THE PHAGOCYTIC ACTIVITY OF PERIPHERAL BLOOD MACROPHAGES IN ASTHMATIC PATIENTS

Thesis

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List of Abbreviations

ABG	Arterial blood gases
AHR	Airway hyperreactivity
AM	Alveolar macrophage
(A-a) d O2	Alveolar-arterial oxygen difference
ATS	American Thoracic Society
BAL	Brocho-alveolar lavage
BHL	Bronchial hyperreactivity
CO2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CD	Cluster of differentiation
CBC	Complete blood count
CPG	Cytosine-phosphate-guanosine
DNA	Deoxyribonucleic acid adenine
ETS	Environmental tobacco smoke
EIA	Enzyme immunoassay
EPO	Eosinophil peroxidase
ECP	Eosinophilic cationic protein
EGFR	Epidermal growth factor receptor
ECM	Extracellular matrix
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative For Asthma
GM-CSF	Granulocyte macrophage colony stimulating

	factor
G-CSF	granulocyte-colony stimulating factor
HLMC	Human lung mast cells
Ig	Immunoglobulin
ICAM-1	Intercellular adhesion molecule-1
IFN	Interferon
IL	Interleukin
LPR	Late phase reaction
LT	Leukotriene
LPs	Lipopolysaccharides
MBP	Major basic protein
MHC	Major histocompitability complex
MIP-1α	Macrophage inflammatory protein-1 alpha
MMS-68	Macrophage derived mucus secretagogue-68
mRNA	messenger ribonucleic acid
MMP	Metalloproteises
MCP	Monocyte chemoattractant protein
NO	Nitric oxide
NSAIDS	Non-steroidal anti-inflammatory drugs
PCO2	Partial pressure of carbon dioxide
PO2	Partial Pressure of oxygen
PEF	Peak expiratory flow
PBS	Phosphate buffer saline
PAF	Platelet activating factor

PDGF	Platelet derived growth factor
P-A	Postero-anterior
PG	Prostaglandin
PC	Provocative concentration
PD	Provocative dose
RADS	Reactive airways dysfunction syndrome
RANTES	Regulated on activation normal T-cell expressed and secreted chemokines
RSV	Respiratory syncytial virus
TC	T-cytotoxic
Th	T-helper
TX	Thromboxane
TIMP	Tissue inhibitory metalloprotease
TLR	Toll-like receptor
TGF	Transforming growth factor
TNF	Tumor necrosis factor
VCAM-1	Vascular cell adhesion molecule-1
VIP	Vasoactive intestinal peptide
WHO	World Health Organization

INTRODUCTION

The global strategy for asthma management which is convened by the National Institute of Health and World Health Organization defined asthma as chronic inflammatory disorder of the airways in which many cells play a role, in particular eosinophils, mast cells and T-lymphocytes. In susceptible individual, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough, particularly at night and in the early morning. These symptoms are usually associated with widespread but variable airflow obstruction that is at least partly reversible either spontaneously or with treatment. The airways inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli ***(Georgitis, 1999).***

Asthma is an extremely common disorder affecting males and females but males are more affected. Epidemiological studies estimate the prevalence of asthma in general population to be about 5-12% and although most cases begin before the age of 25 years old, yet asthma may develop at any time throughout life ***(Drazen, 2000).***

The immunopathology of asthma is characterized by peribronchial infiltration of macrophages, eosinophils and T cells in stable as well as symptomatic periods of the disease. The interaction between these cells, mediators and tissues in the airways results in airflow limitation from acute bronchoconstriction, swelling of the airways walls, increased mucus secretion, airway remodeling and increase in the airways responsiveness ***(Alexis et al., 2001).***

Furthermore, distorted immunoregulatory mechanisms lead to the development of asthma symptoms. In addition to different effector mechanisms, the cellular and humoral

immunity participate in the development of the immune response in bronchial asthma ***(Stankiewicz et al., 2002).***

Among cells involved in asthma, macrophages are critical in removing inhaled particulates and microbes that have the potential to exacerbate asthma. Studies have suggested a link between decreased phagocytic function of peripheral blood phagocytes and asthma. Moreover, T cells in asthmatic patients have been shown to preferentially produce interleukin-4, which has been shown to modulate surface receptors in macrophages. Among those receptors are human leukocyte antigen HLA-DR expression, which is increased following exposure to IL-4, and phagocyte receptor which is decreased after exposure to IL-4 and is also associated with decreased phagocytic function ***(Alexis et al., 2001).***

AIM OF THE WORK

The aim of the present work is to study the phagocytic activity of peripheral blood phagocytes in asthmatic patients and to assess whether or not asthmatic patients have disorder in the phagocytic functions compared to normal population.

