Asthma in children and adults: A shared biological and molecular basis

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The objective of this paper is to describe the important clinical, physiological, immunological and biological similarities among asthmatic infants, children and adults. A comparison of the reported clinical presentation, physiological changes, histology and cellular biology of asthma in different age groups is presented with special emphasis on the abnormal immune response, cellular activation and lymphokine production. Different age groups of asthmatics have important similarities in clinical presentation, lung physiology and histopathology. Eosinophilia and increased immunoglobulin (Ig) E levels are present at every age except in young infants. Signs of cellular activation and increased production of lymphokines of the type 2 helper T lymphocyte, which can increase IgE levels and affect eosinophils, are also found in every age group. These abnormalities have been shown in animal models to cause airway inflammation and physiological changes comparable with those encountered in asthma. In conclusion, future studies should try to identify the specific characteristics of the population at risk for asthma, emphasizing not only primary prevention but also the use of inhibitors or modulators of the inflammatory reaction that is present in the airways of asthmatics.

Key Words: *Asthma, Cytokines, Children, Lymphocyte subsets*

L'asthme chez les enfants et les adultes : Une base moléculaire et biologique partagée

RÉSUMÉ : Cet article a pour objectif de décrire les importantes similitudes biologiques, immunologiques, physiologiques et cliniques que l'on observe parmi les bambins, les enfants et les adultes asthmatiques. On présente une comparaison de la biologie cellulaire, de l'histologie, des changements physiologiques et des symptômes cliniques de l'asthme qui ont été rapportés dans différents groupes. On insiste particulièrement sur l'anormalité de la réponse immunitaire, de la production de lymphokines et de l'activation cellulaire. Des asthmatiques appartenant à des classes d'âge différentes présentent des similitudes importantes dans les symptômes cliniques, la physiologie pulmonaire et l'histopathologie. L'éosinophilie et l'augmentation des taux d'immunoglobulines (Ig)E sont observées à tout âge sauf chez les nourrissons. On observe également dans chaque classe d'âge des signes d'activation cellulaire et d'une production accrue de lymphokines de la classe des lymphocytes T auxiliaires de type 2, qui peuvent accroître les taux d'IgE et avoir une incidence sur les éosinophiles. L'expérimentation animale a démontré que ces anomalies étaient responsables de l'inflammation des voies aériennes et des changements physiologiques, et qu'elles étaient comparables à celles observées dans l'asthme. En conclusion, les chercheurs devront essayer d'identifier les caractéristiques spécifiques de la population à risque pour l'asthme et mettre l'accent non seulement sur le rôle de la prévention primaire mais également sur l'utilisation d'inhibiteurs ou de modulateurs de la réaction inflammatoire présente dans les voies aériennes des asthmatiques.

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ASTHMA IS A DISEASE OF THE LUNG'S AIRWAYS THAT HAS a complex pathogenesis. Unsuccessful attempts at defining asthma may be related to a certain degree of heterogeneity in the triggers of this disease and the increasingly sought for, yet fleeting, 'cause' of asthma. Nevertheless, asthma can be characterized by two important physiological observations: reversible airway obstruction and increased airway responsiveness to specific and nonspecific stimuli (1). The reversibility of airway obstruction in asthma can be ascertained by recognizing an important temporal variation in the symptoms of shortness of breath, cough and wheezing. A clinical impression can then be confirmed by showing a variability in sequential measurements of peak expiratory flow rates or spirometric improvement in airway obstruction after a bronchodilator. The increase in symptoms when patients are exposed to triggers such as cold air, exercise, irritants, allergens and viral infections are signs of airway hyperresponsiveness that can be confirmed in the laboratory by measuring increased airway responsiveness to histamine and methacholine or even by the assessment of an increased airway obstructive response to an antigen (2).

An increase in the number of hospitalizations due to asthma mostly in the age group of zero to four years and the increased mortality in young asthmatic patients during the 1980s (3,4) has led to a broader interest into the pathophysiology of asthma.

