INTERFERON GAMMA AND INTERLEUKIN-5 RELATIONSHIP TO ASTHMA SEVERITY IN ATOPIC AND NON-ATOPIC CHILDREN AND ITS RELATIONSHIP WITH SOME PSYCHOSOCIAL FACTORS

Thesis submitted for Fulfillment of Ph.D.

In Childhood Studies

(Medical Department)

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Acknowledgments

At first and foremost thanks to "Allah' who gave me the power to finish this work.

I find no word by which I can express my deepest thanks and gratitude to my honored ***Prof. Dr. Tareef Hamza Salaam*** *Prof. of Clinical Pathology Faculty of Medicine, Ain shams university, for the continuous kind encouragement, support and guidance, he give me throughout the laboratory work. It has been an honour and privilege to work under his generous supervision.*

Also I would like to express my deepest thanks and appreciation to ***Prof. Dr. Khalid Hussein Taman****, Professor of Pediatrics, Institute of Postgraduate Childhood Studies (Department of Medical Studies) Ain Shams University, for his great support, valuable time, careful supervision and continuous advice, which helped me to overcome numerous difficulties.*

I am also deeply grateful and I would like to express my sincere thanks to ***Dr. Randa Kamal*** *Assistant Professor of Pediatrics, Institute of Postgraduate Childhood Studies, Ain Shams University, for her great help and support, continuous contributions, sincere guidance and helpful suggestions throughout this work.*

Last but not least, I would like to thank my patients who were the cornerstone of this study wishing them recovery

Safinaz Salah Eldin

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LIST OF ABBREVIATIONS

AHR:	Airway hyperresponsiveness
APR:	Acute phase response
ASM:	Atopic asthmatic sensitized
BAL:	Bronchoalveolar lavage
BRs:	Binding regions
CD:	Cluster of differentiation CD numbers are widely used to identify surface molecules in the immune septum
COPD:	Chronic obstructer pulmonary disease
CR:	Complement receptor
ECF:	Eosinophil chemotactic factor
ECP:	Eosinophil cationic protein
EIA NCF:	Exercise-induced asthma neutrophil chemotactic factor
EIA:	Exercise induced asthma
ELISA:	Enzyme linked-immunosorbent assay
$FEV_{1:}$	Forced expiratory volume in one second
gERD:	Gastroesophageal reflux disease
GM-CSF:	Granulocyte macrophage colony stimulating factor
HDM:	House dust mite
Hil-5:	Human interleukin-5
HLMC:	Human lung mast cell
HMW-NCA:	High molecular weight neutrophil chemotactic activity
IFN	Interferon gamma
IgE:	Immunoglobulin E
IL-4	Interleukin-4
IL-5	Interleukin-5
LPR:	Late phase response
LT:	Leukotrins
MBP:	Major Basic protein
MBP:	Major basic protein
MHC:	Major histocompatibility complex (3^{rd} element of immune system)
MPS:	Mononuclear phagocyte system
NCF:	Neutrophil chemotactic factor
NSDIDs:	Non-steroidal anti-inflammatory drugs
PAF:	Platelet activating factor
PBMC:	Peripheral blood mononuclear cell
RANTES:	Regulated on activation normal T-cell expressed and secreted
RAST:	Radioallergosorbant test
T_H2:	T-helper two cells
TMA:	Trimellitic anhydride
TNF:	Tumor necrosis factor
VCAM:	Vascular cell adhesion molecule

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INTRODUCTION

Allergic asthma is the most common chronic disease in children. Asthma is a chronic inflammatory disease of the airway in which mast cells, eosinophils and lymphocytes play a role. Atopic inflammation is primary triggered by excessive IgE-mediated release of mast cell mediators and has been linked to excess production of the T-helper 2, cytokines IL-4 and IL-5 relative to the gamma interferon. Total serum IgE levels are increased in the group with severe asthma or moderated compared with the normal control group ***(Nurse et al., 1997)***.

Atopy represents immunological hyper-responsiveness of the subject in which the reagenic antibodies are readily produced. Over-expression of the gene on long arm of chromosome number 5 in atopics stimulates the production of interleukin-4, interleukin-5, IgE and eosinophilis ***(Pitty, 1994)***.

IL-5 is the most specific cytokine for eosinophils; IFN-gamma has been shown to negatively regulate IL-4 and IL-5 production. Furthermore, information on the release of other cytokines from peripheral blood mononuclear cells (PBMC) of atopic individuals is limited ***(Nurse et al., 1997)***.

IL-5 producing allergen – specific T-cells are thought to play a prominent role in the pathogenesis of allergic inflammation. Multiple effector cells and their pro-inflammatory products are involved. Eosinophils are considered the pre-dominant cells in asthmatic inflammation ***(Denburge, 1996)***.

Elevated IL-5 production is a characteristic of allergen-specific peripheral blood CD+ T-cells from sensitized patients with active atopic disease but not inactive atopy per se ***(Till S, 1997)***.

A combined effect consisting of inhibition of IFN-gamma production and enhancement of IL-5 production was found during inflammation ***(Borgonvo B, 1998)***.

Atopy has been linked to an excess of the T-helper 2 cytokines IL-4 and IL-5 relative to the T-helper 1 cytokine and interferon gamma. Studies on peripheral blood mononuclear cells (PBMC) have shown decreased IFN-gamma release in patients with atopic dermatitis ***(Zepp F, 1997)***.

Studies on blood mononuclear cells have suggested that a defect in IFN-gamma secretion is a primary component of the atopic state. The defective IFN-gamma release is a generalized feature of atopic diseases; the extent of the defect in IFN-gamma release might be related to asthma severity ***(Nurse et al., 1997)***.

