

LEVELS OF INTERFERON-GAMMA (INF- γ) AND INTERLEUKIN-4 (IL-4) IN NEONATES OF ASTHMATIC MOTHERS

Thesis

Submitted in fulfillment of
M. Sc. Degree in pediatrics

By

Enas M.T. Al-Sherbiny

(M.B.B.Ch)

Cairo University

Supervisors

Prof. Dr. Zahraa Ezz El-Din

Professor of Pediatrics

Faculty of Medicine – Cairo University

Prof. Dr. Nevine El Said El Helaly

Professor of Pediatrics

Faculty of Medicine – Cairo University

Dr. Eman Abdel Gahni Abdel Ghani

Lecturer of Pediatrics

Faculty of Medicine – Cairo University

Faculty of Medicine

Cairo University

2009

Acknowledgement

First and foremost, I would like to thank **Allah, the Most Gracious, and the Most Merciful**, for helping me to finish this work.

I wish to express my sincere gratitude to **Professeur Dr. Zahraa Ezz El-Din**, Professor of Pediatrics, Cairo University, for her moral support, kind supervision and valuable advise aiming at the perfection of this work.

I am greatly indebted to **Professeur Dr. Nevine El Said El Helaly**, prof. of pediatrics, Cairo University, for her continuous encouragement, support and meticulous supervision.

I am thankful to **Doctor Eman Abdel Ghani**, lecturer of pediatrics, Cairo University for her great effort to finish this work.

Finally, I want to offer my appreciation to every one support me to finish this work.

CONTENTS

Title	Page no
List of abbreviations	I
List of tables	IV
List of figures	VII
Introduction	1
Aim of the work	2
Allergy	3
-Allergy and pathogenesis of allergic diseases:	3
-The immunological basis of allergic disease	4
-Environmental and genetic factors affect the allergic	4
Components Of The Immune System.	5
-T cells	6
-Antigen-presenting cells: monocytes and macrophages	8
-Neutrophils	9
-Eosinophils	10
-Lymphocytes	11
-Cd4+ t cell activation	11
-Th1 and th2 helper cell subsets	14
-Role of cd4+ t cells in allergic disease	15
-Lymphocytes in asthma	16
-T helper type 2 cell	16
-T helper type 1 cells	17
-Basophils and mast cells	19
-Th1 vs. Th2 responses	19
Cytokines	23
-Cytokine profiles in human disease	24

-Cytokines and the immune system	25
-Cytokines and wheezing child	28
Interferon	29
-Interferon- γ	30
Atopy	33
-New thoughts regarding the genetics of atopy	34
Common atopic diseases	38
Bronchial asthma	38
-Definition	39
-Epidemiology of asthma	40
-Risk factors for developing asthma in the pediatric patient	43
-Genetics of asthma	45
- Maternal fetal immunological interactions and childhood asthma	47
-Classification of asthma	51
-Classification of asthma severity	52
-Levels of asthma control	53
-Diagnosis of asthma	54
-Measurements of lung function	54
-Diagnostic challenges and differential diagnosis	54
Children 5 years and younger	51
-Classification of asthma severity 0-4 years of age	56
- Lines of tretment	58
-Inhaled glucocorticosteroids	58
-Leukotriene modifiers	58
-Long-acting inhaled β 2-agonists	59
-Preventive strategies of allergic diseases	60

-Prevention of asthma	62
Atopic dermatitis	71
A. Pathogenesis	71
B. Diagnosis	71
C. Management	72
Allergic rhinitis	75
i. Classification	75
ii. Epidemiology	76
iii. Pathology	76
iv. Treatment	76
Food allergy	78
i. Definition	78
ii. Risk factors	78
iii. Prevalence	79
iv. Diagnosis	79
v. Evaluation Of The Food Allergic Patient	80
vi. Management of the food allergic patient	81
vii. Future directions	81
Subjects and methods	83
Results	91
Discussion	123
Summary and conclusion	139
Recommendations	142
References	143
Arabic summary	189

LIST OF ABBREVIATIONS

AD	Atopic dermatitis.
AD	Autosomal dominant.
APC	Antigen presenting cells.
API	Allergy Predictive Index
BAL	Broncho-alveolar Savage.
BHR	Bronchial hyper-responsiveness.
CAMP	Cyclic adenosine monophosphate
CB25	Cluster of differentiation 25 positive.
CBMC	Cord blood mononuclear cells.
CD23	Cluster of differentiation 23 positive.
CD28	Cluster of differentiation 28 positive.
CD4+	Cluster of differentiation 4 positive.
CD8+	Cluster of differentiation 8 positive.
CTL	Cytotoxic lymphocyte cell.
DBPCFC	Double blind placebo controlled food challenge.
DNA	Desoxyribonucleic acid.
E.T.I	Endothelln-l
ECP	Eosinophil cationic protein.
FCeRIJ	High affinity receptor for Ig E.
FCsRIB	High affinity receptor for Ig E.
FEV1	Forced expiratory volume in one second.
GALT	Gut associated lymph tissue.
GINA	Global Initiative for Asthma
GM-C3F	Granulocyte macrophage colony stimulating factor.
HDM	House dust mite.
HIV	Human immunodeficiency virus.

