Natural History of Pediatric Asthma and Its Prevention : A Review Article

Md. Rashidul Hassan[1], Md. Ali Hossain[1], Asif Mujtaba Mahmud[2], M. Ruhul Amin[3]
Mostafizur Rahman[4], Md. Jaodad Hasan[5]

Introduction :

Asthma is better characterized as a syndrome rather than a disease, because a single causative mechanism has not yet been defined[1]. It is a chronic inflammatory disorder of the airways characterized by dyspnoea, wheezing, coughing and chest tightness. These cardinal symptoms of asthma are caused by recurrent airway obstruction. Another very important characteristic of asthma is increased airway responsiveness to various stimuli[2]. This is why smaller concentrations of inhaled bronchocnstrictor agonist are needed to trigger narrowing of the airway in asthma patient in comparison to normal subjects. Airway hyperresponsiveness, fluctuating airflow obstruction and the cardinal symptoms of asthma are the consequences of cellular inflammation[3].

Over the last ten years, research has been primarily focused on factors that influence the development of asthma. Effective preventive measures for asthma may be developed provided we can understand the natural history of asthma. This prompted us to review the latest concept regarding natural history of asthma and its possible prevention.

Natural History

Asthma is not a new disease and presumably most, if not all, of the current causes of asthma have been known for hundreds of years. However, there has been a dramatic increase in asthma and it has become very important to elucidate the causes of the increase. Evidence about the causes of asthma has come from several cross sectional studies, from population studies and provocation experiments[4]. On the other hand, investigation of the natural history is largely dependent on prospective studies. In 1954 Rackeman reported a 20-year follow-up on a large series of children with allergic disease[5]. He identified the sequential nature of sensitization to foods; then house dust and pollens. He also recognized that patients could spontaneously recover. In a more recent study Rawle et al examined the long-term outcome of asthma in dust allergic patients[6]. That study confirmed that most patients do well in the long-term and suggested that symptoms may improve before sensitization wanes.

Factors associated with asthma can be summarized as :

i) The structure and size of the lungs;

ii) The relationship between exposure and sensitization to inhalant allergens:

iii) Factors primarily genetic that influence the onset of sensitization; and

iv) Nonspecific enhancers of the immune or inflammatory response that can increase the severity of symptoms.

a) The size of the lungs :

The size of the lungs at birth has a major influence on the risk of acute respiratory episodes in the first two years of life[7]. However, this effect declines after age -2 and does not appear to be a significant determinant of asthma in childhod. Given that the primary cause of acute episodes in the first two years is infection with respiratory syncytial virus (RSV), it seems likely that due to wall swelling, the smaller airways will be obstructed and cause symptoms.

b) Sensitization to Indoor Allergens :

There is now little argument about the importance of sensitization to indoor allergens as a risk factor for asthma among children age 6-16. [4, 8, 12] However, there are major issues about when the critical events occur.

i) The traditional view is that children first develop positive skin tests to dust mite or cat allergens

1. Assistant Professor, IDCH, Mohakhali, Dhaka-1212, 2. Jr. Consultant, IDCH, Mohakhali, Dhaka-1212, 3. Associate Professor, Dhaka Shishu Hospital, Sher-E-Bangla nagar, Dhaka4. Associate Professor, IDCH, Mohakhali, Dhaka-1212, 5. HMO, Dhaka Shishu Hospital, Sher-E-Bangla Nagar, Dhaka

between 2 years and 6 years and it is assumed that exposure over the preceding months or years is relevant to this. It has been shown that the concentration of mite allergen at age 1-2 was a good predictor of sensitization at age 10[8].

ii) Many studies have now shown a significant association between month of birth and sensitization[13]. This strongly suggests that there is a window of time in early childhood when inhaled allergens can be recognized and processed. Clearly, this could represent priming of T cells without significant production of antibodies.

iii) Two reports in the last 4 years have suggested that infants may be sensitized in utero[14,15]. The evidence comes from T-cell proliferative responses to dust mite antigens using chord blood lymphocytes. However, calculation of the quantities of allergen inhaled by the mother makes this difficult to understand. If the mother inhales 50ng/day then the serum concentration would be of the order of 10pg/ml. It is very difficult to understand how the fetus would recognize these concentrations. Furthermore, those authors found less consistent response to ovalbumin or beta-lactoglobulin. The quantities of egg and milk proteins absorbed by the mother are much higher, i.e. grams/day. At present the evidence for intra-uterine sensitization to inhalant allergens should be considered to be an interesting area that requires more study.

iv) The immune system is extensively under genetic control. These controls are both general and antigen specific. However, children in "atopic" families becomes sensitive to those antigens to which they are exposed implying that the major controls are general. Atopic children are genetically predisposed to develop immune responses to inhalant allergens which include T_H2,IgE, IgG and IgG4 antibodies.

v) The next question is whether antigen exposure, other than inhalant allergens, during the first two years of life can alter the immune response to inhalants. The obvious candidates are viral infections, bacterial infections and immunization. The best-studied viral infection in early childhood is respiratory syncytial virus (RSV).

