Immune Response Shifting of Asthma in Aging

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Abstract: Decrease of the expiratory flow leads to a change in the flow volume curve. Alterations in T-Cell Immunity with Aging and many significant changes are appearing in immune system with aging. The aging process is accompanied by qualitative and quantitative changes in the immune system. The cytokine profiles were different between the two groups of young and old person. asthma was thought to be a Th2 cell-mediated disease with the involvement of the cytokines. Despite the observation that allergic disease has a decreased prevalence in older adults, the severity of allergic disease remains a significant concern due to the fact that multiple organ systems suffer a functional decline. age-associated changes in cytokine patterns might provide a new way to treatment of asthma in aging process. Therefore asthma is a significant change with age, so treatment protocol should be different between elderly and young.

Key words: Asthma • Age • Response Shifting • Treatment

INTRODUCTION

Physiological Changes in the Aging Lung: Lung Capacity reduces even in the healthy individuals and these changes are the extension of their spaces without alveolar destruction, reduction in the surface of gas exchange and loss of the supportive tissue in the peripheral air ways. Decrease of the expiratory flow lead to a change in the flow volume curve that is similar to small airway obstruction. Aging related changes can mimic the obstructive pulmonary diseases because Hypoxia sensitivity of the respiratory centers decreases and bronchial hyper-reactivity increases, but a disturbance occurs in the perception of broncho-constriction [1, 2].

Epidemiology of Asthma in the Elderly: Prevalence of asthma in the elderly is same with the other age groups(15%), but the diagnosis rate is quite low. Mortality rate is very higher than the other age groups. Majority of the persons died from asthma are aged 65 and above[3-5].

T Cell Changes: The most age related changes are in T cell populations that decrease in the number of naïve cells and the accumulation of sensitized cells. Moreover, a further decrease of this lymphocyte population can be observed when the exposure to new pathogens induces there placement of old memories for new ones. The decrease of naive T lymphocytes contributes to the impoverishment of lymphocyte repertoires with defective responses to new antigens. Many studies showed that a reduction in the number of CD45RA naive lymphocytes in lymph nodes with aging [6-10].

The expression of different isoforms of CD45R is thus regulated during the maturation and activation of T cells. T cells with a naive phenotype express CD45RA differentiation markers and diminish throughout life, which is associated with a gradual onset of memory phenotypes. When asthmatics are exposed to allergen stimulation only CD45R0 cells can express activation markers [11, 12].

Some study showed a significant reduction in the expression of CD45RA in elderly health individuals when compared with a young control group and this finding confirms the reported decrease of naive cells during the aging process. It was also decided to evaluate if the asthma condition posed an additional risk for this reduction. The expression of CD45RA on CD4 and CD8 was also reduced in asthma [13-15].
Alterations in T-Cell Immunity with Aging [16-18]

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Cytokine Change: In the elderly, decline in IL-2 and IFN-γ is observed while IL4 and IL6 production is kept within normal values. This adjustment in the cytokines balance is accomplished by a normal or increased humoral response and a decrease in cellular response [19, 20]. The cytokine profiles were different between the two groups. Aged model had increased production of IL-5 and INF-γ in the lung tissues and spleen cell culture, whereas young model had increased levels of IL-4 and IL-13. These findings support the notion that aging may affect airway hyper-responsiveness and inflammation. Aging is associated with alterations in T-cell immunity, which is a critical component in the development of asthma. However, additional investigations are required to determine whether and how such alterations could promote asthma in humans [21, 22].

Asthma Progressing: Asthma has been considered a disease primarily affecting children and young adolescents but a substantial number of asthmatic patients develop this problem in elderly stage and elderly asthmatic patients appear to have more severe disease. T cells have a major role in the pathogenesis of asthma. Traditionally, asthma was thought to be a Th2 cell-mediated disease with the involvement of the cytokines IL-4, IL-5 and IL-13, which could promote IgE switching, eosinophilia, mast cell recruitment, mucus production and airway hyper-responsiveness. Although data regarding the effect of aging on the pathogenesis of asthma are limited, aging may affect airway hyper-responsiveness. Aged model developed greater airway and lung inflammation in response to ovalbumin challenge compared with young [23-25].

T Cells in Asthma: Recent studies indicate the involvement of many types of Th cells, such as Th2, Treg, Th17, Th9 and TCD8+ cells. Allergic challenges promoted airway inflammation, hyper-responsiveness and neutrophilia by inducing Th17-cell response. Th17 cells enhanced Th2-mediated eosinophilic inflammation. Th9 cells may participate in inducing airway inflammation and hyper-responsiveness, although its exact role is yet to be determined given the mixed results of the studies on IL-9 over expression and IL-9 deficiency in a mouse model of asthma [26-29]. Treg cells also appear to have a role in regulating airway inflammation in asthma. Induction of Treg cells can reduce airway inflammation and airway hyper-responsiveness. CD8+ T cells With IL-5, IL-13 and IFN-g production are involved in the development of asthma. So a range of immunologic alterations in T-cell immunity occurs with aging, encompassing from cell function to the proportion of T-cell subsets [30-33].

