Autologous Serum Skin Test (ASST) Reactivity In Asthma Patients; A Probable Link To The Role Of Autoimmunity In The Pathogenesis Of Non-Allergic Asthma

Thesis
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فاعلية اختبار حقن المصل المستمد من الشخص نفسه فى اثبات دور المناعة الذاتية فى باثولوجيا الربو الغير مسبب بالحساسية

رسالة

توطئة للحصول على درجة الماجستير فى أمراض الباطنة العامة

مقدمة من

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الملخص العربي

إن مرض حساسية الصدر يعد مشكلة كبري في العالم أجمع حيث يعاني منه اكثر من ثلثمائة مليون شخص. وقد قدرت منظمة الصحة العالمية عدد المرضي التي تتأثر حياتهم بالسلبية نتيجة الاعاقة الصحية التي يسببها مرض حساسية الصدر بحوالي خمس عشر مليون مريضا.

تمت هذه الدراسة علي 20 مريضا بمرض الربو المسبب بالحساسية و 20 مريضا بالربو الغير مسبب بالحساسية 20 شخص اصحاء وتم اختيار هؤلاء المرضي في مستشفيات جامعة عين شمس بالعيادات الخارجية.

هدف الرسالة هو دراسة فاعلية اختبار حقن المصل المستمد من الشخص نفسه في مرضي الربو المسبب والغير مسبب بالحساسية كاختبار مسحي لوجود اجسام مضادة ذاتية وذلك لاثبات دور المناعة الذاتية في باثولوجيا الربو الغير مسبب بالحساسية.

بمقارنة نتائج اختبار حقن المصل المستمد من الشخص نفسه بين مجموعتي الربو المسبب بالحساسية والربو الغير مسبب بالحساسية وجد أن هناك فارق إحصائي واضح.

أيضا أثبتت الدراسة عدم وجود فارق إحصائي بين المجموعتين من حيث نتائج معدلات (الاجسام المضادة للنواة) .

List of Abbreviations

AHR	: Airway hyper-responsiveness
ANA	: Antinuclear antibodies
APCs	: Antigen presenting cells
ASM	: Airway smooth muscle
ASST	: Autologous serum skin test
BAL	: Bronchoalveolar lavage.
BHR	: Bronchial hyper-responsiveness
CCL	: CC- chemokine ligand
CCR	: CC- chemokine receptor
CIU	: Chronic idiopathic urticaria
CXC	: Chemo taxis chemokine
CXCL	: Chemokine (C-X-C motif) ligand
CysLTs	: Cysteinyl leukotrienes
DCs	: Dendritic cells
EPR-3	: Expert Panel Report-3
FceR	: Fc receptor for IgE
FEV1	: Forced expiratory volume in one second
FVC	: Forced vital capacity
GINA	: Global Initiative For Asthma
GM-CSF	: Granulocyte macrophage-colony stimulating factor
15- HETE	: 15-hydroxyeicosatetraenoic acid
HMW	: High molecular weight
ICT	: Intracutaneous test
IFN- γ	: Interferon γ
IgE	: Immunoglobulin E
IL-4	: Interleukin 4
LMW	: Low molecular weight
LTRA	: Leukotriene receptor antagonists
LTs	: Leukotrienes
MCP	: Monocyte chemoattractant protein
MDAS	: Multiple drug allergy syndrome
MDC	: Macrophage Derived Chemokine
MHC	: Major Histocompatibility Complex

List of Abbreviations (Cont.)

MIP	: Macrophage Inflammatory Protein
NAAR	: Non-allergic asthma and rhinitis
NK cells	: Natural Killer cells
NKT cells	: Natural killer T cells
NO	: Nitric oxide
PAR	: Population attributable risk
PEF	: Peak expiratory flow
PG-E2	: Prostaglandin E2
PGs	: Prostaglandins
SCF	: Stem Cell Factor
SCG	: Sodium cromoglycate
SD	: Standard deviation
SLC	: Secondary Lymphoid Tissue Chemokine
SPT	: Skin prick test
TCR	: T cell receptor
TGF	: Transforming Growth Factor
Th1	: T helper type 1
Th2	: T-helper type 2
TNF α	: Tumor Necrosis factor α
VC	: Vital Capacity
WHO	: World Health Organization

List of contents

List of Figures

List of Tables

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First and foremost, thanks to ***God*** *who; gave me the ability to complete this work.*

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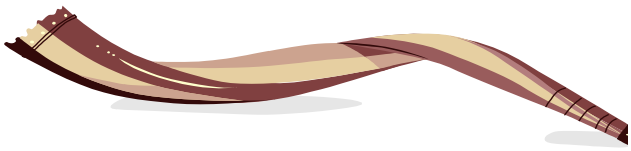

Omneya Mohamed Zeyada

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. Atopy appears to be an important host factor that predisposes individuals to developing asthma. The available epidemiological evidence suggests that the population-based proportion of asthma cases attributable to atopy is about 50%.

The results of several studies provide an indication that multiple immune reactions may be involved in the pathogenesis of asthma ***(Bartunková et al., 2009)***.

