Monocyte chemotactic protein-1 in urine as a marker for disease activity in pediatric lupus nephritis

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By

Ahmed Salah ElDin Sayed Mohamed Zeid

Supervised by

Prof. Dr.

Fatina Ibrahim Fadel

Professor of Pediatrics

Faculty of medicine

Cairo University

Prof. Dr.

Hala Salah ElDin Mohamed Talaat

Professor of Pediatrics

Faculty of medicine

Cairo University

Prof. Dr.

Hebat Allah Mohamed Ibrahim

Professor of Clinical and Chemical Pathology

Faculty of medicine

Cairo University

Prof. Dr.

Samar Mohamed Sabry

Assistant Professor of pediatrics

Faculty of medicine

Cairo University

Faculty of medicine

Cairo University

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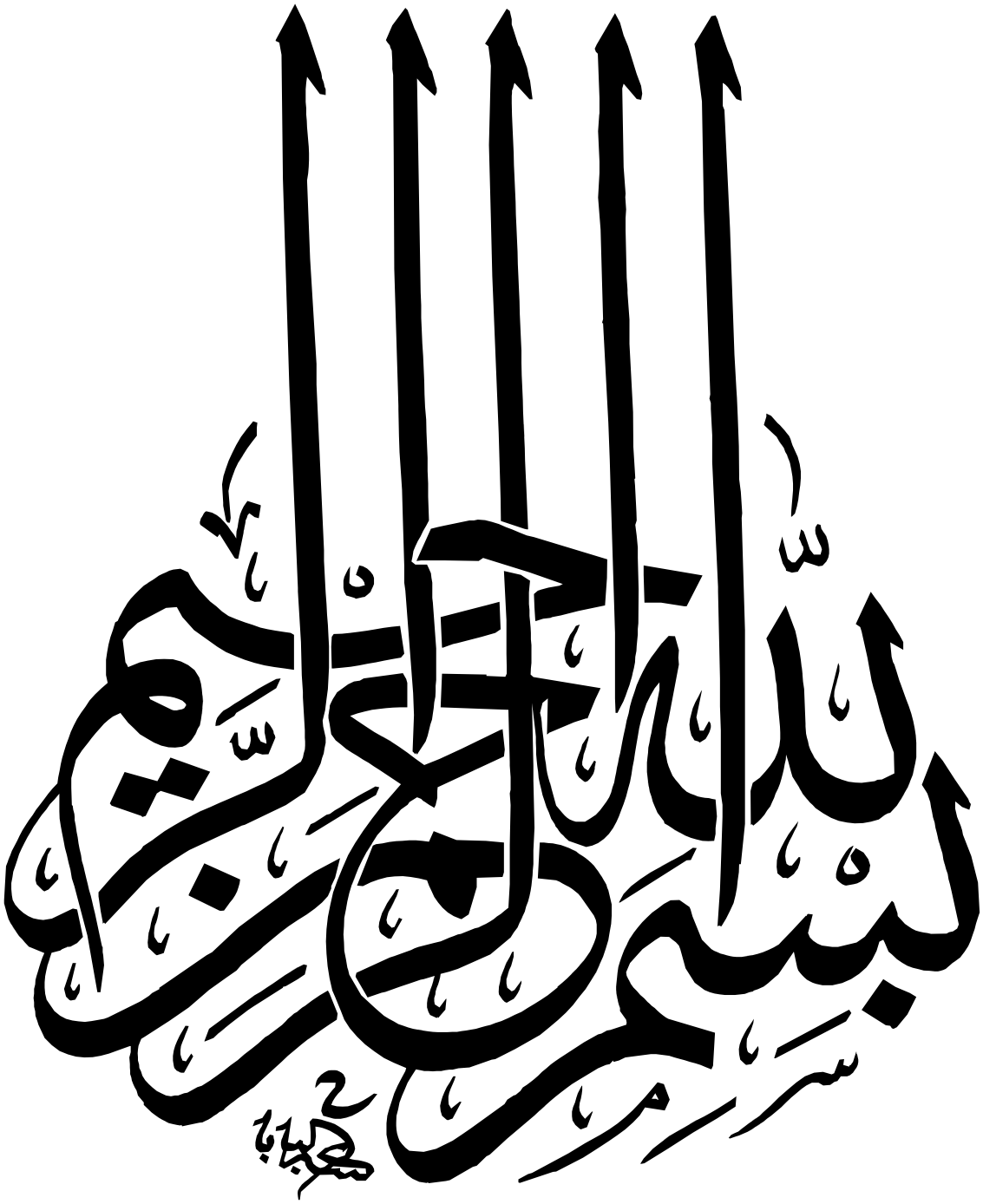
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Abstract:

