



Assessment of Serum and Tissue Level of Interleukin 33 in Patients with Atopic Dermatitis

Thesis

*Submitted for Partial Fulfillment of the Master Degree in
Dermatology, Venereology and Andrology*

By

Engy Aly Eldean Yehia Ibrahim

M.B.B.CH. Faculty of Medicine - Ain Shams University 2012

Under the Supervision of

Prof. Dr. Rania Adel Lotfy

*Professor of Dermatology, Venereology and Andrology
Faculty of Medicine - Ain Shams University*

Dr. Ahmed Abdel Fattah Afify

*Lecturer of Dermatology, Venereology and Andrology
Faculty of Medicine - Ain Shams University*

*Faculty of Medicine
Ain Shams University
2018*

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا انك لا تعلم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgment

*First and foremost, I feel always indebted to
ALLAH, the Most Kind and Most Merciful.*

*I'd like to express my respectful thanks
and profound gratitude to **Prof. Rania
Adel Lotfy**, Professor of Dermatology,
Venereology and Andrology, Faculty of
Medicine- Ain Shams University for her keen
guidance, kind supervision, valuable advice and
continuous encouragement, which made
possible the completion of this work.*

*I am also delighted to express my deepest
gratitude and thanks to **Dr. Ahmed Abdel
Fattah Afify**, Lecturer of Dermatology,
Venereology and Andrology, Faculty of
Medicine, Ain Shams University, for his kind
care, continuous supervision, valuable
instructions, constant help and great assistance
throughout this work.*

*I would like to express my hearty thanks
to all **my family** for their support till this
work was completed.*

*Last but not least my sincere thanks and
appreciation to all patients participated in this
study.*

Engy Aly

List of Contents

Title	Page No.
List of Tables	i
List of Figures	ii
List of Abbreviations	iv
Introduction	1
Aim of the Study	4
Review of Literature	
📖 Atopic Dermatitis	5
📖 Pathogenesis of Atopic Dermatitis	49
📖 Interleukin 33	82
Patients and Methods	94
Results	102
Discussion	116
Conclusion	121
Recommendations	122
Study Limitations	123
Summary	124
References	127
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	Hanifin-Rajka criteria for AD.....	19
Table (2):	The area score	25
Table (3):	Severity score	25
Table (4):	Four signs of eczema used to calculate EASI severity score	26
Table (5):	Recording the EASI score	27
Table (6):	Selected cytokines and their primary activities....	84
Table (7):	Interleukin 1 family members and their propereties	87
Table (8):	IL-33 in skin diseases.....	90
Table (9):	Comparison between cases and controls as regard age and sex	102
Table (10):	Comparison between cases and controls regarding IL-33 level	105
Table (11):	Relation between sex, personal history of atopy, family history and tissue IL-33 level among cases	106
Table (12):	Relation between sex, personal history of atopy, and family history of atopy and serum IL-33 level among cases	107
Table (13):	Correlation between EASI score, age, duration of the disease and IL-33 among cases.....	109
Table (14):	Relation between serum & tissue IL-33 level and disease severity.....	111
Table (15):	Mild cases vs moderate cases regarding tissue IL-33 level & serum IL-33 level	114
Table (16):	Moderate cases vs severe cases regarding serum IL-33	115

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Infantile atopic dermatitis	8
Figure (2):	Childhood atopic dermatitis.....	9
Figure (3):	Dirty neck sign in adult atopic dermatitis	9
Figure (4):	Pityriasis alba on the face	11
Figure (5):	Chronic atopic dermatitis of eyelids.....	12
Figure (6):	Dennie-Morgan lines	13
Figure (7):	Allergic shiners	13
Figure (8):	Periorbital milia as a sign of AD.....	14
Figure (9):	Marked palmer hyperlinarity as a phenotypic marker of AD	15
Figure (10):	Staphylococcal infection in AD.....	16
Figure (11):	Eczema herpeticum.....	17
Figure (12):	Histologic features of acute eczema	30
Figure (13):	Histologic features of subacute eczema.....	30
Figure (14):	Histologic features of chronic eczema.....	31
Figure (15):	Schematic of the immune response in AD skin lesions	54
Figure (16):	Model of sequential T helper cell involvement in AD	68
Figure (17):	Role of Tregs in AD	70
Figure (18):	The role of eosinophils in AD.....	76
Figure (19):	Sequential steps of leukocyte extravasation and the various tethering and adhesion molecules, chemokines, and receptors involved.....	79

List of Figures (cont...)