The other mechanisms apart from atopy remain to be clarified. Inflammatory alterations of respiratory airways have been found in patients with non-allergic asthma, but the triggering event has not been defined. An autoimmune activation of inflammatory cells has been hypothesized. Is there any pathogenic connection between asthma and autoimmunity. Although dysregulation of immune responses is involved in both asthma and autoimmunity, it had been accepted by most observers that disparate immune mechanisms are involved in asthma and most autoimmune disorders ***(Rottem et al., 2003)***.

Most cases of asthma are characterized by excessive activity of T-helper type 2 (Th2) lymphocytes and an eosinophil-predominant inflammatory reaction of the airways. In contrast, putative autoimmune disorders such as type I diabetes mellitus, rheumatoid arthritis, and certain inflammatory bowel diseases are thought to be mediated by Th1-type lymphocytes.

However, the relationship between asthma and autoimmunity may be more complex than it seems. The presence of increased levels of auto antibodies, sometimes

specific for a single tissue, is a hallmark of autoimmune disorders. Are such auto antibodies present in increased frequency in asthma? Some studies suggest that this does occur to a limited extent. Previous study found an incidence of antinuclear antibodies (ANA), generally in low titer, in 55% of patients with aspirin-induced asthma, 41% of those with non allergic asthma, 39% of those with allergic asthma, and 11% of normal controls ***(Tirosh et al., 2006).***

Intradermal injection of autologous serum in some patients can induce wheal and flare response. This observation had led to the recognition of circulating auto antibodies in chronic urticaria and provides the basis of autologous serum skin test (ASST). The demonstration of a positive ASST result led to the demonstration of functional auto antibodies. Autologous serum skin test is a screening test for histamine releasing auto antibodies ***(Sabroe et al., 1999)***.

Recent data indicate that the autologous serum skin test (ASST) shows a high rate of reactivity not only in chronic idiopathic urticaria (CIU) but also in cases with non-allergic asthma and rhinitis (NAAR), multiple drug allergy syndrome (MDAS) and even in some healthy people.

A positive reaction to the autologous serum skin test (ASST), reflecting the presence of auto antibodies capable to degranulate the mast cells, is regarded as a reliable in vivo diagnostic test in chronic urticaria patients .

Positive reaction to the (ASST) was associated with significant response to auto-hemotherapy.

An ASST reactivity is reported for the first time in allergy-like respiratory patients. Eighty-six percent of the pediatric patients and 61% of the adults having an allergy respiratory disease associated with an allergy-like condition had a positive ASST reactivity. A higher prevalence of

reactive subjects has been recorded in all the pediatric subsets without gender differences, whereas female reactivity is prevalent among adults ***(Mari, 2004).***

A recent work found that patients with intrinsic asthma are frequently positive on autologous serum skin test, a typical feature of at least one half of chronic urticaria patients; moreover, in some cases respiratory symptoms were associated with chronic urticaria ***(Asero and Madonini, 2006)***. These findings were confirmed by another study that found a prevalence of 58% of positive autologous serum skin test among non-allergic asthmatics vs. 0% in allergic controls ***(Tedeschi et al., 2005).***

Recent findings indicate that ASST is positive in about half patients with non-allergic asthma .ASST was positive in 29/55 non-allergic asthmatics (53%), whereas it was negative in all 30 control subjects. In addition, predominance of female sex and frequent ANA positivity are in line with an autoimmune basis of non-allergic asthma ***(Bergman et al.,2007)***.Other workers reported that 13 (27.7%) of asthma patients(allergic and non allergic) had a positive autologous serum skin test (ASST). Of them 8 (28.6%) were regarded as having autoimmune origin.

Aim of The Work

The aim of this thesis is to study autologous serum skin test (ASST) reactivity in non allergic versus allergic asthma patients (as a screening test for recognition of circulating auto antibodies) to verify the possibility of autoimmunity role in the pathogenesis of non allergic asthma.

Bronchial Asthma

Introduction :

Asthma is a common and complex respiratory disease that results from the interaction of genetic, environmental, social and psychological factors. In addition to the complex pathogenesis of asthma, the clinical expression is heterogeneous and may be subdivided into allergic, non-allergic, exercise-induced, and aspirin-sensitive asthma. The heterogeneous clinical expression can make the diagnosis of asthma difficult and may lead to misclassification. These factors may confound asthma research resulting in inaccurate reporting of asthma prevalence and morbidity. Despite these limitations, there are well-documented disparities among racial and ethnic groups with respect to asthma prevalence, mortality and drug response ***(Burchard et al., 2004; Choudhry et al.,2006; Barnes et al.,2007)***. It is a serious public health problem throughout the world, affecting people of all ages. When uncontrolled, asthma can place severe limits on daily life, and is sometimes fatal ***(GINA, 2009).***

Definition :

Asthma is a chronic lung disease characterized by airway inflammation, hyper responsiveness, remodeling, and obstruction ***(Busse et al., 2001)***. The lung phenotype in asthma is believed to be determined by the interaction of the environment with the patient's genetic background ***(Castro-Giner et al., 2006)*** .This interaction leads to dramatic change in the airway microenvironment that includes activation of inflammatory pathways, recruitment of immune cells that are not usually present in the airway, and a dramatic change in the phenotype resident cells ***(Karp et al., 2000)***. The involved immune cells include activated mast cells, eosinophils, T-lymphocytes, neutrophils, macrophages, and epithelial cells.