Abbreviations

HLA	Human lymphocyte antigen.
ICAM-1	Intercellular adhesion molecule - 1.
IFN-γ	Intereferon gamma
IgA	Immunoglobulin A.
IgG	Immunoglobulin G.
IgM	Immunoglobulin E.
IL	Interleukin
LAR	Late asthmatic reaction.
LFA-1	Leucocytes expressing the integren-1.
LPR	Late phase reaction.
LPS	Lipopolysaccharide.
LTC4	Leukotrein C4
LTD4	Leukotrein D4
LTE4	Leukotrein E4
M-CSF	Monocyte colony stimulating factor.
MCT	Mast cell tryptase.
MCTC	Mast cell tryptase chymase.
MHC	Major histocompatibility complex.
m-RNA	Messenger RNA.
NIH	National Institute of Health
NK	Natural killer cells.
OVA	Ovalbumm
PAF	Platelet activating factor.
PBMC	Peripheral blood mononuclear cell.
PEAK	Prevention of Early Asthma in Kids
PGD2	Prostaglandin D2
PGE2	Prostaglandin E2
PGF2a	Prostaglandin F2 alpha.

Abbreviations

PHA	Phytohaemagglutinin.
PIV	Para influenza Virus
PST	Prick skin test
RANTES	Regulated on activation normal T-cell expressed and secreted.
RAST	Radioallergo- Sorbant test.
RSV	Respiratory syncytial virus.
S. IgA	Secretory immunoglobulin A.
SCF	Stem cell factor.
SEE	Staphylococcal Enterotoxin E.
TCR	T cell receptor.
TGFB	Transforming growth factor B.
Th1	T helper 1.
Th2	T. helper 2.
TNF α	Tumor necrosis factor alpha
VCAM-1	Vascular cell adhesion molecule one
VLA-4	Very late antigen 4.
VLA4 - VCAM	Very late antigen 4 vascular cell adhesion molecule.

LIST OF TABLES

Table No.	Content	Page
Table 1-1	Diseases Caused by T cells producing inappropriate profiles of Cytokines	14
Table 1-2	properties of different cytokines	26
Table 1-3	Definition of asthma	39
Table 1-4	Prevalence of Rhinoconjunctivitis, recent wheeze and Physician-diagnosed asthma in the Middle East and the UK	41
Table 1- 5	API and Modified API Criteria	44
Table 1- 6	Classification of asthma severity by clinical features before treatment.	
Table 1-7	Levels of Asthma Control	49
Table 1-8	Classification of Asthma Severity 0-4 years of age	52
Table 1-9	Effectiveness of Avoidance Measures or Some Indoor Allergens	61
Table 2-1	Individual Clinical Data of Group "A" (High risk group).	88
Table 2-2	Sex Distribution among neonates of Group "A" high risk group.	89
Table 2-3	Birth weight distribution among neonates of Group "A" high risk group.	90
Table 2-4	precipitating Factors of Asthma Symptoms in atopic Mothers of Group "A" study Group.	92
Table 2-5	Individual Clinical data of Group "B" Control Group with No family history of	94
Table 2-6	Sex Distribution among neonates of Group "B"	95

Tables

Table 2-7	Birth weight Distribution among of Group "B"	96
Table 2-8	The Mean birth weight of the two groups (A and B)	97
Table 2-9	Blood count of atopic mothers (group A).	98
Table 2-10	Blood counts the non atopic mothers (group B) control group.	99
Table 2-11	Blood Counts of (High risk neonates group A).	100
Table 2-12	Blood counts of neonates of control Group "B" with no family history of atopy (Low risk group)	101
Table 2-13	The mean eosinophilic count both in atopic mothers (group A) and non atopic mothers (group B).	102
Table 2-14	The mean eosinophilic count in, both high risk (group A) and in low risk neonates (group B).	103
Table 2-15	Immunoglobulin "E" Levels in High risk group (A) for both mothers and neonates.	104
Table 2-16	The mean values of Immunoglobulin "E" levels in mother of both groups ("A" high risk and "B": low risk).	105
Table 2-17	The mean value of Immunoglobulin "E" in neonates of both groups ("A" high risk and "B" low risk).	106
Table 2-18	Immune profile of atopic mothers (group A).	107
Table 2-19	Immune profile of high risk neonates (group A).	108
Table 2-20	Immune profile of non atopic mothers with no family history of atopy (Group B).	109
Table 2-21	Immune profile of low risk control neonates (group B)	110
Table 2-22	Comparative study of mean CD4 levels among mothers of the two groups. (A "atopic mother" and B non atopic).	111

