Antibodies to Ribosomal P Proteins in Lupus Nephritis

Thesis

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Abstract:

Objective: Lupus nephritis is an immune complex glomerulonephritis that develops as a frequent complication of SLE and is the major predictor of poor prognosis**.** Since anti-ds DNA is not a universal finding in patients with lupus nephritis, increasing attention has been paid to the relationship of autoantibodies to anti-Rib P with lupus nephritis. The aim of this study is to determine the association of anti-Rib P antibodies and lupus nephritis.

Patients and Methods: sixty three female SLE patients with nephritis served as case and twenty five female SLE patients without nephritis served as control were selected from the in-patient section of Rheumatology and Rehabilitation department, Faculty of Medicine, Cairo University hospitals. All patients and controls fulfilled the ACR revised criteria for classification of SLE. A complete routine laboratory evaluation and clinical examination were performed in each patient and control. Anti-Rib P antibodies were detected by ELISA using ORG 517 Anti-Rib-P kit. ANA and anti-dsDNA were done. Disease activity was assessed using SLEDAI.

Results: anti- Rib P antibodies in SLE were found to be associated with higher disease activity ($P=0.02$), fever ($P<0.001$), and alopecia ($P=0.017$) but were not associated with lupus nephritis ($P=0.4$).

Conclusion: there was no association between anti-Rib P antibodies and lupus nephritis. However, there was association between anti-Rib P antibodies and higher disease activity, fever, and alopecia.

Keywords: Systemic lupus erythematosus- lupus nephritis- anti-ribosomal P antibodies - disease activity.

Contents

List of abbreviations

ACE-I	Angiotensin converting enzyme inhibitors
ACR	American Colleague of Rheumatology
AIH	Autoimmune hepatitis
ALMS	Aspreva Lupus Management Study
ALT	Alanine transaminases
ANA	Antinuclear antibody
AVN	Avascular necrosis
anti-RNP	Anti-ribonucleoprotein
anti-Sm	Anti-smith
APCs	Antigen presenting cells
ARBs	Angiotensin receptor blockers
ARBs	Angiotensin receptor blockers
AST	Aspartate aminotransferase
AZA	Azathioprine
BAFF	B-cell activating factor
BlyS	B lymphocyte stimulator
BP	Blood Pressure
BSA	Body surface area
C	Complement
CAMs	Cell adhesion molecules
CBC	Complete blood picture
CCR5	C-C chemokine receptor type 5
CD	Cluster of differentiation
CKD	Chronic kidney disease
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CYC	Cyclophosphamide
DCs	Dendritic cells
DN	Double negative
DNA	Deoxyriboneuclic acid
ds-DNA	Double stranded deoxyriboneuclic acid
DVT	Deep venous thrombosis
ENAS	Extractable nuclear antigen antibodies
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
Fcγ	The constant fragment of antibody gamma
fhT	Follicular helper T cells
GBM	Glomerular base membrane
GDCN	Glomerular Disease Collaborative Network
GM-CSF	Granulocyte macrophage colony stimulating factor
GN	Glomerulonephritis

HB	Hemoglobin
HCQ	Hydroxycholoroquine
HLA	Human leukocyte antigen
HRP	Horseradish peroxidase
ICAM-1	Intracellular adhesion molecule-1
ICs	Immune complexes
IFN-α	Interferon alpha
IPF	interstial pulmonary fibrosis
Ig	Immunoglobulin
IL	Interleukin
i-NOS	Inducible nitric oxide synthase
IPF	Interstitial pulmonary fibrosis
ISN/ RPS	International Society of Nephrology/ Renal Pathology Society
IV	Intravenous
IVIG	Intravenous immunoglobulin
L Th17	Th17 Lymphocytes
LN	Lupus nephritis
LPL	lipoprotein lipase
LUNAR	The Lupus Nephritis Assessment with Rituximab
mAb	Monoclonal antibodies
MAC	Complement membrane attack complex
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemotactic protein-1
MCPs	Metacarpophalangeals
MCV	mean corpuscular volume
mDCs	Myeloid DCs
MMF	Mycophenolate mofetil
MP	Methyl prednisolone
MPA	Mycophenolic acid
MTPs	Metatarsophalangeal**s**
NFAT	Nuclear factor of activated T cells
NF*κβ*	Nuclear factor kappa
NIH	National Institutes of Health
NKs	Natural killer T cells
NO	Nitric oxide
NPSLE	Neuropsychiatric systemic lupus erythematosus
NZB	New Zealand Black
PDGF	Platelet-derived growth factor
PIPs	Proximal interphalangeals
PLT	Platelet
PMNs	Polymorph nuclear leucocytes
PTEC	Proximal tubular epithelial cells