Systemic lupus erythematosus is a multi-systemic, autoimmune disorder which is episodic in nature with a broad spectrum of clinical and immunological manifestations. As the course of lupus nephritis is often unpredictable, it is important to identify reliable, noninvasive methods to repeatedly assess the condition of the kidneys in these patients during follow up.

To assess the potential use of MCP1 as a marker for disease activity in lupus nephritis 56 SLE patients were recruited. They were divided into three groups one with active lupus nephritis (n=19), another with inactive lupus nephritis (n=25) and a third formed of SLE patients who had no renal affection. Two other groups were added for comparison one formed of 12 cases who had non-lupus nephritis and another of age and sex matched healthy controls (n=19).

Urinary MCP1/creatinine ratio was found to be significantly higher in the two groups of active nephritis –both lupus and non-lupus- ($p<0.0001$). Among the lupus groups, it correlated positively with rSLEDAI ($r=0.486214$, $p=0.0001$) as well as with other known markers of lupus activity including the ESR($r=0.58189$, $p=0.0001$), leucopenia and hypertension. Also, across all the study groups, the MCP1/creatinine ratio correlated positively with the protein/creatinine ratio ($r=0.551$, $p<0.0001$).

Urinary MCP1/creatinine ratio increases in active nephritis regardless of its cause and thus it can be used as a non-invasive indicator of active renal affection in known cases of systemic lupus.

Keywords: MCP-1, urinary biomarkers, lupus nephritis.

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Abbreviations

ACR: American College of Rheumatology

AGP: α -1-acid-glycoprotein (AGP)

AKI: acute kidney injury

ANA: anti-nuclear antibodies

Anti-DNA: anti-double-stranded DNA

Anti-Sm: anti-Smith

APCs: antigen-presenting cells

APL: anti-phospholipid antibodies

BILAG: British Isles Lupus Assessment Group index

C1q: complement component 1q

CCL2: chemokine ligand 2

CKD: chronic kidney disease

CNS: Central nervous system

CP: ceruloplasmin

CPK: creatinine phosphokinase

Creat.: creatinine

CRP: C-reactive protein

CsK: c-src tyrosine kinase.

CTLA4: cytotoxic T-lymphocyte antigen 1

CVA: cerebro-vascular accident

CXCL10: CXC motif chemokine 10

dsDNA : double stranded deoxy-ribonucleic acid

ECLAM: European Consensus Lupus Activity Measurement

EM: electron microscopy

EMG: electromyogram

Fc: fragment crystallizable

FOXP3: The forkhead transcription factor

GFR: glomerular filteration rate

GN: glomerulonephritis

HLA: human leukocyte antigen

I/F: immunoflurescence

ICAM: intercellular cell adhesion receptor

IFN-α inducible protein MxA: Myxovirus (influenza virus) resistance 1, interferon-inducible protein

IFN-α: interferon-alpha

IFN-γ: interferon-gamma

IgG: immunoglobulin G

IL-10: interleukin 10

IL-6 : interleukin 6

IRF: interferon regulatory factor

IV: intra-venous

L/M: light microscopy

LAI: Lupus Activity Index

LE cells: lupus erythematosus cells

LFABP: fatty acid binding protein in liver

L-FABP: Liver-type fatty acid binding protein

LN: lupus nephritis

L-PGDS: lipocalin-type prostaglandin d-synthetase (L-PGDS)

LSD: least significant difference.