Tables

Table 2-23	The Mean CD4 levels among neonates of the two groups (A "high risk" and B "low risk" group)	112
Table 2-24	The mean value of (Th1) expressing INF- γ in mothers of both groups ("A" atopic and "B" non atopic)	113
Table 2-25	The Mean (Th1) expressing IFN- γ among neonates of the both groups ("A" high risk and "B" low risk).	114
Table 2-26	The mean value of (Th2) expressing in mother of both groups ("A" Atopic and "B" non atopic).	115
Table 2-27	The mean value of Th2 expressing IL4 in high risk neonates (A) and low risk neonates (B)	116
Table 2-28	The mean value of Th0 expressing both IFN- γ and IL-4 in mothers of both groups (A&B)	117
Table 2-29	The mean value of (Th0) expressing both IFN- γ and IL-4 in neonates of the both groups ("A" high risk and' "B" low risk).	118

LIST OF FIGURES

Figure No.	Content	Page
Figure 1-1	Components of the Immune System.	5
Figure 1-2	T Cells Maturation	7
Figure 1-3	Generation of T helper types 1, 2, and 17	13
Figure 1-4	Differentiation of T Cells	21
Figure 1-5	Asthma Prevalence and Mortality	42
Figure 1-6	Materno-placento-fetal interaction	48
Figure 1-7	The consequence of protection of the pregnancy	49
Figure 1-8	Factors counter balance the drive to a fully committed Th2 response to allergens in the fetus	50
Figure 2-1	Maternal age distribution among Group "A" study group.	89
Figure 2-2	Sex Distribution among neonates of Group "A"	89
Figure 2-3	Birth weight distribution among neonates of Group "A"	90
Figure 2-4	Precipitating Factors of Bronchial asthma in atopic mothers (group A).	92
Figure 2-5	Maternal age distribution among group "B" control group	95
Figure 2-6	Sex Distribution among neonates of Group "B"	95
Figure 2-7	Birth weight Distribution among of Group "B"	96
Figure 2-8	The Mean birth weight of the two groups (A and B)	97
Figure 2-9	The mean eosinophilic count both in atopic mothers (group A) and non atopic mothers (group B).	102
Figure 2-10	The mean eosinophilic count in, both high risk	103

(group A) and in low risk neonates (group B).

Figure 2-11	The mean values of Immunoglobulin "E" levels in mother of both groups ("A" high risk and "B": low risk).	105
Figure 2-12	The mean value of Immunoglobulin "E" in neonates of both groups ("A" high risk and "B" low risk).	106
Figure 2-13	Comparative study of mean CD4 levels among mothers of the two groups. (A "atopic mother" and B non atopic).	111
Figure 2-14	The Mean CD4 levels among neonates of the two groups (A "high risk" and B "low risk" group)	112
Figure 2-15	The mean value of (Th1) expressing INF- γ in mothers of both groups ("A" atopic and "B" non atopic)	113
Figure 2-16	The Mean (Th1) expressing IFN-y among neonates of the both groups ("A" high risk and "B" low risk).	114
Figure 2-17	The mean value of (Th2) expressing in mother of both groups ("A" Atopic and "B" non atopic).	115
Figure 2-18	The mean value of Th2 expressing IL4 in high risk neonates (A) and low risk neonates (B)	116
Figure 2-19	The mean value of Th0 expressing both IFN- γ and IL-4 in mothers of both groups (A&B)	117
Figure 2-20	The mean value of (Th0) expressing both IFN- γ and IL-4 in neonates of the both groups ("A" high risk and' "B" low risk).	118

INTRODUCTION

In the last decade, cytokines, which are low molecular weight glycoproteins produced by immune as well as nonimmune cells, have captured the attention of the scientific and clinical communities.

In young children at risk for asthma or allergy, decreased allergen-induced IFN-gamma secretion is associated with atopic disease and, in some cases, with increased IgE levels. Increased allergen-induced IL-13 secretion is most strongly associated with early life increase of IgE (*Contreras JP et al, 2003*).

IFN- γ supports differentiation of "allergy protective" Th1 cells and antagonizes the development of Th2 cells (*Gajewski et al, 1988; Maggi et al 1992; Demeure et al, 1997*).

Cytokine disturbances, especially increased interleukin-4 (IL-4) and/or decreased interferon-gamma (IFN- γ), are considered to be a major factor responsible for allergy development. IL-4, a major pro-allergic cytokine, promotes the differentiation and activation of Th2 lymphocytes. IL-4 has also been found to suppress the Th1 population and IFN- γ production, thus emphasizing the great role of the IL-4 receptor (IL-4R) on Th cells in the development of allergy (*Romagnani S, 2004*).

IL-4R-dependent over-signaling in newborns' monocytes and Th lymphocytes could contribute to Th₁/Th₂ imbalance. IL-4R over expression on newborns' monocytes and lymphocytes could be an early risk marker of allergy development (*Grzela K et al, 2007*).

AIM OF THE WORK

In the past 20-30 years, there has been a progressive increase in the prevalence of allergic diseases, in particular atopic asthma, with an associated increase in management costs.

Primary Prevention aims to identify at risk individuals at an early stage and to begin prophylactic therapy to prevent development of chronic disorders.

For this purpose we aim in this work to measure the level of Interferon gamma (IFN- γ) and its producing Th1 cell and Interleukin-4 (IL-4) and its producing cell in neonates at high and low genetic risk of atopy. This is done in an attempt to find an accurate test that early predict atopy for early prevention and better prognosis.