Study of Serum IL-31 level in Patients of Urticaria & its Relation to Disease Severity

Thesis
Submitted for partial fulfillment of master degree in Dermatology and Venereology

By Noha Mostafa El-Maleh

M.B.B.Ch Faculty of Medicine-Ain Shams University

Under Supervision of

Prof. Dr. Nehal Mohamed Zu El Fakkar

Professor of Dermatology and Venereology Faculty of Medicine – Ain Shams University

Dr. Nermeen Samy Abdel Fattah

Assistant Professor of Dermatology and Venereology Faculty of Medicine – Ain Shams University

Dr.Eman Saleh El Hadidi

Assistant Professor of Clinical pathology Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2014

Acknowledgement

First and foremost thanks to Allah, who is behind every success.

I wish to express my deep appreciation and gratitude to **Dr. Nehal Mohamed Zu El Fakkar** Professor of Dermatology, Venereology & Andrology, Faculty of Medicine, Ain Shams University for her great help and continuous encouragement throughout whole research.

I am especially grateful to **Dr. Nermeen Samy Abdel Fattah**, Assistant Professor of Dermatology, Venereology & Andrology, Faculty of Medicine, Ain Shams University for her willing assistance, patience, guidance and encouragement during this study.

I am especially grateful to **Dr.Eman Saleh El Hadidi**, Assistant Professor of clinical pathology, Faculty of Medicine, Ain Shams University for her willing assistance during the course of this study.

Abbreviations

ACD	Allergic contact dermatitis
ACEI	ACE inhibitors
ACU	Autoimmune chronic urticaria
AD	Atopic dermatitis
ANA	Anti-nuclear antibody
AU	Acute Urticaria
CBC	Complete blood count
cDNA	Complimentary DNA
CIC	Circulating immune complex
CNTF	Ciliary neurotrophic factor
CRP	C-reactive protein
CT-1	Cardiotrophin-1
CIU	Chronic idiopathic urticaria
CU	Chronic urticaria
DPU	Delayed pressure urticaria
EACA	ε-Aminocaproic acid
EGF	Epidermal growth factor
ESR	Erythrocyte sedimentation rate
Fcε RI	High-affinity receptor for IgE
FcR	Fc portion of Igs
G6PD	Glucose-6-phosphate dehydrogenase
GLM-R	Gp130-like monocyte receptor

Gp130	Glycoprotein 130
HPC	Hematopoietic progenitor cells
HS	Hypersensitivity
IEC	Intestinal epithelial cell
IL	Interleukin
IL-31	Interleukin 31
IL-31Rα	IL-31 receptor alpha
ITAM	Immune recognition receptor tyrosine-based activation motif
LIF	Leukaemia inhibitory factor
LIFR-like	Leukemia inhibitory factor receptor-like
LPS	Lipopolysaccharides
LTRA	Leukotriene receptor antagonists
MCP-1	Monocyte chemoattractant protein-1
MCP-3	Monocyte chemoattractant protein-3
MMPS	Matrix metalloproteinases
MPC	Myeloid progenitor cells
NSAID	Nonsteroidal anti-inflammatory drugs
OSMR	Oncostatin M receptor
OSMRβ	Oncostatin M receptor beta
PBMC	Peripheral blood mononuclear cells
PUVA	Phototherapy with UV light
SEMF	Subepithelial myofibroblasts
SIgE	Serum immunoglobulin E

STAT-3	Signal transducer and activator of transcription 3
TNF-α	Tumor necrosis factor -α
VEGF	Vascular endothelial growth factor

Table of Contents

	Title	Page No.
INTRODUCTION		1
AIM OF THR WORK		4
REVIEW OF LITERATURE		
Chapter 1: Urticaria		5
D	Definition	5
Н	Iistory	6
E	pidemiology	6
M	Mortality & Morbidity	7
Pa	athogenesis	8
C	Clinical picture	23
C	Classification	28
C	Causes	30
D	Diagnosis	33
Ti	reatment	35
Chapter 2: Interleukin-31		
D	Definition	51
D	Discovery of IL-31 and IL-31 receptors	52
С	Characterization of IL-31 receptors	53
В	Biological activities of Interleukin-31	56
R	cole of IL-31 in diseases	58
S	ummary	62
Chapter 3: Interleukin 3	1 & chronic urticaria	
Ir	ntroduction	64
R	cole of anti IL-31 in treatment of CU	66
SUBJECTS AND METHODS	-	68
RESULTS	-	75
DISCUSSION		91
CONCLUSION AND RECOMM	MENDATIONS	96
SUMMARY		98
REFERENCES		100

