شبكة المعلومات الجامعية

بسم الله الرحمن الرحيم

شبكة المعلومـــات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الالكتروني والميكروفيلم

﴿ قـسـم ﴾

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأفلام قد اعدت دون آية تغيرات

يجب أن

تحفظ هذه الأفلام بعيداً عن الغبار

في درجة حرارة من 15 – 20 مئوية ورطوبة نسبية من 20-40 %

To be kept away from dust in dry cool place of
15 – 25c and relative humidity 20-40 %

بعض الوثائق الأصلية تالفة

بالرسالة صفحات

لم ترد بالأصـــل

DEMOGRAPHIC, LABORATORY AND CLINICAL STUDY OF THE POTENTIALLY FATAL BRONCHIAL ASTHMA

THESIS

Submitted to the Faculty of Medicine
University of Alexandria
in partial fulfilment of the requirements for

Master Degree

of

Chest Diseases and Phthisology

By

YEHIA IBRAHIM MOHAMED

MBBCh, Asuot

Faculty of Medicine
Alexandria University
2002

SUPERVISORS

Prof. Dr. HATEM ABDEL BADIE EL MALLAWANY

Professor of Chest Diseases

Faculty of Medicine

University of Alexandria

Prof. Dr. ABDEL MONEIM KAMEL RABIE

Professor of Chest Diseases

Faculty of Medicine

University of Alexandria

Dr. MOHAMED MABROUK EL-HOFY

Lecturer of Chest Diseases

Faculty of Medicine

University of Alexandria

ACKNOWLEDGMENT

Thanks God, for everything done in this work.

It is great honour to express my deepest gratitude and cordial appreciation to Prof. Dr. ***HATEM ABDEL BADIE EL MALLAWANY,*** *Professor of Chest Diseases, Faculty of Medicine, University of Alexandria for his meticulous supervision, constant guidance and encouragement. He did every effort and spared no time to offer his help up to the utmost.*

I also thank Professor Dr. ***ABDEL MONEIM KAMEL RABAE,*** *Professor of Chest Diseases, Faculty of Medicine, University of Alexandria for his valuable contributions, teachings, suggestions, encouragement and supervision allover the course of this work.*

I would like to express my great appreciation and thanks to Dr. ***MOHAMED MABROUK EL-HOFY,*** *Lecturer of Chest Diseases, Faculty of Medicine, University of Alexandria, for his sincere cooperation and the lot of time he spent sharing in this work.*

Finally, my great appreciation is given to all those who shared practically & morally in the creation of this work. I specially mention my family, my friends, the patients involved and the staff of Chest Disease Department.

CONTENTS

INTRODUCTION

INTRODUCTION

Bronchial asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes 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 airway obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyper-responsiveness to a variety of stimuli.[1]

This summary of features of asthma serves well as a description of the major features of the disease, but it does not hold up as a definition. No feature is unique to asthma, and no feature is universal in those with the condition. For example, all tests of airway caliber may be normal between attacks, even in patients whose attacks are sudden and severe.[1]

Bronchial responsiveness may be normal over most of the year in patients with seasonal asthma.[1]

Bronchial hyper-responsiveness is often found in people with allergic rhinitis but without asthma.[2]

Some patients with recurrent episodes of wheezing and dyspnea associated with reversible air-flow obstruction and bronchial hyper-

responsiveness have no evidence of eosinophilic inflammation in bronchial biopsies. Some patients with severe asthma have a predominance of neutrophils, not eosinophils, in their bronchial mucosa.[2]

Genetics and asthma

Asthmas has been suspected of having a strong genetic component at least since 1860, when Henry Salter stated that he found "distinct traces of inheritance in two cases out of every five.[3]

Studies of twins suggest that a genetic factor confers susceptibility to asthma because the concordance of asthma in monozygotic twins is significantly greater than in dizygotic twins. But members of families share common environment, so familial "clustering" of a disease may reflect the effect of a common environmental exposure, rather than a genetic cause. Also asthma in an offspring is more likely if one parent has asthma and even more likely if both have asthma.[3]