Fig. No.	Title	Page No.
Figure (20):	Cytokine network	83
Figure (21):	Potential role of IL-33 and ST2 (suppression of tumorigenicity 2) in skin inflammation and pathophysiology of atopic dermatitis.....	93
Figure (22):	Description of risk factors among cases of AD.....	103
Figure (23):	Description of disease severity among cases according to EASI score.	104
Figure (24):	Relation between tissue IL-33 and disease severity.	112
Figure (25):	Relation between serum IL-33 and disease severity.	112
Figure (26):	ROC curve for serum and tissue IL-33 in differentiation between mild and moderate cases of AD.....	114
Figure (27):	ROC curve for serum IL-33 in differentiation between moderate and severe cases of AD.....	115

List of Abbreviations

Abb.	Full term
<i>AD</i>	<i>Atopic Dermatitis</i>
<i>AMPS</i>	<i>Antimicrobial Peptides</i>
<i>AZA</i>	<i>Azathioprine</i>
<i>BB</i>	<i>Broadband</i>
<i>c-AMP</i>	<i>Cyclic Adenosine Monophosphate</i>
<i>CIU</i>	<i>Chronic Idiopathic Urticaria</i>
<i>CYA</i>	<i>Cyclosporine</i>
<i>DDC</i>	<i>Dermal Dendritic Cell</i>
<i>EASI</i>	<i>Eczema Area and Severity Index</i>
<i>EDC</i>	<i>Epidermal Differentiation Complex</i>
<i>ESL</i>	<i>E-selectin Ligand</i>
<i>FLG</i>	<i>Fillaggrin Gene</i>
<i>HDM</i>	<i>House Dust Mite</i>
<i>HSPG</i>	<i>Heparan Sulfate Proteoglycan</i>
<i>HSV</i>	<i>Herpes Simplex Virus</i>
<i>IDEC</i>	<i>Inflammatory Dendritic Epidermal Cell</i>
<i>IEDC</i>	<i>Inflammatory Epidermal Dendritic Cell</i>
<i>IL</i>	<i>Interleukin</i>
<i>INF-α</i>	<i>Interferon Gamma</i>
<i>INF-β</i>	<i>Interferon Beta</i>
<i>INF-γ</i>	<i>Interferon Gamma</i>
<i>JAK</i>	<i>Janus Kinase</i>
<i>JAM</i>	<i>Junctional Adhesion Molecules</i>
<i>KC</i>	<i>Keratinocyte</i>
<i>LC</i>	<i>Langerhans Cell</i>
<i>LFA</i>	<i>Leukocyte Function-Associated Antigen</i>
<i>MCC1</i>	<i>Mast Cell Chymase 1</i>

List of Abbreviations (cont...)

Abb.	Full term
<i>MCV</i>	<i>Molluscum Contagiosum Virus</i>
<i>MED</i>	<i>Minimal Erythema Dose</i>
<i>MHC</i>	<i>Major Histocompatibility Complex</i>
<i>MMF</i>	<i>Mycophenolate Mofetil</i>
<i>MTX</i>	<i>Methotrexate</i>
<i>NB</i>	<i>Narrowband</i>
<i>NF</i>	<i>Nuclear Factor</i>
<i>NMF</i>	<i>Natural Moisturizing Factor</i>
<i>NPs</i>	<i>Neuropeptides</i>
<i>PAR-2</i>	<i>Protease Activated Receptor-2</i>
<i>pDCs</i>	<i>Plasmacytoid DCs</i>
<i>PDE</i>	<i>Phosphodiesterase Enzyme</i>
<i>PDE4</i>	<i>Phosphodiesterase Type 4</i>
<i>PECAM-1</i>	<i>Platelet / Endothelial Cell Adhesion Molecule 1</i>
<i>PML</i>	<i>Progressive Multifocal Leukoencephalopathy</i>
<i>PSGL</i>	<i>P-Selectin Glycoprotein Ligand</i>
<i>PUVA</i>	<i>Psoralen plus UVA</i>
<i>RAST</i>	<i>Radioallergosorbent Test</i>
<i>S.aureus</i>	<i>Staphylococcus Aureus</i>
<i>SCCE</i>	<i>Stratum Corneum Chymotryptic Enzyme</i>
<i>ST2</i>	<i>Supression of Tumorigenicity 2</i>
<i>TCI</i>	<i>Topical Calcineurin Inhibitors</i>
<i>TCR</i>	<i>T- Cell Receptor</i>
<i>TCS</i>	<i>Topical Corticosteroids</i>
<i>TGF α</i>	<i>Tissue Growth Factor Beta</i>
<i>Th</i>	<i>T helper</i>
<i>TIM-1</i>	<i>T-cell Immunoglobulin Domain and Mucin Domain 1</i>

List of Abbreviations (cont...)