ASTHMA AND INFLAMMATION

A detailed analysis of the clinical, biological and histological characteristics of asthma has led to the conclusion that asthma is an inflammatory disease of the airways and that the inflammation that is present in the airways of asthmatics could lead to chronic and possibly irreversible changes affecting the physiological responses to different stimuli (5-7).

Histopathology shows typical changes. The submucosa is infiltrated with eosinophils, lymphocytes, mast cells and macrophages and the blood vessels are dilated (5-7). The epithelium is particularly damaged, vacuolated, infiltrated by inflammatory cells and cilia are often absent. In places the epithelium is sloughed off leaving a bare basement membrane thickened by collagen deposition. There is also an increase in mucosal goblet cells, bronchial mucus glands and hypertrophy or hyperplasia of smooth muscle cells.

The finding of inflammation in the airways of asthmatics even at a clinically early stage of the disease has led to the hypothesis that the underlying inflammation is a major contributor to the physiological changes in asthma (7). This hypothesis has been strengthened by the finding that inflammatory cells will release specific mediators during the asthmatic response that have the capacity to cause some of the histological and physiological changes that are found in asthma (8,9). In addition, Hogg and colleagues (5,10) have elegantly demonstrated that moderate amounts of airway wall thickening, as seen with inflammation, could profoundly affect the airway narrowing caused by smooth muscle shortening. However, it still remains to be demonstrated

Figure 1 Presentation of antigen to a T lymphocyte (T_H): an antigen presenting cell (APC) absorbs and processes the antigen and presents a peptide to a T lymphocyte in association with its major histocompatibility complex (MHC). The lymphocyte recognizes a specific antigen through its receptor (TCR) in association with MHC and CD4 or 8, depending on whether the T lymphocyte is a helper or cytotoxic/suppressor cell, respectively. Certain helper lymphocytes communicate with APCs by releasing the lymphokines interleukin (IL)-2 or -4. Some APC communicate with T lymphocytes by releasing the cytokine IL-1.

which cell(s) or which mediator(s) are important players in the chronic changes found in the airways of asthmatics.

ASTHMA IN CHILDREN COMPARED WITH ADULTS

Because of the characteristics of the disease, there are important similarities between the different features of asthma in every age group (11). Symptoms such as shortness of breath, cough, phlegm, wheezing, and the physical signs of tachypnea, tachycardia, wheezing and increased expiratory time are present in infants, children and adults. Laboratory tests show reversible bronchial obstruction and increased airway responsiveness to histamine or methacholine in every age group. Eosinophilia is found in the blood of asthmatic and atopic children and adults but usually not in the blood of infants (12).

The prevalence of asthma depends on the age and the sex of the group that is studied but usually varies between 5 and 10% (3). Asthma usually begins in childhood and up to 85% of individuals experience their first symptoms of asthma before the age of 40 years (13,14). Although a substantial number of children have a remission of asthma at puberty, approximately 50% of children with asthma will still have symptoms in adult life (14). The development of asthma for the first time is rare in the elderly; however the prevalence of asthma in people over 70 is similar to that found in other age groups (13).

LYMPHOKINES AFFECTING THE ACTIVATION AND PROLIFERATION OF INFLAMMATORY CELLS

Figure 2) Communication between T lymphocytes and other inflammatory cells: T lymphocytes release mediators or 'lymphokines', which can activate and/or induce the proliferation of other inflammatory cells. GM-CSF Granulocyte and macrophage colony stimulating factor; HRF Histamine releasing factor; IL, Interleukin

There is a difference in the factors that provoke asthma in different age groups. Infants and young children are more susceptible to viral infections (11,12). Children, adolescents and young adults are more susceptible to allergens (4,11) and older adults can be affected by all the different provoking factors, although the prevalence of allergic factors in asthma decreases with age (13).

The histopathology of the airways of patients who die from asthma is the same irrespective of age. Consistent changes are epithelial cell desquamation, thickening of the basement membrane, an inflammatory cell infiltration and hypertrophy or hyperplasia of smooth muscle (1,6). An association between asthma and atopy exists mostly in children and young adults and a direct correlation has been reported between serum immunoglobulin (Ig) E levels and the presence of asthma in children and adults (13,15,16).