Studies of distribution o f asthma have been complicated by a lack of an agreed definition of the diseases, but its distribution does not seen to follow any simple mendalain pattern. Asthma is therefore thought to be both multi-factorial and complex involving many genes that interact to determine susceptibility. As DM, hypertension, atheroscerlosis, and arthritis, asthma is a complex genetic disorder i.e. not autosomal dominant, recessive, or sex linked. There may be more than one gene in the same individual (polygneic inheritance) or different combinations of genes in different individuals (genetic heterogeneity).[4]

Asthma and atopy genes:[4]

11q13: (Atopy gene)

- It coincides with the gene for the high affinity IgE FC receptor (Fc...Rib). A variant of the receptor (Leu 181) is segregated with atopy when maternally inherited.
- This mutation increases signal transduction activity of the receptor causing increase in level of activation of mast cell releasing IL-4 leading to increased IgE synthesis.

Linkage to 5q 31-33 and (CK) gene cluster:

The linkage between the 5q 31-33 region and asthma attracted attention because the region is known to contain the gene encoding many of the cytokins that are thought to be important in the pathogenesis of atopic disease (e.g. IL-3, IL-4, IL-5, IL-9, and IL-13).[5]

Linkage to 14q and T cell antigen receptor on chromosomes 7 and 14:

- There is a linkage between the alpha region of the TCR locus and specific IgE responses.
- Polymorphism within TCR genes may limit an individual's ability to response to specific antigens.[5]

Asthma severity VS B_2-adrenergic receptor polymorphism[6]

B_2-adrenergic receptor is a candidate for NSBHR linkage. Mutations in B_2-adrenergic receptor gene do not play a major role in the pathogenesis of asthma but modulates severity of symptoms in affected individuals.

There could be a one point mutation; for example substitution of glycine for arginine at position 16. It correlates with more severe asthma as indicated by the use of steroids and immunization therapy. This mutation is

more prevalent in asthmatics with nocturnal asthma. At present, it is clear that the susceptibility to asthma is inherited but the specific genes responsible have yet to be identified. Most data suggests that asthma susceptibility is transmitted by multiple genes, with the variants features of the disease under independent genetic regulation, there is strong reason to believe that other genes modify asthma severity and its responsiveness to various treatment even thought they may not contribute to its causation. Identification of the genes that are primarily responsible is certain to lead to further revisions in specific conceptions of the diseases and ultimately to the development of far more effective strategies for prevention and treatment.[6]

Pathology of bronchial asthma

Chronic asthma is characterized by inflammation of the airway, with abnormal accumulation of eosinophils, lymphocytes, mast cells, macrophages, dendretic cells, and myofibroblasts. Inflammatory mediators and proteins secreted by these and other cells contribute directly and indirectly to change in airway structure and functions. The structural changes are found in both the epithelium and the submucosa and include abnormal deposition of collagen in the subepithelium and hyperplasia and/or hypertrophy of goblet cells, submucosal gland cells, smooth muscle cells, and blood vessel cells.[7]

Structural changes in the airway

-Epithelial changes

Epithelial desquamation or denudation is a pathogenic feature of asthma. There were several reports of epithelial damage and epithelial denudation in endobronchial biopsies from asthmatic subjects. In areas of

intact epithelium, squamous metaplasia has been described as pathogenic feature of asthma but it is not consistently mentioned in all pathologic studies. Goblet cell hyperplasia or hypertrophy is consistent feature of case reports or case series of patients with fatal asthma.[7]

-Eosinophilic inflammation

A pathologic hallmark of asthma is an increase in the numbers of activated eosinophils in the airway epithelium and submucosa. Eosinophil numbers are often increased in the peripheral blood, but peripheral blood eosinophilis is not as sensitive as sputum eosinophilia as an indicator of asthma.[8]

-Subepithelial changes

Increased amount of collagen type III and type V, as well as fibronectin and tenascin, are deposited immediately beneath the bronchial epithelium in the asthmatic airway. These structural proteins differ from typical basement membrane proteins such as collagen IV and laminin; therefore, the epithelial fibrosis of asthma is not a thickening of true basement membrane but rather a deposition of a layer of interstitial collagens immediately beneath it. The likely source of these structural proteins is myofibroblasts, which are increased in number in asthma.[9]

The number and size of the bronchial blood vessels are increased in asthma. These vessels may have an important role in regulating airway caliber; because an increase in vascular volume can swell the mucosa and narrow the airway lumen. Many inflammatory mediators cause vasodilatation, a response that may be accompanied by increased