Ageing and Allergic Asthma: Although asthma is more frequent in young people, it affects individuals of all ages that has a severe impact on patients’ quality of life in different domains. Asthma is a chronic inflammatory disorder of the airways, characterized by a wide spread but variable bronchial obstruction and by hyper-responsiveness to several triggers. And share environmental and genetic risk factors. Treatment of upper airway disease can improve asthma symptoms and decrease lower airway hyper-responsiveness. Characterizing asthma in young people with cough, dyspnea, chest tightness and wheezing that are also present in the elderly an accurate differential diagnosis with chronic obstructive pulmonary disease, congestive heart failure, pulmonary emboli, ischemic heart disease, gastro-esophageal reflux, recurrent aspiration, lung tumors and laryngeal dysfunction should be considered [34-37]. The evolution of asthma and the limitation to the airway flow depend on the additional effect of localized
inflammatory process, airway remodeling and smooth muscle contraction. The poorer prognosis and higher death rates of asthma in older patients are probably associated with chronic systemic inflammation and recurrent exacerbations characteristic of the disease. The prevalence of respiratory allergic diseases in the elderly is increasing and mortality rates are highest among patients over 65 years old with asthma [36-38].

**Elderly Asthma and Co-Morbidity:** Allergic respiratory diseases are multi-factorial and inflammatory mediators such as histamine, leukotriene, prostaglandins and cytokines are released in response to each trigger. These mediators enter the peripheral blood and a systemic inflammation becomes established. This sequence of phenomena may increase the risk of cerebrovascular thrombotic events that can increase risk for stroke and for hospital admissions caused by other vascular pathologies [39-41]. So asthma has an increased susceptibility to atherosclerosis, which is probably connected with inflammatory pathways inherent to both diseases. Cysteinylleukotrienes are potent inflammatory mediators implicated in the pathogenesis of asthma and atherosclerosis [42-44].

The vascular branches in CNS, Heart and kidney are vital therefore more attention and checking of these in asthmatic patients should be applied [45-47].

Many studies showed that hyperglycemia and asthma are associated with systemic inflammation and that is associated with impaired lung function [47-49].

Older people have weakened defenses against infection. Pneumonia and influenza infection are the most common health problems in the old people. The infection causes inflammation, deterioration of lung function and increasing breathing effort.

In elderly when these problems correlate with asthma, complicated status is appeared and this needs care and treatment with focusing on many parameters such allergy, viral infection, vascular disorders, respiratory function, cytokine pattern, inflammation and the most important factor difference treatment between young and old people [48-51].

**Age Effects on Immune Function:** Number of the peripheral B cell are unaffected by aging but there is a decline in the production of naive B cells from the bone marrow. In addition, there is decreased diversification of B cells exhibiting lower affinity and avidity is produced, leading to an overall lower quality antibody response [52-54].

Function of the Neutrophil including adhesion, migration and phagocytosis, remains intact, some aspects of neutrophil mediated for bacterial lysing are diminished in older adults and apoptosis of neutrophils is increased in older adults. Increased peripheral blood Eosinophil’s were associated with increased interleukin 6 levels in older adult from the Health and Aging study, thus demonstrating that a marker of allergic inflammation correlates with a marker of age-related systemic inflammation [55-57].

Reduced eosinophil degranulation and production of superoxide in response to stimuli are observed in older asthma patients relative to young patients. The age-related decline in degranulation may contribute to more severe respiratory infections with viral etiologies. With regard to natural killer cells, their absolute number is increased with aging, their activity; cytotoxicity, proliferation and INF-γ production in response to IL-2 are modestly diminished [58-60].

In the aging decreased pro-inflammatory cytokine production by macrophages and diminished ability for antigen presentation, as evidenced by decreased expression of surface MHC-II molecules [61-63].

Most immune cells are compelling evidence for a decline in some functional aspect and the clinical impact of these changes is not well-defined. Many of the functional defects may result in exaggerated inflammation. This is often referred to as “inflamm-aging,” and is most notably associated with increased IL-6 and TNF-α level in the serum [64-66].

**Atopy of Asthma in Older Adults:** Despite the observation that allergic disease has a decreased prevalence in older adults, the severity of allergic disease remains a significant concern due to the fact that multiple organ systems suffer a functional decline. Declining forced expiratory volume in 1 s (FEV1) and smooth muscle tone are a few examples of age-related changes [67-70].