Since up to 80% of asthma exacerbations in 6 to 8 year olds is related to nasal rhinovirus infection, it is of interest to understand the link between nasal and bronchial inflammation. However, the key pathophysiological events of rhinovirus infection are poorly understood. Rhinovirus infection leads to 4 to 7 fold increases in vascular permeability, and 2 - fold hypersecretion of gel phase mucous components[16]. Vascular permeability may be increased due to bradykinin, and leads to the profuse watery rhinorrhea,. Vasodilatation leads to nasal congestion and swelling. Nociceptive nerves are stimulated, which accounts for the itch and recruited sneeze (systemic) and glandular discharge (parasympathetic) reflexes. There is increased sensitivity to inhaled irritants and endothelin that represents mucosal hyperresponsiveness[17,18].

Cytokines may be responsible for many of these effects. IL-8 and IL-6 are increased on about Day 3 and 4 after rhinovirus inoculation in humans. IL-11 has also risen to prominence since it is released into nasal secretions in humans in vivo after rhinovirus inoculation. Epithelial cells, fibroblasts, and possible mononuclear cells may produce Il-11. IL-1 appears to be produced after infection with viruses that are associated with asthma such as rhinovirus and parainfluenza virus, but not influenza, which is thought not to be associated with bronchospasm. IL-11 may play a role in bronchial hyper-responsiveness[14,15]. Administration of a single intranasal dose of 10µg of IL-11 to mice leads to bronchial hyperresponsiveness (increased bronchoconstriction) with minimal inflammation. It is a neurokine' that increases the sensitivity of nociceptice (paincarrying) neurons to activation and increases neural responses to painful stimuli[19].

Once maternal antibody levels have waned, infants become progressively susceptible to bacterial infections; e.g. pneumonia, rheumatic fever, and chronic suppurative ear infections[5]. Since the advent of oral broad-spectrum antibiotics, it has become routine for children to be treated so that the course of infection is dramatically shortened. However, bacterial infections are thought to induce T_{H1} responses by a mechanism that includes high levels of IL-12 production from macrophages. The question is therefore whether antibiotic treatment will change the immune response to bacteria and in some way increase the T_{H2} response to inhalants. Taken one step further, the next question is whether the widespread use of antibiotics in early childhood by

changing the immune response to bacteria, has influenced the development of chronic sinusitis[20].

Prevention :

- Consists of both prevention of development of disease (primary) and prevention of exacerbations in established disease (secondary).
- Prevention methods, such as prevention of allergen sensitization and avoidance, as well as early therapeutic intervention, can theoretically prevent development of disease.
- Secondary prevention includes both pharmacologic and non-pharmacologic interventions.

Primary prevention of Bronchial asthma

As asthma is an inflammatory disorder which persists almost throughout life, our aim would be primary prevention of disease i.e. prevention of development of disease.

It is now clear that although, in asthma, cause of inflammation is unknown; continuous avoidance of allergen, proper control of ARI, less use of antibiotic and early use of anti-inflammatory drugs may prevent development of asthma in children.

Even after adequate control of inflammation in asthma patients, the hyperresponsiveness of airway to multiple stimuli persist almost throughout the life. So, to prevent hyperresponsiveness of airway, two types of anti-inflammatory drugs may be used for long time.

Two types of anti-inflammatory drugs are now available in our country.

1) Cromolyn

2) Inhaled corticosteroids

Recently in has been documented that the growth of asthmatic children is impaired due to use of inhaled corticosteroid[36], although it has long been recognized that asthma itself can impair growth[37]. So it is clear that for primary prevention of asthma inhaled corticosteroids are not at all an acceptable drug. Cromolyn will be the best drug for the prevention of early asthma and early inflammation of airway especially for children.

Secondary prevention of Asthma :

Asthma therapy should include patient education and assessment and treatment of those factors that can make asthma worse, including rhinosinusitis, GERD and allergen sensitivity and exposure. Pharmacotherapy, while essential for symptom control, is by itself not adequate[21].

Pharmacotherapy of asthma includes :

1. Anti-inflammatory drugs such as Cromolyn, nedocromil and corticosteroids[22,23].
2. Bronchodilating drugs such as short-and long-acting beta agonists, theophylline and anti-cholinergic agents[24,25].

Cromolyn and nedocromil have relatively limited clinical efficacy compared to the inhaled corticosteroids, therefore their use is limited largely to children, where there are concerns regarding growth retardation with the use of inhaled steroids. Cromolyn and nedocromil may also be used to block the response to specific allergen exposures or exercise.