LYP: lymphoid-specific protein tyrosine phosphatase.

MBL : mannose-binding lectin.

MBP: Mannose-binding protein.

MCP-1: monocyte chemo-attractant protein-1

MCTD: mixed connective tissue disease

mERCP: Membrane endothelial protein C receptor

MHC: major histocompatability complex

MIF: macrophage inhibitory factor

MMF: mycophenolate mofetil

NGAL: neutrophil gelatinase associate lipocalin

NK cells: natural killer cells

NOD2/CARD15: caspase recruitment domain-containing protein

PARP: Poly (ADP-ribose) polymerase

PDCD1: programme cell death domain 1

Plt: platelet

Ptn: protein

PTPN22 :protein tyrosine phosphatase 22

RANTES: Regulated upon Activation, Normal T-cell Expressed, and Secreted.

SLAM: Systemic Lupus Activity Measure

SLE: Systemic lupus erythematosus

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

SNPs : single nucleotide polymorphisms

ssRNA: single stranded ribo-nucleic acid

STAT-1: signal transducer and activator of transcription

TLC: total leuococytic count

TLR : Toll-like receptor

TNF-α : tumour necrosis factor-alpha

TWEAK: Tumor necrosis factor-like inducer of apoptosis

TYK2: tyrosine kinase 2

VCAM: vascular cell adhesion receptor

VEGF: vascular endothelial growth factor

WHO: world health organization

Introduction and aim of the work:

Systemic lupus erythematosus is an unpredictable, multi-systemic, autoimmune disorder which is episodic in nature with a broad spectrum of clinical and immunological manifestations. It is characterized by wide-spread inflammation of blood vessels and connective tissues. Diagnosis is classically made by grouping 4 out of eleven criteria established by the American College of Rheumatology in 1997. (Marks et al., 2008). Biopsy-proven lupus nephritis occurs in around 80% of all cases of childhood-onset SLE. (Marks et al., 2008).

As the course of LN is often unpredictable, it is important to identify reliable, noninvasive methods to repeatedly assess the condition of the kidneys in these patients.

Among the blood investigations marking disease activity are anemia, leucopenia, thrombocytopenia, elevated ESR as well as reduced C3 and C4. (Marks et al., 2008).

Urinary biomarkers are easily obtained and probably are best at reflecting the current renal status, as they specifically represent local inflammatory activity. Among the potential urinary biomarkers are TWEAK, Lipocalin-2, MCP-1, IL-10, IL-6, and IL-8. (Schwartz et al.,2007). MCP-1 is a key chemokine involved in monocyte chemotaxis and it is consistently found at high levels in the urine of patients with active LN. (Li et al., 2006).

Aim of the work:

This study aims to assess the use of MCP-1 in urine as an early marker for disease activity in cases of lupus nephritis.

Chapter One

Pathogenesis of SLE

The pathogenesis of Systemic lupus erythematosus (SLE) is complex. Target tissue damage is caused by pathogenic autoantibodies and immune complexes. The abnormal immune response that permits persistence of pathogenic B and T cells has multiple components, including activation of the innate immune system by DNA and RNA-containing antigens, processing of increased quantities of self –antigens by APCs (antigen-presenting cells), hyperactivation of B and T cells, and failure of multiple regulatory networks to interrupt this process. The immunological abnormalities occur in a framework of interactions among multiple susceptibility genes (and insufficient protective genes), gender influences, and environmental stimuli (Hahn &Tsao,2010).

Genome scan studies have identified eight chromosomal regions with significant linkage to SLE that are confirmed by individual cohorts, suggesting that susceptibility genes may be identified within each of these loci. Linkage studies and single nucleotide polymorphisms (SNPs) have led to the identification of positional candidate genes, and their functional allelic variants have demonstrated molecular pathogenesis of the disease. The discovery of positional candidate genes that are associated with various autoimmune diseases signifies a common pathway in the mechanism of these diseases. Copy polymorphisms in susceptibility genes provide evidence in how genetic plasticity affects complex phenotypes as seen in SLE (Wong&Tsao,2006).