Some studies have demonstrated that an atopic history appears to be the strongest predictor of asthma and its severity in the older adult population. One other factor contributing to increased morbidity of allergic disease in older adults is their poor perception of allergic disease symptoms. These validate the concern regarding allergic disease monitoring in older adults and the need for an appropriate atopic evaluation [71-73].
Atopy is the strong predictor of asthma and its severity in all age groups, including older adults. Lower mean levels of the total serum IgE and lower prevalence of comorbid allergic rhinitis in older patients compared with younger ones, but the older patients had worse lung function as measured by pre-bronchodilator and post-bronchodilator FEV1. Biological information show relationships between atopy and asthma. So atopy has a strong association with asthma of varying severity, regardless of age [74-76].

**Changing asthma in the Elderly:** Lung function decreases with age and the decrease is greater in men than women. As a result, elderly asthmatic patients have reduced response to bronchodilators and glucocorticoids. They also have immunosenescence. But there is a lesser decrease in innate immunity. Eosinophil function remains the same, but neutrophil numbers increase. There is greater inflammation in aged than in young. Asthma that begins in children and adults younger than 40 years. However, asthma beginning later in life is rarely IgE mediated and in the elderly it often develops with a component of irreversible airway obstruction [77-80].

There are three important characteristics of asthma in the elderly. First, there is great variability in the duration and severity of the disease. Second, the onset can have been at any time since childhood but more often begins in middle age or later. Third, many of these patients have severe irreversible obstruction unrelated to the duration of the disease [81-83].

In elderly, airway remodeling is greater with more severe disease. Remodeling not only includes widespread thickening of the basement membrane and hypertrophy of smooth muscle but also hypertrophy of submucous glands in some central cartilaginous. So that proteases elastase from neutrophils and chymase from mast cells stimulate mucus secretion [84-86].

In airway disease the most important external agent is bacterial endotoxin and Viral that stimulates Toll-like receptor. Stimulation of TLR-4 (with bacteria) results in neutrophilic inflammation and increased. Latent viral infection might also be a factor in the development of asthma, but they found the presence of latent viruses in epithelial cells of asthmatic patients to be no different from that seen in non asthmatic subjects. Perhaps patients with asthma respond differently. These results in attraction and activation of eosinophil s and neutrophils, degranulation of eosinophil s and mast cells, increased response of afferent neurons, smooth muscle contraction and hypertrophy, angiogenesis and fibrosis [86-89].

**Epigenetic, Asthma and Aging:** Influence of environmental factors and aging on the genomic are important. Epigenetics is defined as heritable changes in gene expression that occur without alterations in DNA sequence. Epigenetic changes or marks can play a major role in atopic disorders with regulation of gene expression. The most common examples of epigenetic marks are DNA methylation and modification of histone proteins, particularly acetylation deacetylases [90-92].

Asthma is a markedly heterogeneous disease and recent evidence suggests that environmentally induced epigenetic changes contribute to asthma phenotypes and that airway inflammation in patients with asthma. The incidence of asthma in the elderly resembles the incidence of common diseases. Unlike genetic variants that contribute to disease, epigenetic changes can be reversed [93-95].

**CONCLUSION AND DISCUSSION**

Maternal atopy, but not paternal atopy, showed a strong linkage with a suppressed mucosal cytokine and chemokine signature in asymptomatic neonates, suggesting imprinting by the maternal milieu in utero or perinatal life [96, 97].

In the elderly, the main problem of the immune system is the reduced proliferative cell capacity and the delay of clonal expansion in response to antigens as a result of stem cell decrease. In the elderly the production of specific antibodies in response to vaccines and to environmental antigens for example viral infection is reduced but the production of auto-antibodies is increased and the total serum immunoglobulin levels remain unchanged. So any weak infection such as influenza virus is very dangerous for aging people and autoimmune diseases are common in these people [98, 99].

The aging process is accompanied by qualitative and quantitative changes in the immune system. This process, also called immunosenescence, is followed by alterations in cytokine production. Immunosenescence is characterized by decreases in protective immune responses and increases in inflammation and autoimmunity [100, 101].
Asthma might have persisted from early years or had its onset at any time, even late in life. Asthma that persists from youth remains relatively stable, but asthma beginning in the elderly is more severe and progressive and less reversible. Patients with intrinsic asthma have a higher rate of decrease in lung function and are more likely to die of asthma than patients with allergic asthma and the death rate is higher in poor and minority populations. Death in elderly patients is seasonal (cold season) and this is presumably due to respiratory tract infections [102-104].

The importance of both genetic and environmental influences in regulation of these markers has been emphasized. So these have different effects on older people compared with younger persons and Cytokine patterns are different in older people compared with younger persons [105, 106].

However, manipulation of age-associated changes in cytokine patterns might provide a new way to treatment of asthma in aging process [107, 108]. But drug intake should also be carefully evaluated. Because the immune system and the body's response systems are different in the two groups of young and old patients. Therefore Asthma is a significant change with age. So treatment protocol should be different between elderly and young. Because they have different physiological and pathological conditions that so have a different response pattern.

REFERENCES