List of Figures

Fig. No.	Title	Page No.
1	Immunological and nonimmunological activation of mast cells	10
2	Interleukin-31 is produced mainly by activated CD4+ T cells, and targets a broad range of cells expressing IL-31RA and OSMR. Monocytes express IL-31RA and OSMR when activated by IFN-γ and LPS. Expression of both receptor units is found in many tissues	55
3	Interleukin-31 produces a number of biological effects, and causes several diseases when over-expressed	63
4	Correlation between disease severity and IL-31 among group 1(AU).	89
5	Correlation between disease severity and IL-31 among group 2(CU).	90

List of Tables

Table No.	Title	Page No.
1	Clinical classification of urticaria and angioedema	29
2	Patient's and investigator's rating scale of symptom severity	71
3	Personal characteristics of group 1 of patients	76
4	Personal characteristics of group 2 of patients	76
5	Personal characteristics of group 3 of controls.	77
6	Personal characteristics of group 4 controls	78
7	Comparison between cases and controls as regards sex	78
8	Comparison between cases and controls as regards age	79
9	Comparison between cases and controls as regards occupation	79
10	Urticaria severity among cases	80
11	IL-31 level among cases	81
12	IL-31 level among controls	81
13	Comparison between Cases and controls as regards the mean IL31	82
14	Comparison between the four studied groups as regards the mean IL 31 using analysis of variance test ANOVA testing	83
15	Comparison between the four studied groups as regards the mean IL 31 using Non parametric testing Krsukhal Wallis testing	84
16	Comparison between AU and CU patients as regard IL-31	85
17	Comparison between AU and AD patients as regard IL-31	85
18	Comparison between AU and normal as regard IL-31	86
19	Comparison between CU and AD as regard IL-31	86
20	Comparison between CU and normal as regard IL-31	87
21	Comparison between cases with different disease severity as regard IL-31 among group 1(AU)	87
22	Comparison between cases with different disease severity as regard IL-31 among group 2(CU)	88
23	Spearman correlation coefficient between severity of disease and IL 31 in group I(AU)	88
24	Spearman correlation coefficient between severity of disease and IL 31 in group II(CU)	89

Abbreviations

ACD	Allergic contact dermatitis
ACEI	ACE inhibitors
ACU	Autoimmune chronic urticaria
AD	Atopic dermatitis
ANA	Anti-nuclear antibody
AU	Acute Urticaria
CBC	Complete blood count
cDNA	Complimentary DNA
CIC	Circulating immune complex
CNTF	Ciliary neurotrophic factor
CRP	C-reactive protein
CT-1	Cardiotrophin-1
CIU	Chronic idiopathic urticaria
CU	Chronic urticaria
DPU	Delayed pressure urticaria
EACA	ε-Aminocaproic acid
EGF	Epidermal growth factor
ESR	Erythrocyte sedimentation rate
Fcε RI	High-affinity receptor for IgE
FcR	Fc portion of Igs
G6PD	Glucose-6-phosphate dehydrogenase
GLM-R	Gp130-like monocyte receptor

Gp130	Glycoprotein 130
HPC	Hematopoietic progenitor cells
HS	Hypersensitivity
IEC	Intestinal epithelial cell
IL	Interleukin
IL-31	Interleukin 31
IL-31Rα	IL-31 receptor alpha
ITAM	Immune recognition receptor tyrosine-based activation motif
LIF	Leukaemia inhibitory factor
LIFR-like	Leukemia inhibitory factor receptor-like
LPS	Lipopolysaccharides
LTRA	Leukotriene receptor antagonists
MCP-1	Monocyte chemoattractant protein-1
MCP-3	Monocyte chemoattractant protein-3
MMPS	Matrix metalloproteinases
MPC	Myeloid progenitor cells
NSAID	Nonsteroidal anti-inflammatory drugs
OSMR	Oncostatin M receptor
OSMRβ	Oncostatin M receptor beta
PBMC	Peripheral blood mononuclear cells
PUVA	Phototherapy with UV light
SEMF	Subepithelial myofibroblasts
SIgE	Serum immunoglobulin E