It is generally agreed that psychosocial factors per se do not play a primary causal role in asthma, but they can profoundly affect the severity of the condition and the success of treatment ***(Imatus, 1981)***. In some children asthma symptoms can be related to emotional stimuli such as excitement, fear or anger. Psychosocial problems ***(Strunk, 1987)*** and depression ***(Miller, 1987)*** can lead to poor self-management.

Aim of the Study

1. To evaluate IL-5 and IFN-gamma production by peripheral blood T-lymphocytes in atopic and non-atopic asthmatic children.
2. To investigate the relationship of IL-5 and IFN-gamma to asthma severity.
3. Relationship of some psychosocial factors.
4. Effect of environmental factors on asthmatic children concluded from the history.

REVIEW OF LITERATURE

Definition of Asthma

Asthma is the most common chronic disease of the childhood affecting 5% of children and 2% of adults ***(Mark Peakman, 1997)***.

Asthma can be defined operationally as a disorder characterized by variable airflow obstruction, airway hyperresponsiveness to specific and nonspecific stimuli, and symptoms of wheezing, chest tightness, cough and occasionally, dyspnea ***(Fish et al., 1998).***

Asthma is more likely a syndrome, one that comprises multiple disorders manifesting common symptoms but having distinct and probably different pathogenetic and etiologic mechanics. Phenotypic heterogeneity is evident not only in terms of the etiologic factors involved but also in terms of the severity and natural history of the disorder among different patients ***(Fish et al., 1998).***

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role particularly 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 airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli ***(Martinez et al., 1995).***

Epidemiology

Asthma is the most common chronic disease of childhood throughout the world .It can be a significant burden not only in terms of health care costs, but also decreased productivity and achievements and reduced participation in family and social life ***(Alfred P et al., 1998)***.

The prevalence of asthma among Egyptian children aged 3-5 years was estimated to be 8.2%. The prevalence varies in different parts of the world with values in the United States of about 3-5 % of all children and as high as 15% in Great Britain ***(Strachan DP et al., 1994)***.

Asthma morbidity and mortality rates continue to rise despite decades of improved understanding of the pathophysiologic processes and treatment of the disease. Of major concern is a 10 % annual increase in mortality ***(Strachan et al., 1994)***.

Epidemiologic. Physiologic, and social factors appear to be associated with an increased risk of asthma. These include poverty, air pollution, large family size, bad housing, increased crowding index, indoor smoking and exposure to different indoor allergens ***(El-Hefny et al., 1999)***.

Classification of Asthma

For many years, Asthma has been classified as extrinsic or intrinsic, depending on the suspected role of allergens as etiologic factors. By convention, atopic subjects are considered to have extrinsic asthma. However, this nomenclature has been used with diminishing frequency because it lacks sufficient discriminative power to aid in establishing an etiologic diagnosis or to help in defining treatment strategies ***(Ignacio-Garcia, 1995)***.

TABLE (1): Classification of Asthma Severity

	Symptoms	***Night time symptoms***	***Lung function***
Step 4: Severe persistent	• Continued symptoms • Limited physical activity • Frequent exacerbations	Frequent	FEV_1 or PEF <60% predicted
Step 3: Moderate persistent	• Daily symptoms • Daily use of inhaled short acting β2 agonist • Exacerbations >2 times a week – may last days	>1 time a week	FEV_1 or PEF >60% - 80% predicted PEF variability >30%
Step 2: Mild persistent	•Symptoms>2 times/week •Exacerbations may affect activity	2 times a month	FEV_1 or PEF >80% predicted PEF variability 20-30%
Step 1: Intermittent	•Symptoms <2 times a week •Asymptomatic and normal PEF between exacerbations •Exacerbations brief (from a few hours to a few days) •Intensity may vary	<2 times a month	FEV_1 or PEF >80% predicted PEF variability <20%

(Stephen, 1999)

Asthma covers a broad clinical spectrum, ranging from mild, readily reversible, bronchospasm, to severe chronic intractable obstruction to air flow**.** The disease is difficult to define since reversibility of airway obstruction may be impossible to demonstrate on certain occasions; for instance, the mild episodic asthmatic may be free of symptoms and have

normal lung function for prolonged periods of time, whereas in acute severe asthma, airways obstruction may take several days before any reversibility can be demonstrated ***(Kay, 1986)***.

The disease is almost invariably accompanied by some degree of nonspecific bronchial hyperreactivity but whether this is a primary feature or secondary to other factors such as bronchial inflammation remains uncertain. The presence of atopy, often defined by the presence of skin test sensitivity to aeroallergens, does not, by itself, indicate that allergens are the important triggers of asthma, since a large percentage of skin-sensitive persons report no allergic symptoms. Moreover, exercise and viral respiratory infections may play a more prominent role than allergens as triggers of symptoms in some atopic subjects ***(Kay, 1986)***.

Classifying patients, as having intrinsic asthma is problematic also, since it implies that all possible allergen in the environment have been excluded as etiologic factors a task that is nearly impossible to achieve**.** Although allergens are often triggers of acute asthma, there is a growing appreciation of their role as inducers of sub-clinical inflammation that may lead to enhanced airway responsiveness and greater susceptibility to the provocative effects of exercise and viral infections ***(Tollerud, 1991)***.

Attempts have been made to categorize severity of asthma on the basis of symptoms, impairment of activity, pulmonary function, degree of bronchial hyperreactivity, number of emergency visits, number of hospitalizations and medication use. Although there is no universal acceptance of formal severity designation a combination of subjective and objective criteria can be used as a guide to severity in individual patients. Severity of asthmatic symptoms can be ranked on the basis of duration throughout the day or night, as well as persistence throughout the week ***(Tarlo et al., 1998)***.

Restrictions of activity in asthmatic patients can be based on inability to work attend school, as well as how many days per week or month the