Cromolyn Sodium and Nedocromil :

The two compounds are equally effective against allergen challenge, although nedocromil appears to be more potent than Cromolyn in inhibiting bronchospasm provoked by exercise, by cold dry air, and by bradykinin aerosol[22,27].

Both compounds have been shown to reduce asthma symptoms, improve morning peak flow, and reduce need for quick-relief β_2-agonists Comparison of nedocromil MDI 2 mg qid to Cromolyn MDI 5 mg qid demonstrated that they are generally comparable in mildly allergic patients and that nedocromil was more effective than Cromolyn in nonallergic patients using inhaled corticosteroids.

The clinical response to Cromolyn and nedocromil is less predictable than the response to inhaled corticosteroids. Both compounds have a strong safety profile[22].

Inhaled corticosteroids (ICS)

Inhaled corticosteroids (ICS) reduce asthma symptoms, but also reduce bronchial hyper-responsiveness during asthma exacerbation[26,28]. Several studies suggest that they are most effective if they are introduced soon after the onset of asthma symptoms[29].

The short-acting beta -agonists are excellent for relief of symptoms and for pretreatment to prevent exercise induced bronchospasm, but their duration

of action is too brief for them to be useful for maintenance bronchodilator therapy[29]. Maintenance bronchodilation is best accomplished with either long-acting beta-agonists[71]. or sustained release theophylline[25]. There is virtually no role for anti-cholinergic therapy in the treatemnt of asthma except for acute exacerbations poorly responding to inhaled beta-agonists[26,30]. Both the long-acting beta-agonists and sustained release theophylline have proven effective in preventing nocturnal asthma[31]. However, long-acting beta-agonists are generally more effective and cause less side effects. Theopylline, on the other hand, has been shown to have some anti-inflammatory actions, which are lacking in the beta-agonists[32,33]. The importance of these anti-inflammatory actions of theophylline is uncertain.

Currently it is recommended that all patients with asthma who required daily therapy receive an anti-inflammatoy agent[21]. If symptoms persists, either the dose of inhaled corticosteroids can be increased or a long-acting bronchodilator added[22]. Direct comparisons suggest that the combination of anti-inflammatory and long-acting beta-agonist control symptoms better than high dose inhaled corticosteroid alone[34]. Pharmacologic therapy is used to prevent and control asthma symptoms, reduce the frequency and severity of asthma exacerbations, and reverse inflammatory airflow obstruction. These reflect the scientific concept that asthma is a chronic disorder with recurrent episodes of airflow limitation, mucus production, and cough. Asthma medications are thus categorized into two general classes : long-term-control medications taken daily on a long-term basis to achieve and maintain control of persistent asthma (also known as long-term preventive, controller, or maintenance medications) and quick-relief medications taken to provide prompt reversal of acute airflow obstruction and relief of accompanying bronchoconstriction (also known as reliever or acute rescue medications). Patients with persistent asthma require both classes of medication.

Conclusion :

In considering the causes of the increase in asthma, it is essential to evaluate all the factors that have changed over the last 40 years. Clearly, there continues to be a very profound association between asthma and sensitization to indoor allergens. However, the evidence that simple increase in indoor allergens has caused the increase in asthma is not unequivocal. Specific changes that could relate to the increase include :

a) Changes in houses; decreased ventilation; increased carpeting and furnishing; increased temperatures and changes in management.

b) Introduction of broad-spectrum antibiotics from 1960 onwards.

c) Dietary changes have been suggested and the major issues are increased sodium and/or decreased fish in the diet.

d) Outdoor air pollution and indoor passive smoking.

e) The most pervasive changes in lifestyle are those that have followed the introduction of television, computers and other forms of home entertainment. The consequences of changes in exercise secondary to sitting still 3 hours per day are still not well understood. The increased obesity is well known and the decreased outdoor activity is obvious, however, there are further interesting questions concerning the consequences of spending 3 hours/day sitting on an excellent source of allergen exposure.

f) Early uses of anti-inflammatory drugs along with environmental control are the sheet anchor of the primary and secondary prevention of asthma.

References :

1. Leff AR. Future directions in Asthma therapy. Chest 1997; 111(2) : 61s-68s.

2. Hargreave FE, Ryan A, Thomson NC et al. Bronchial responsiveness to histamine or methacholine in asthma. measurement & clinical significance. J. Allergy clin Immunol 1981; 68 : 347-55.

3. O'Byrve PM, Adelorth E, Airway epithelial inflammation and functional consequences. In : Immnopharmacology of epithelial barriers. Goldie R.G. ed. London. Academic Press. 1994; 147-55.

4. Kroegel C, Liu MC. Hubbard WC Lichtenstein LM, Bochner BS. Blood and bronchoalveolar eosinophils in allergic subjects after segmental antigen challenge : surface phenotype, density heterogeneity, and prostanoid production. J Allergy Clin Immunol 1994; 93 : 725-34.