BRONCHIAL ASTHMA

In the past, asthma has been used to refer to almost any sort of difficulty in breathing, especially if it occurred in episodes, no matter what its cause. Medically "asthma" without qualification would now generally be taken to refer to a disease of the respiratory system. The adjective "bronchial" may be used in context where confusion with paroxysmal dyspnea of cardiac origin is possible ***(Scadding, 1981).***

Asthma is a disease that affects people of all ages, in all parts of the world, despite greatly increased knowledge of the immunopathological process characteristic of the disease, and apparent improvement in treatment morbidity (and in some countries) mortality is increasing rather than decreasing ***(Crompton, 2000).***

DEFINITIONS

The definition of bronchial asthma is still controversial. In ***1962, Menely et al.*** defined asthma as a disease of the respiratory passages characterized by dyspnea of an obstructive type which predominantly is expiratory, reversible at least partially and of varying severity and duration and manifested by eosinophil infiltration and desquamative epithelial changes.

In 1997, National Institute of Health defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

In 1998, the Egyptian Society of Chest Diseases and Tuberculosis defined asthma as an inflammatory disorder of the airways in which many cells, including mast cells and eosinophils, play a prominent role leading to damage of the respiratory epithelium, widespread but variable airways obstruction over a short period of time which is usually reversible spontaneously or with treatment, and an increase in airways responsiveness to a variety of stimuli, the condition is usually intermittent and is subjected to spontaneous and prolonged remissions.

From a clinical standpoint, airway inflammation is the most likely factor to account for varying severity of asthma and is therefore the element most responsive to controller medications such as inhaled glucocorticosteroids. However, even in the absence of symptoms and overt airflow limitation, asthma continues to exist in the form of mild airway inflammation and airway hyperresponsiveness ***(Jacoby et al., 2001)***.

Prevalence of asthma

Many studies suggest that the prevalence of asthma is rising in children and adolescents. This increase has been accompanied by an increase in morbidity, as measured by the proportion of children consulting their general practitioner and hospital admissions from asthma ***(Ulrik et al., 1996).***

In United States more than 17.3 million Americans, or 7% of the U.S. population, are affected by asthma, with the prevalence increasing steadily over the past several years ***(Centers for Disease Control and Prevention 2001).*** Between 1980 and 1996 the number of people reporting a history of asthma increased by 75% ***(Centers for Disease Control and Prevention 2002).***

In Egypt, ***Faris (1986),*** studied the prevalence of asthma among Heliopolis primary school children in private and

government schools and found that the rate was 4.7% and 1.7% respectively, while the ratio of male to female was 2.6:1.

El-Hefny and Haddad (1991) studied the prevalence of asthma in many cities in Egypt. In Cairo, the prevalence of asthma was 8.2% in 13028 children of age group 3-14 years old. While in Benha city, was 3.6% of 7258 and in Tanta 3% of 1559 child. The difference between the prevalence of asthma in Cairo, Benha and Tanta was explained on environmental differences, as Cairo has more population than the two other cities. The study confirmed that the prevalence of asthma is increasing and is equal to many reports from all over the world.

Abdel Latif (2000), studied the prevalence of asthma among school children on 2321 students obtained from two schools in each district, there were 130 students asthmatics (5.6%) of which 60 males (46.2) and 70 females (53.8%). The mean age of onset of asthma in both sexes was 6.68±4.26.There was a highly significant relation between the crowding index and the prevalence of asthma.

The World Health Organization (WHO) (2000) surveys demonstrated that between 100 and 150 million people around the globe suffer from asthma and the number is rising. Worldwide, deaths from this condition have reached over 180.000 annually.

Current data from different countries all over the world suggest that asthma prevalence over all ages is 4.1 per 100 populations, with rates for children under 18 years being 5.7 per 100 populations. Thee prevalence rates were based on response to questions as to whether the person had seen a physician for asthma before in his life ***(Weiss, 2000).***

Categories of asthma

- **Extrinsic atopic asthma:**

This refers to the large group in whom asthma is due to IgE mediated hypersensitivity to inhaled antigens commonly present in the air. Many of them also have seasonal or perennial allergic rhinitis. Most of them start having wheezy: breathlessness early in life, in some after infantile eczema. The susceptibility of these patients to develop IgE antibodies because of minor exposure to common environmental antigens is presumably genetic. It has been called atopy. In the name used for this sort of asthma "extrinsic" implies that asthma is precipitated by contact with environmental antigens and "atopic" refers to the sort of hypersensitivity reaction that is concerned ***(Clark et al., 1992***)

- **Extrinsic non atopic asthma:**

This non-atopic term had been suggested to refer to patients in whom asthma can be attributed to reaction between inhaled antigens and antibodies of sort other than IgE type associated with atopy, but with IgG antibody. Usually they develop symptoms 4 to 6 hours after exposure to environmental antigens ***(Nagy et al., 1982).***

- **Intrinsic asthma (Cryptogenic asthma):**

These patients have well-marked asthma, though none of the recognized types of hypersensitivity reaction or external causal factors can be found. They can be categorized as "asthma of unknown cause". It seems useful to distinguish this group on certain clinical criteria:

i. Non seasonal incidence.

ii. Possibility of onset without previous respiratory symptoms at any age, especially later in life than is usual in extrinsic atopic asthma.