STAT-3	Signal transducer and activator of transcription 3
TNF-α	Tumor necrosis factor -α
VEGF	Vascular endothelial growth factor

Table of Contents

	Title	Page No.
INTRODUCTION		1
AIM OF THR WORK		4
REVIEW OF LITERATURE		
Chapter 1: Urticaria		5
D	Definition	5
Н	Iistory	6
E	pidemiology	6
M	Mortality & Morbidity	7
Pa	athogenesis	8
C	Clinical picture	23
C	Classification	28
C	Causes	30
D	Diagnosis	33
Ti	reatment	35
Chapter 2: Interleukin-31		
D	Definition	51
D	Discovery of IL-31 and IL-31 receptors	52
С	Characterization of IL-31 receptors	53
В	Biological activities of Interleukin-31	56
R	cole of IL-31 in diseases	58
S	ummary	62
Chapter 3: Interleukin 3	1 & chronic urticaria	
Ir	ntroduction	64
R	cole of anti IL-31 in treatment of CU	66
SUBJECTS AND METHODS	-	68
RESULTS	-	75
DISCUSSION		91
CONCLUSION AND RECOMM	MENDATIONS	96
SUMMARY		98
REFERENCES		100

List of Figures

Fig. No.	Title	Page No.
1	Immunological and nonimmunological activation of mast cells	10
2	Interleukin-31 is produced mainly by activated CD4+ T cells, and targets a broad range of cells expressing IL-31RA and OSMR. Monocytes express IL-31RA and OSMR when activated by IFN-γ and LPS. Expression of both receptor units is found in many tissues	55
3	Interleukin-31 produces a number of biological effects, and causes several diseases when over-expressed	63
4	Correlation between disease severity and IL-31 among group 1(AU).	89
5	Correlation between disease severity and IL-31 among group 2(CU).	90

List of Tables

Table No.	Title	Page No.
1	Clinical classification of urticaria and angioedema	29
2	Patient's and investigator's rating scale of symptom severity	71
3	Personal characteristics of group 1 of patients	76
4	Personal characteristics of group 2 of patients	76
5	Personal characteristics of group 3 of controls.	77
6	Personal characteristics of group 4 controls	78
7	Comparison between cases and controls as regards sex	78
8	Comparison between cases and controls as regards age	79
9	Comparison between cases and controls as regards occupation	79
10	Urticaria severity among cases	80
11	IL-31 level among cases	81
12	IL-31 level among controls	81
13	Comparison between Cases and controls as regards the mean IL31	82
14	Comparison between the four studied groups as regards the mean IL 31 using analysis of variance test ANOVA testing	83
15	Comparison between the four studied groups as regards the mean IL 31 using Non parametric testing Krsukhal Wallis testing	84
16	Comparison between AU and CU patients as regard IL-31	85
17	Comparison between AU and AD patients as regard IL-31	85
18	Comparison between AU and normal as regard IL-31	86
19	Comparison between CU and AD as regard IL-31	86
20	Comparison between CU and normal as regard IL-31	87
21	Comparison between cases with different disease severity as regard IL-31 among group 1(AU)	87
22	Comparison between cases with different disease severity as regard IL-31 among group 2(CU)	88
23	Spearman correlation coefficient between severity of disease and IL 31 in group I(AU)	88
24	Spearman correlation coefficient between severity of disease and IL 31 in group II(CU)	89

INTRODUCTION

Urticaria is a common, heterogeneous group of disorders with a large variety of underlying causes. It is characterized by the appearance of fleeting wheals, which each last 1–24 hours and/or angioedema lasting up to 72 hours (*Zuberbier et al.*, 2009).

Urticaria is often classified as acute, chronic based on duration of symptoms. Urticaria is not a single disease but a reaction pattern that represents cutaneous mast cell degranulation, resulting in extravasation of plasma into the dermis. Urticaria is characterized by hives or wheals, which are edematous pruritic papules or plaques. The variety of potential triggers of urticaria, especially for acute urticaria, can make the approach to diagnosis and treatment a challenge (*Kaplan.*, 2009).

Chronic urticaria (CU), defined as urticaria that persists for longer than 6 weeks, is a frustrating condition for both patients and caregivers. An important characteristic of urticarial lesions is their transient nature. An individual wheal typically lasts for