The differences in serum IgE levels are also accompanied by cellular activation, as shown by an increased expression of the interleukin (IL)-2 receptor, human leukocyte antigen (HLA) DR, and virus-like antigen-I on the surface of cells obtained from blood or lung lavage of asthmatic patients (17-19). It is not known whether cellular activation is present

TABLE 1
Lymphokines produced by helper T lymphocyte clones in mice

	TH1	TH2
Interferon gamma	+	—
Interleukin-2	+	—
Lymphotoxin	+	—
GM-CSF	+	+
Tumour necrosis factor	+	+
Interleukin-3	+	+
Interleukin-4	—	+
Interleukin-5	—	+
Interleukin-6	—	+
Interleukin-10	—	+
Interleukin-13	—	+

GM-CSF Granulocyte and macrophage colony stimulating factor

in asthmatic infants. In a recent study we found an increased expression of the IL-2 receptor and CD23 (low affinity IgE receptor) on the mononuclear cells obtained from the blood of infants admitted to the hospital for acute bronchiolitis, a disease characterized by shortness of breath, hyperinflation with or without wheezing and fever that is followed by persistent wheezing in up to 50% of the affected infants (12). The level of expression of these two receptors, although increased, seems to be less than that found on blood mononuclear cells obtained from older asthmatics during an exacerbation (20,21).

The important association among serum IgE levels, cellular activation and asthma suggests that the mechanisms involved in cellular activation and IgE production may modulate the increased airway responsiveness found in asthma. A better understanding of the abnormalities of the immune response described in this disease could thus lead to a better treatment of asthma.

EFFECT OF ANTIGENIC STIMULATION ON THE IMMUNE RESPONSE

When an antigen comes into contact with the immune system it is generally absorbed or phagocytosed by an antigen-presenting cell, which could be a macrophage, a B lymphocyte or a dendritic cell. The antigen-presenting cell modifies the antigen and presents a peptide obtained from it to a T lymphocyte that has differentiated to recognize specifically the peptide sequence (epitope) that is presented (Figure 1).

Antigen presentation involves the major histocompatibility complex (HLA) and adhesion molecules, and is generally followed by cellular activation, expression of adhesion molecules that are specific for activation and the progressive release of different messengers called cytokines. These changes occur whether the antigen is an allergen or a virus and will usually be followed by cellular proliferation. The lymphokines (cytokines produced by lymphocytes) that are released could lead to activation or proliferation of lymphocytes, mast cells, eosinophils, macrophages and neutrophils (Figure 2).

Several types of helper lymphocytes can be described on the basis of the mRNA for the lymphokines produced. In mice, two major types of cellular clones have been described (22). The TH1 type of helper T lymphocyte plays a role in delayed type hypersensitivity reactions, and the TH2 type of helper T lymphocyte affects immediate hypersensitivity reactions (Table 1). This separation is important in understanding atopy and asthma for the following reasons: IL-5 is one of the most important factors involved in activation and proliferation of eosinophils (23); and IL-4 is an important modulator of increased IgE production, whereas interferon gamma blocks the production of IgE and favours the production of specific IgG (24,25).

It has recently been shown in adult asthmatics that helper T lymphocytes in the blood and lungs express and produce more of the TH2 profile of lymphokines or, at least under certain circumstances, do not express more interferon gamma than control patients (26-28). These observations have also been found in the blood of children with asthma (personal communication). In studies performed at Hôpital Ste-Justine in Montreal we have found a significant correlation between the serum level of IL-4 and the number of days of wheezing in infants, between one and four months after a first bronchiolitis (29). Since IL-4 positively affects IgE production, this observation could explain the relationship between the appearance of IgE in the lungs of infants after bronchiolitis and the development of asthma after bronchiolitis (30).