RAAS	Renin angiotensin aldosterone system
Rag 1	Recombination activating gene 1
RANTES	Regulated on activation, normal T cell expressed and secreted
RCTs	Randomized controlled trials
ROR	Retinoid-related orphan receptors
ROS	Reactive oxygen species
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
ss-DNA	Single stranded deoxyriboneuclic acid
TCR	T cell receptor
TGF	Transforming growth factor
TGFβ	Transforming growth factor beta
Th1	T helper 1
Th17	T helper 17
Th2	T helper 2
TIAS	Transient ischemic attacks
TLC	Total leucocyte count
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
TTP	Thrombotic thrombocytopenic purpura
TWEAK	TNF-related weak inducer of apoptosis
VCAM-1	Vascular cell adhesion molecule-1
WHO	World Health Organization

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Introduction

Lupus nephritis is an immune complex glomerulonephritis that develops as a frequent complication of SLE **(Lech and Anders, 2013).**

It is one of the most serious SLE complications since it is the major predictor of poor prognosis **(Salgado and Herrera-Diaz, 2012).**

Currently, anti-ds DNA is the best available biomarker for lupus nephritis since it correlates well with renal activity, worse prognosis and histology severity **(Dooley, 2007)**. But as it is not a universal finding in patients with lupus nephritis, increasing attention has been paid to the relationship of autoantibodies to anti-Rib P with lupus nephritis **(Toubi and Shoenfeld, 2007) (Kiss and Shoenfld, 2007).**

Anti-Rib P are directed to 3 phosphoproteins (P0, P1, and P2), which are located on the larger 60S subunit of eukaryotic ribosomes, and have molecular weights of 38, 19, and 17 kDa, respectively. They have been shown to react a common linear determinant that is present in the carboxyl-terminal 22-amino-acid sequence **(Elkon et al, 1986)**.

Aim of Work

The aim of this study is to determine the association of anti-Rib P antibodies and lupus nephritis.

Pathogenesis of Lupus Nephritis

Lupus nephritis (LN) is a potentially devastating complication of systemic lupus erythematosus (SLE) **(Schwartz et al, 2014)**.

Although all renal compartments including glomerular, tubulointerstitial, and vascular components may be injured by the disease; however, the term "lupus nephritis" is mainly used to define the immune complex-mediated glomerulonephritis (GN) (**Kiremitci and Ensari, 2014**).

It is a serious potential feature of SLE. Though SLE typically cycles through periods of flares and remission, patients often eventually succumb to end-stage kidney or cardiovascular damage **(Sterner et al, 2014).**

The incidence and prevalence of LN varies depending on the studied population. The LN incidence is higher in people of Asian (55%), African (51%), and Hispanic (43%) ancestry compared with Caucasians (14%) **(Ortega et al, 2010)**.

Up to 25% of these patients still develop end-stage renal disease (ESRD) 10 years after onset of renal compromise. In terms of outcome, the 5- and 10-year renal survival rates of LN in the 1990s ranged between 83–93% and 74–84%, respectively **(Mok, 2010).**

In addition, LN develops early in the course of SLE thus becoming a major predictor of poor prognosis **(Anaya et al, 2011).** However, in about 5% of the cases, LN may appear several years after the onset of SLE (i.e., delayed LN) **(Varela et al, 2008).**

In susceptible individuals suffering of SLE, in situ formation and deposit of immune complexes (ICs) from apoptotic bodies occur in the kidneys as a result of an amplified epitope immunological response **(Salgado and Herrera-Diaz, 2012).**

IC glomerular deposits generate release of proinflammatory cytokines and cell adhesion molecules (CAMs) causing inflammation. This leads to monocytes and polymorphonuclear cells chemotaxis. Subsequent release of proteases generates endothelial injury and mesangial proliferation. Presence of ICs promotes adaptive immune response and causes dendritic cells (DCs) to release type I interferon (IFN). This induces maturation and activation of infiltrating T cells, and amplification of T helper 2 (Th2), T helper 1 (Th1) and T helper 17 (Th17) lymphocytes. Each of them, amplify B cells and activates macrophages to release more proinflammatory molecules, generating effector cells that cannot be modulated promoting kidney epithelial proliferation and fibrosis **(figure 1) (Salgado and Herrera-Diaz, 2012)**.