5. Sporik RB, Chapman MD. Platts - Mills TAE. House dust mite exposure as a cause of asthma (Editorial). Clin Exp Allergy 1992; 22 : 897-906.

6. Rackemann FM, Edwards RC,. Asthma in children : Follow-up study of 688 patients after an interval of 20 years N Eng J Med 1952; 246-815 & 858.

7. Rawle FC. Burr ML, Platts - Mills TAE, Long-term falls in antibodies to dust mite and pollen allergens in patients with asthma or hay fever. Clin Allergy 1983; 13 : 409-417.

8. Taussig LM. The conundrum of wheezing and airway hyperreactivity in infancy. Ped Pul 1992; 13 : 1-3.

9. Sporik R, Holgate ST, Platts - Mills TAE, Cogswell J. Exposure to house dust mite allergy (Der P 1) and the development of asthma in childhood : A prospective study. N Eng J Med 1990; 323 : 502-507.

10. Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts - Mills TAE. Association of asthma with serum IgE and skin-test reactivity to allergens among children living at high altitude : Tickling the dragon's breath. Am J Resp Crit Care Med 1995; 151 : 1388-1392.

11. Call RS, Smith TF, Morris E, Chapman MD, Platts - Mills TAE. Risk factors for asthma in inner city children J Pediatr 1992; 121 : 862-866.

12. Peat JK, Salome CM, Woolcock AJ. Longitudinal changes in atopy during a 4 year period : relation to bronchial hyperresponsiveness and respiratory symptoms in a population sample of Australian school children. J Allergy Clin Immunol 1990; 85 : 65-64.

13. Sears MR, Hervison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to gratass pollen, house dust mite, and cat dander in the development of childhed asthma. Clin Exp allergy 1989; 19 : 419-424.

14. Upham JW, Holt BJ, Baron -Hay Mj, Yabuhara A, Hales BJ, Thomas WR, LohRKS, O'Keeffe PT, Palmar L, Lesouef PN, Sly PD, Burton PR, Robinson BWS, Holt PG> Inhalant allergen - specific T-cell reactivity is detectable in close to 100% of atopic and normal individuals ; covert rexponses are unmasked by serumfree media. Clin Exp Allergy 1995; 25 : 634-42.

15. Miles EA, Warner JA, Lane AC, Jones AC, Colwell BM, Warner JO, Altered T, lymphocyte phenotype at birth in babies born to atopic parrents. Ped Allergy Immunol 1994; 5 : 202-8.

16. Elias JA, Zheng T, Einarsson O, Landry M, Trow T, Rebert N, Panuska J. Epithelial interleukin-11. Regulation by cytokines, respiratory syncytial virus, and retinoic acid. J Biol Chem 1994; 269 : 22261-22268.

17. Einarsson O, Geba GP, Panuska JR, Zhu Z, Landry M, Elias JA. Asthma - associated viruses specifically induce lung stromal cells to produce interleukin-11, a mediator of airways hyperreactivity, Chest 107 (3 supply) : 133S, 1995.

18. Yuta A, Van Deusen M, Gaumond E, Ali M, Baraniuk JB, Doyle W, Cohen S, skoner D. Vascular permeability and mucous hypersecretion after rhinovirus infection. Am J Respir Crit Care Med 1996; 153 : A865.

19. Igarashi Y, Skoner DP,Doyle WJ, White MV, Fireman P, Kaliner MA. Sources of nasal secretions during phases of experimental rhinovirus upper respiratory tract infections (URI). J Allergy Clin Immunol 1993; 92 : 722-731.

20. Duff AL, Pineranz ES, Gelber LE,Price GW, Farris H, Hayden FG, Platts-Mills TAE, Hayman PW, Risk factors for acute wheezing in infants and children : viruses, passive smoke, and IgE antibodies to inhalant allergens. Pediatrics 1993; 92 : 535-540.

21. Sheffer AL. National Heart Lung and Blood Institute National Asthma Education Program Expert panel Report : guidelines for the diagnosis and management of asthma. J Allergy Clin Immunol 1991 : 88 : 425-536-4.

22. Schwartz HJ, Blumenthal M, Brady R, Braun S, Lockey R, Myers D, et al. A comparative study of the clinical efficacy of nedocromil sodium and placebo.. How does cromolyn sodium compare as an active control treatment/ Chest 1996; 109 : 945-52.

23. Juniper EF, Kline PA, Vanzieleghem MA, er al. Effect of long-term treatment with an inhaled corticosteroid (Budesonide) on airway hyperresponsiveness and clinical asthma in non-steroid-dependent asthmatics. Am Rev Respir Dis 1990; 142 : 832.