ROLE OF CELLULAR ACTIVATION AND CYTOKINES IN AIRWAY HYPERRESPONSIVENESS

Our studies have recently focused on the lymphocyte and its lymphokines. We have studied the effects of IL-2 (T cell growth factor), a lymphokine produced by T lymphocytes after antigen is presented. Systemic administration of IL-2 to rats can increase the cholinergic responsiveness of the airways and airway responsiveness to ovalbumin in rats that have been previously sensitized (31-33). Administration of

IL-2 also increases cellular inflammation around the bronchovascular tree in rats.

When lymphocytes are obtained from the blood of asthmatic subjects and stimulated with IL-2, their supernatant causes increased survival of eosinophils and increased proliferation of eosinophil progenitors compared with supernatant obtained from control lymphocytes stimulated with IL-2 (21). Since IL-2 causes eosinophilia in humans by increasing the production of IL-5 (34), and since IL-5 is released in the lungs of asthmatics after antigen challenge (23), it thus seems that cellular immunity and lymphokine production can play a role in airway inflammation and hyperresponsiveness in asthmatics.

CONCLUSION

Exposure of the immune system to a provoking factor such as a virus, an allergen or even a 'self' antigen will cause inflammation of the airways in the individual with a genetic predisposition. Inflammation will persist in every age group either by continued exposure to triggers or by absence of suppression of the immune reaction and can cause the histological and physiological changes found in asthma.

The treatment of asthma should focus on prevention of exposure to triggering factors, inhibition of activation of inflammatory cells or of the release of specific mediators. In the future, certain therapies will focus on modulation of inflammation by cytokines or by their specific inhibitors. Since important similarities exist among the clinical, physiological and cellular changes found in every age group with asthma, prevention should be implemented at the youngest age possible (35,36). However, we have not been able to identify the specific characteristics of the population at risk for asthma (37,38). Until research on this topic has enlightened us further, avoidance of exposure to allergens, especially in infants with neonatal respiratory complications or a family history of atopy, should be implemented. The substances that should be avoided are allergens such as the house dust mite, cockroaches and cigarette smoke.

REFERENCES

- Barnes PJ. A new approach to the treatment of asthma. *N Engl J Med* 1989;321:1517-27.
- O'Byrne PM, Dolovich J, Hargreave FE. Late asthmatic responses. *Am Rev Respir Dis* 1987;136:740-51.
- Weiss KB, Wagener DK. Changing patterns of asthma mortality. Identifying target populations at high risk. *JAMA* 1990;264:1683-7.
- Gergen PJ, Weiss KB. Changing patterns of asthma hospitalization among children: 1979 to 1987. *JAMA* 1990;264:1688-92.
- James AL, Paré PD, Hogg JC. The mechanics of airway narrowing in asthma. *Am Rev Respir Dis* 1989;139:242-6.
- Dunnill MS. The pathology of asthma, with special reference to changes in the bronchial mucosa. *J Clin Pathol* 1960;13:27-33.
- Laitinen LA, Laitinen A, Haahela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. *Am Rev Respir Dis* 1993;147:697-704.
- Gerblich AA, Salik H, Schuyler MR. Dynamic T-cell changes in peripheral blood and bronchoalveolar lavage after antigen bronchoprovocation in asthmatics. *Am Rev Respir Dis* 1991;143:533-7.
- Cookson WOCM, Craddock CF, Benson MK, Durham SR. Falls in peripheral eosinophil counts parallel the late asthmatic response. *Am Rev Respir Dis* 1989;139:456-62.
- Wiggs BR, Bosken C, Paré PD, James A, Jogg JC. A model of airway narrowing in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992;145:1251-8.
- Larsen GL. Asthma in children. *N Engl J Med* 1992;326:1540-5.
- Wohl MEB, Chernick V. State of the art. Bronchiolitis. *Am Rev Respir Dis* 1978;118:759-81.
- Braman SS, Kaemmerlen JT, Davis SM. Asthma in the elderly. A comparison between patients with recently acquired and long-standing disease. *Am Rev Respir Dis* 1991;143:336-40.
- Gerritsen J, Koeter GH, Postma DS, Schouten JP, Knol K. Prognosis of asthma from childhood to adulthood. *Am Rev Respir Dis* 1989;140:1325-30.
- Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991;325:1067-71.

16. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 1989;320:271-7.
17. Corrigan CJ, Haczku A, Gemou-Engesaeth V, et al. CD4 T-Lymphocyte activation in asthma is accompanied by increased serum concentrations of interleukin-5. Effect of glucocorticoid therapy. *Am Rev Respir Dis* 1993;147:540-7.
18. Ferguson AC, Wong FWM. Bronchial hyperresponsiveness in asthmatic children. Correlation with macrophages and eosinophils in bronchoalveolar fluid. *Chest* 1989;96:988-91.
19. Walker C, Bode E, Boer L, Hansel TT, Blaser K, Virchow JC Jr. Allergic and nonallergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. *Am Rev Respir Dis* 1992;146:109-15.
20. Yang JP, Spier S, Turgeon J, Drblik SP, Pedneault L, Renzi PM. Lymphocyte profile and cytokine production in the blood of infants with acute bronchiolitis. *Am Rev Respir Dis* 1993;147:A132. (Abst)
21. Yang JP, Renzi PM. Interleukin-2 and lymphocyte-induced eosinophil proliferation and survival in asthmatic patients. *J Allergy Clin Immunol* 1993;91:792-801.
22. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clones. 1. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 1986;136:2348-57.
23. Ohnishi T, Kita H, Weiler D, et al. IL-5 is the predominant eosinophil-active cytokine in the antigen-induced pulmonary late-phase reaction. *Am Rev Respir Dis* 1993;147:901-7.
24. de Vries JE, Gauchat JF, Aversa GG, Punnonen J, Gascan H, Yssel H. Regulation of IgE synthesis by cytokines. *Curr Opin Immunol* 1991;3:851-8.
25. Finkelman FD, Katona IM, Urban JF Jr, et al. IL-4 is required to generate and sustain in vivo IgE responses. *J Immunol* 1988;141:2335-41.
26. Robinson DS, Hamid Q, Ying S, et al. Predominant TH2-Like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992;326:298-304.
27. Krishnaswamy G, Liu MC, Su SN, et al. Analysis of cytokine transcripts in the bronchoalveolar cells of patients with asthma. *Am J Respir Cell Mol Biol* 1993;9:279-86.
28. Corrigan CJ, Kay AB. CD4 T-lymphocyte activation in acute severe asthma. *Am Rev Respir Dis* 1990;141:970-7.
29. Spier S, Yang JP, Drblik SP, Turgeon S, Marcotte JE, Renzi PM. Infantile wheezing (W): correlates with T-Lymphocyte helper 2 (TH2) cell activity but not bronchial reactivity (Br). *Am Rev Respir Dis* 1993;147:A132. (Abst)
30. Welliver RC, Kaul TN, Ogra PL. The appearance of cell-bound IgE in respiratory-tract epithelium after respiratory-syncytial-virus infection. *N Engl J Med* 1980;303:1198-202.
31. Renzi PM, Du T, Sapienza S, Wang NS, Martin JG. Acute effects of interleukin-2 on lung mechanics and airway responsiveness in rats. *Am Rev Respir Dis* 1991;143:380-5.
32. Renzi PM, Sapienza S, Wasserman S, Du T, Olivenstein R, Wang NS, Martin JG. Effect of interleukin-2 on the airway response to antigen in the Rat. *Am Rev Respir Dis* 1992;146:163-9.
33. Renzi PM, Spienza S, Du T, Wang NS, Martin JG. Lymphokine-induced airway hyperresponsiveness in the rat. *Am Rev Respir Dis* 1991;143:375-9.
34. Enokihara H, Furusawa S, Nakakubo H, et al. T cells from eosinophilic patients produce interleukin-5 with interleukin-2 stimulation. *Blood* 1989;73:1809-13.
35. Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992;339:1493-7.
36. Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen (Der pI) and the development of asthma in childhood. *N Engl J Med* 1990;323:502-7.
37. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM, and the Group Health Medical Associates Personnel. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988;319:1112-7.
38. Young S, Le Souef PN, Geelhoed GC, Stick SM, Turner KJ, Landau LI. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991;324:1168-73.