Apoptosis

Apoptosis is a tightly regulated process of programmed cell death that regulates the late phase of immune responses. Disordered regulation of both apoptosis and the clearance of apoptotic products have been implicated in the pathogenesis of SLE and LN **(Kamradt et al, 2001).**

The idea of impaired apoptosis had gained a crucial role in pathogenesis of SLE. Auto-antigens are found in apoptotic and necrotic material and they are recognized by autoimmune sera from SLE patients **(Muñoz et al, 2005).**

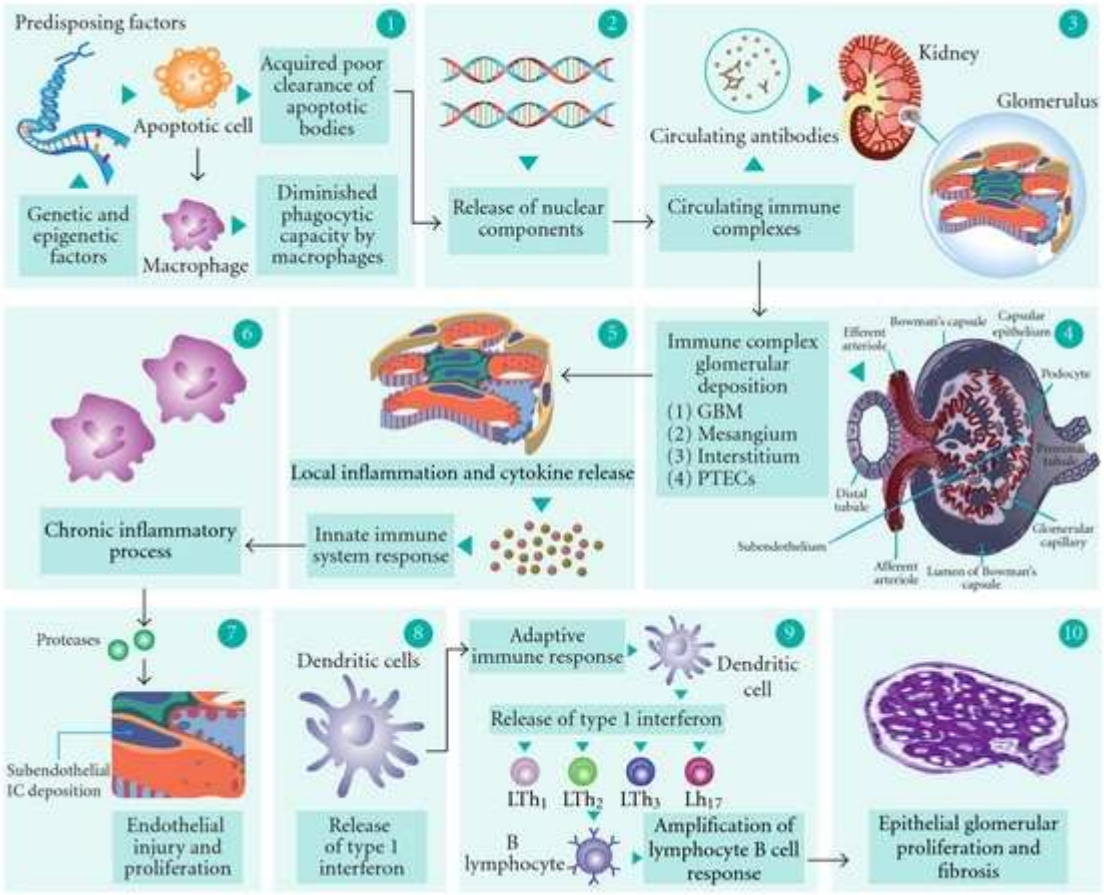

Figure 1: Lupus nephritis: an imbalance between cytokine homeostasis and I.C. deposition. In predisposing susceptible individuals who develop SLE, there is an acquired poor clearance of apoptotic bodies and a diminished phagocytic capacity by macrophages **(1).** Early formation of ICs include antinucleosomes, anti-dsDNA, DNA extractable nuclear antigen antibodies (ENAS), antibodies against C1q complex of the complement system, free DNA, antiribonucleoproteins (anti-RNP), and histones as byproducts of inefficient phagocytosis of apoptotic bodies **(2).** Circulating ICs are deposited initially at the GBM, mesangium, and interstitial tissue within the PTECs **(3)** and **(4).** The deposited ICs initiate the release of proinflammatory cytokines and chemokines such as MCP-1, IL-1, IL-6 and CAMs thus establishing a chronic inflammatory process **(5).** The resulting overload of the mesangial phagocytic system (innate immune system) leads to deposits of subendothelial ICs becoming an easy target for monocyte migration and infiltration and generating endothelial injury and proliferation **(6)** and **(7).** In turn, the adaptive immune system is activated secondary to the presence of ICs and DCs **(8),** which subsequently trigger release of type 1 IFN and induce maturation and activation of infiltrating T cells. This activation leads to sequential amplification of Th2, Th1, and Th17 **(9).** Each of these amplifies lymphocyte B cell response and further activates macrophages, generating a second general response, which increases recruitment of effector cells that can no longer be modulated by regulatory T cells and resulting in the end in epithelial glomerular proliferation and fibrosis **(10) (Salgado and Herrera-Diaz, 2012).**