Abb.	Full term
<i>TNF</i>	<i>Tumor Necrosis Factor</i>
<i>TNF-α</i>	<i>Tumour Necrosis Factor Alpha</i>
<i>TSLP</i>	<i>Thymic Stromal Lymphopoietin</i>
<i>VCAM-1</i>	<i>Vascular Cell Adhesion Molecule-1</i>
<i>VIP</i>	<i>Vaso Active Intestinal Peptide</i>
<i>VLA</i>	<i>Very Late Antigen</i>
<i>WWT</i>	<i>Wet-Wrap Therapy</i>

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by an early T helper type 2 (Th2) immune response in which patients suffer from relapsing eczematous and occasionally generalized lesions associated with severe pruritus (**Bonness and Bieber, 2007 & Boguniewicz and Leung, 2011**). Scratching reactions to pruritus typically exacerbate the inflammatory skin reactions (**Hong et al., 2011**).

The key events in AD may be subdivided as an interplay among infiltrating immune cells (Th2 cells and later Th1 cells, macrophages, dendritic cells, mast cells, and eosinophils), skin-resident keratinocytes & endothelial cells and activated peripheral sensory nerves. The multicellular action is believed to orchestrate disease onset and progression (**Steinhoff et al., 2006 & Cevikbas et al., 2007**).

Interleukin (IL)-33 is a recently described member of the IL-1 family (**Schmitz et al., 2005**), which has been shown to induce the production of Th2 cytokines (IL-4, IL-5 and IL-13), and exerts its effects by activating the suppression of tumorigenicity 2 (ST2) receptor on different type of cells, including mast cells and Th2 cells (**Chackerian et al., 2007**).

IL-33 is a nuclear cytokine released by the epithelial cells in various tissues and organs, including keratinocytes, endothelial cells, and immune cells, and by necrotic structural cells, as fibroblast or keratinocytes (*Chackerian et al., 2007 & Liew et al., 2010*).

IL-33 has been described as an epithelial “alarmin” defense system, released upon cellular damage through the activation of various immune cells through its ST2 receptor, which leads to the production of various molecules (*Allakhverdi et al., 2007; Ohno et al., 2012; Gangemi et al., 2013 & Vocca et al., 2015*).

The IL-33 induced production of proinflammatory cytokines is a critical event that aggravates atopic diseases, playing an important role as a bridge between innate and adaptive immune responses in allergic diseases (*Lloyd, 2010 & Vocca et al., 2015*).

Savinko et al. (2012) investigated the expression profiles of IL-33 and ST2 in different mouse models of atopic-like dermatitis, emphasizing a regulatory role for this novel cytokine pathway. Different allergens, when applied topically (ovalbumin, house dust mites, or staphylococcal enterotoxin B) to mice, led to the upregulation of IL-33 and ST2 messenger RNA expression. These results indicate that IL-33 as well as its

receptor may be induced in AD when exposed to AD trigger factors. Whether these results reflect the human situation remains unknown and needs further evaluation.

Tamagawa-Mineoka et al. (2014) measured serum level of IL-33 in patients with AD for quantitative detection of IL-33 and found that serum level of IL-33 is significantly elevated in patients with AD compared with healthy control subjects. Serum IL-33 level was significantly associated with the disease severity of AD. These findings suggest that IL-33 released from mechanically injured or barrier-disrupted skin may increase inflammation in AD.

AIM OF THE STUDY

To quantify serum and tissue IL-33 level in patients with AD and to correlate its level with the disease severity.

Chapter 1

ATOPIC DERMATITIS

Atopy is defined as a genetically determined state of hypersensitivity to environmental allergens. AD is a common, complex and chronic inflammatory skin disorder characterized by eczema, pruritus and cutaneous hyper-reactivity to allergic, irritant or microbial triggers, and affected individuals suffer significant morbidity (*Vickery, 2007*).

The word atopic comes from atopy, which is derived from a Greek word (atopos) that means “out of place” (*Gale, 2006*).

AD has been given many other names like "Besnier prurigo", "neurodermitis", "endogenous eczema", "flexural eczema", "infantile eczema" and "prurigo diathesique" (*Abels and Proksch, 2006*).

Incidence and Prevalence:

The lifetime prevalence of AD is 10-20% in children and 1-3% in adults (*Leung et al., 2004*).

The prevalence of AD is higher in children of cold countries, 19.7% in Norwegian children (*Selnes et al., 2002*), 22.9% in Danish children, 13.1% in German children, 15.5% in Sweden children (*Larsen et al., 1996*), 11.5-14% in English children (*William, 1995*) and 9.5-24% in Japanese children (*Sugiura et al., 1997*). In contrast, in children of hot countries like Tanzania the prevalence of AD is only 0.7% (*Henderson, 1995*).