree of airflow obstruction. Two SNPs in TSLP (rs1837253 and rs2289276) are of particular interest. The first is associated with a lower risk of asthma in men, but the second is associated with a higher risk of asthma in women. Whether this differential effect is regulated by gender or by sex-related differences in the hormonal profile is unknown[15].

Periostin is another protein under investigation for its relationship with the immune system. It is expressed in the periosteum of long bones but also in many other tissues and organs, including the heart, kidney, skin and lungs, and is enhanced by mechanical stress or injury. Periostin has a relevant physiological function in promoting injury repair in a large number of tissues. However, its over-expression was observed in different diseases characterized by inflammation, fibrosis and tumor genesis.

A specific focus regards the correlation between the level of periostin and lung diseases and the identification of periostin as an inflammatory key effector in asthma, where it is closely associated with airway eosinophilia. Indeed, periostin seems to be a useful biomarker of the "Th2-high" asthma rather than the "Th2-low" asthma phenotype and a predictor of response to therapeutic agents[16]. In a certain subtype of asthma defined by Th2 cytokine-induced expression of genes in bronchial epithelium, including periostin, which is detected in approximately half of all asthmatic patients and correlates with eosinophilic airway inflammation, serum periostin levels were significantly increased in asthmatic patients with eosinophilic airway inflammation and were found to be the single best predictors of airway eosinophilia[17]. As periostin also plays a role in normal gestation and pregnancy, a recent study investigated plasma periostin levels in non-pregnant and pregnant asthmatic patients compared to healthy pregnant and non-pregnant women, also evaluating the relationship between periostin levels and asthma control. Plasma periostin levels were similar in asthmatic non-pregnant patients and healthy non-pregnant controls, whereas they were significantly higher in the two pregnant groups (asthmatic and healthy) than in the control groups, and in asthmatic pregnant women periostin correlated negatively with FEV_1[18].

Epidemiology and clinical features

Asthma in early childhood is generally associated with male gender, poor socioeconomic status, and exposure to soot, exhaust and/or household tobacco, wood or oil smoke [19,20]. However, asthma in early childhood was only seen to be associated with obesity in young girls, not in young boys, in two large cross-sectional series from China and the Netherlands[21, 22], and in two longitudinal cohorts from the United Kingdom and Taiwan. In adolescence, asthma becomes more severe and prevalent in girls[23].

This gender-switch after puberty has been related to the increase in sex hormones[24-26]. The transition from childhood to adulthood is characterized by a higher odds ratio of persistence of wheezing in females[27,28], and by asthma improvement in males but worsening in females[29]. In two cohorts of patients followed longitudinally until the age of 18 years, male gender was independently associated with asthma remission[30-32]. After the age of 11 years, the provocative concentration of methacholine necessary to cause a 20% decrement in FEV_1 (PC20) increased in adolescent boys, suggesting an improvement in airway responsiveness during puberty in boys, but not in girls[33].

By contrast, in adult women with stable well-controlled asthma, PC20 decreases by more than half over the course of the menstrual cycle, with the lowest PC20 occurring at peak estrogen and progesterone levels in the luteal phase[34]. The cyclic changes in PC20 have been attributed to abnormal β2 adrenoceptor regulation in premenstrual asthma[34].

It has been suggested that β2 adrenoceptors are influenced by ovarian sex-steroid hormones, and that this is the mechanism underlying the gender differences in β2 bronchodilator responses[35]. This concept is supported by the paradoxical down-regulation of β2 adrenoceptors when progesterone is given during the follicular phase to women with premenstrual asthma[35,36]. On the other hand, estrogen supplementation during the follicular phase had no effect on β2 adrenoceptor responses or airway reactivity[37]. Interestingly, whereas a higher progesterone to estrogen ratio occurs during the luteal phase of fertile cycles[38,39], the opposite occurs during the menopausal transition, where women are exposed to unopposed estrogen stimulation[40]. Thus, it remains unclear as to whether progesterone and/or estrogen or a balance between the sex hormones is responsible for the premenstrual worsening of asthma.

Sex hormones have a wide variety of effects beyond the β2 adrenoceptor: for example, they alter epithelial cell function. The progesterone receptor is expressed in airway epithelium and progesterone inhibits the beat frequency of cilia, which may impact mucociliary clearance during the menstrual cycle among women[41].

Many reports have linked female sex hormones to asthma severity. Women with premenstrual asthma are at a higher risk of severe asthma, required more bursts of corticosteroid therapy, and have a higher risk of emergency room visits, hospitalization, and admission to the intensive care unit[42]. Interestingly, asthmatic women receiving oral contraceptives have attenuated cyclical

changes in airway reactivity associated with a suppression of the upsurge in progesterone and estradiol during the luteal phase[43]. In multiparous women, asthma prevalence increases linearly with the number of births[44].

The role of pregnancy

During pregnancy asthma may worsen, improve or remain unchanged, with no significant difference in frequency of these three outcomes. In a survey on 366 pregnancies, asthma was unchanged in 33% of women, worsened in 35%, and improved in 28%. Based on diary sheets, asthma was significantly less frequent and less severe during the last 4 weeks of pregnancy. In the 3 months post-partum, asthma returned to its pre-pregnancy course in 73% of women[45]. In 2003, in a US study according to the National Asthma Education Program Working Group on Asthma and Pregnancy, which defined asthma severity as mild, moderate, or severe as assessed by symptoms and spirometry, the initial asthma classification was found to be significantly related to subsequent asthma morbidity during pregnancy, including hospitalizations, unscheduled visits, corticosteroid requirements, and asthmatic symptoms during labor and delivery. Exacerbations during pregnancy concerned 12.6% of patients initially classified as mild, 25.7% of patients classified as moderate, and 51.9% of patients classified as severe ($p < 0.001$), with 30% of initially mild patients reclassified as moderate-severe during pregnancy, and 23% of the initially moderate-severe patients reclassified as mild later in pregnancy[46]. A review by Gluck et al. concluded that the course of asthma during pregnancy is variable, with about one third of women improving, one third experiencing increased symptoms, and one third remaining unchanged. A number of physiologic changes during pregnancy as well as the severity of the pre-existing asthma may influence the course of asthma. Factors associated with an increased risk of uncontrolled asthma during pregnancy included smoking, inhaled corticosteroid use at the beginning of pregnancy, and higher maternal age[47].

One new interesting factor linked to the risk of asthma severity in pregnant women is the sex of the fetus.

Whereas many reports have reported that carrying a female fetus during pregnancy is associated with increased asthma symptoms, greater use of asthma medications and a higher risk of asthma-related hospitalization[48,49], a larger Canadian study did not confirm this finding[50]. Recent reports have demonstrated sex-specific alterations in the expression of placental genes of pregnant women with asthma compared to the placenta of non-asthmatic mothers. Six genes were seen to have altered expression in the placenta of asthmatic women carrying male fetuses, compared to 59 genes with altered expression in the placenta of asthmatic mothers carrying female fetuses. The genes were linked to growth, inflammation and immune pathways and might contribute to the fetal-sex dimorphic differences in asthma severity and fetal growth during pregnancy[51].

The role of menopause

Another period at risk for asthma is the menopause and menopausal status has been associated with accelerated lung function decline[52]. Although the underlying mechanisms are not yet understood, it is possible that a role is played by airway remodeling, which is driven by immunologic and inflammatory mechanisms.

The influence of sex difference on airway remodeling was investigated in an animal model. Following induced sensitization to ovalbumin, male or female BALB/c mice were challenged with aerosolized ovalbumin on 3 days/week for 5 weeks, and BHR, airway inflammation, and airway remodeling were measured. In ovalbumin-sensitized and challenged female mice, there was a higher increase of total and ovalbumin-specific IgE eosinophils, lymphocytes, T-helper type 2 cytokines, and growth factors in bronchoalveolar lavage than in male mice. The histological features of airway remodeling were also increased in female mice[53].

Key messages

- Gender differences in asthma and respiratory allergy condition incidence, prevalence and clinical phenotypes are extensively reported in medical literature.
- Asthma is prevalent in males during childhood, but becomes more frequent and severe in females between adolescence and adulthood, suggesting that a role is played by sex hormones as important modulators of immune response.
- Like asthma, allergic rhinitis has a male predominance in prevalence during childhood that switches to a female predominance in adolescence and adulthood.
- Males and females differ in the strength of immune responses. Sex hormones act as important modulators of immune response; the male sex hormone testosterone is generally immunosuppressive, whereas the female sex hormone estrogen tends to be immunoenhancing.
- Sex differences in immune response are particularly strong in immune functions associated with type 2 responses, and less pronounced with type 1 responses.

Conclusions

There is solid evidence in favor of gender effects on asthma incidence and severity throughout the course of life. Whereas the clinical and epidemiological data support the role of sex hormones on asthma incidence and severity, the data are confounded by many internal and external factors, such as aging, obesity, atopy, and gender differences in behavior and exposure[54]. Further work is needed to establish the gender impact on asthma *in utero*, in early life, puberty, adulthood and the menopause transition and to provide new insights for pathway-based therapies.

As regards allergic rhinitis, the studies available thus far indicate, as for asthma, a male predominance in prevalence during childhood that switches to a female predominance in adolescence and adulthood, but further research is needed.

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