Antinucleosome Antibodies and Systemic Lupus Erythematosus

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في الروماتيزم والتأهيل

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Dedication

To my family who inspired this work
and is the spirit of my life,
thanks a lot.

Shimaa

Abstract

- **Objective:** The aim of this study is to investigate the prevalence of antinucleosome antibodies in systemic lupus erythematosus and their association with disease activity and renal involvement.

- **Methods:** Fifty SLE patients of a mean age of 28.28 years and a mean disease duration of 5.46 years, were subjected to full history taking, full clinical examination, serum ANA, antidsDNA, and antinucleosome antibodies, with thirty healthy adults served as a control group.

- **Results**: A highly significant correlation was found between patients and control as regards the prevalence of antinucleosome antibodies. A non significant difference was detected between the presence of antinucleosome antibodies and the nephritis.

- **Conclusion:** Antinucleosome antibodies are present with a very high frequency in SLE but no association with disease activity or renal involvement could be detected

- **Keywords:** Systemic Lupus Erythematosus-Lupus nephritis-Antinucleosome antibodies-Disease activity-AntidsDNA.

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ACLE	Acute cutaneous lupus erythematosus
ACR	American Rheumatism Association criteria
aCT	Antichromatine antibodies
AIH	Autoimmune hepatitis
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ANOVA	Kruskal Wallis analysis of variance
Anti-AnN	Antinucleosome antibodies
Anti PM-1	Anti polymyositis type 1 antbodies
Anti SCL-70	Anti scleroderma 70 antibodies
Anti-dsDNA	Anti double stranded DNA
Anti-NCS	Antinucleosome antibodies
Anti-Ncs	Antinucleosome antibodies
AST	Aspartate transaminase
Bcl-2	B- cell lymphoma 2
bp	Base pairs
C3	Complement 3
C4	Complement 4
C5-C9	Complement components
Caspases	Cysteine-aspartic proteases or cysteine-depended aspartic-directed proteases
CCLE	Chronic cutaneous lupus erythematosus
Ch-50	Complement profile-total hemolytic complement.
CLE	Chronic lupus erythematosus
CNS manifestations	Central nervous system manifestations
Cr	Creatinine
CRP	C reactive protein
CVA	Cerebrovascular accident
DIL	Drug induced lupus
DM	Diabetes mellitus
dsDNA	Double stranded DNA
ELISA	Enzyme linked immunosorbant assay
EM	Electrone microscopy
ESR	Erythrocyte sedimentation rate
ESRD	End stage renal disease

FC	Fragment crystallizable
FC receptors	Fragment crystallizable receptors
GBM	Glomerular basement membrane
GN	Glomerulonephritis
HB	Heamoglobine
HRP	Horseradish peroxidase
HS	Heparan sulphate
HTN	Hypertention
IF	Immunofluorescence microscopy
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ISN/RPS	International Society of Nephrology/Renal Pathology Society Classification of Lupus Nephritis
JCA	juvenile chronic arthritis
JSLE	Juvenile Systemic Lupus Erythematosus
LE	Lupus Erythematosus
LGN	Lupus glomerulonephritis
LM	Light microscopy
LSc	Localized scleroderma
MCTD	Mixed connective disease
PLT	Platelets
RA	Rheumatoid arthritis
RBC	Red blood cell
RNP	Ribonucleoprotein
ROC	Receiver operator characteristic
S.crt	Serum creatinine
SACLE	Subacute cutaneous lupus erythematosus
SACQ	Serologically Active Clinically Quiescent
SD	standard deviation
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
Sm	Smooth muscle
SS	Sjögren's syndrome
SSc	Scleroderma
TLE	Tumid lupus erythematosus

TLRs	Toll like receptors
TNFα	Anti-tumor necrosis factor alpha
UV	Ultraviolet
WBC	White blood cell

Introduction

Systemic lupus erythematosus (SLE) is a chronic, inflammatory autoimmune disorder. It may affect the skin, joints, kidneys, and other organs. Normally, the immune system controls the body's defenses against infection. In SLE and other autoimmune diseases, these defenses are turned against the body and rogue immune cells attack tissues ***(Steven, 2005).***

The pathologic findings of SLE occur throughout the body and are manifested by inflammation, blood vessel abnormalities that encompass bland vasculopathy and vasculitis, and immune-complex deposition. The best characterized pathology involves the kidney, which displays increases in mesangial cells and mesangial matrix (Inflammation, cellular proliferation, basement membrane abnormalities, and immune-complex deposition) ***(Weening et al., 2004).***

Antibodies reacting with double strands DNA (dsDNA) are highly specific for SLE and have been found in approximately 50–80% of the patients. The presence of anti-dsDNA antibody is one of the 11 criteria for the classification of SLE and is important for clinical monitoring of the disease. ***(Duzgun et al., 2007).***

It has been proposed that the nucleosome is the principle antigen in the pathophysiology of SLE. The nucleosome (chromatin) is the native complex of DNA and histones. It consists of a 146 base pairs segment of DNA wrapped in two superhelical turns around an octameric core complex containing four pairs of the histone proteins H2A, H2B, H3, and H4. Its crystal structure has been

demonstrated. Nucleosomes become immunogenic under particular conditions. ***(Lugher et al., 1997).***

Antinucleosome and anti-dsDNA antibodies were found in 74.5% and 78.4% (respectively), in patients with lupus nephritis, and antinucleosome antibodies were 31.4% in SLE patients lacking of anti-dsDNA antibodies ***(Duzgun et al., 2007)***.

It could be demonstrated that antinucleosomes antibodies are detected in 84-88% of patients with lupus. It has been reported that anti-nucleosome immunoglobulin G antibodies are a more sensitive marker of SLE than anti dsDNA, and are almost exclusively found in lupus, scleroderma, and mixed connective tissue diseases. Furthermore, it has been shown that antinuclear autoantibodies complexed to nucleosomes can bind to heparin sulphate in the glomerular basement membrane (GBM) via the histone part of the nucleosome in SLE nephritis ***(Berden et al., 1999).***

Aim of work:

The aim of this study is to investigate the prevalence of antinucleosome antibodies in systemic lupus erythematosus and their association with disease activity and renal involvement.

CHAPTER 1

LUPUS NEPHRITIS

Definition

Lupus Erythematosus (LE) is a heterogeneous connective-tissue disease associated with polyclonal B-cell activation and is believed to result from the interplay of genetic, environmental, and hormonal factors ***(Callen, 2006).***

Systemic Lupus Erythematosus (SLE) is an autoimmune disease where the immune system is misdirected against self-antigens, and the resulting immune effector pathways cause specific tissue damage. This damage is assumed to be initiated predominantly by immune complex deposition or direct autoantibody binding. Lupus nephritis is one of the most serious manifestations in SLE ***(Fenton and Rekvig, 2007).***

Incidence:

It is well known that women, especially those of reproductive age, with a peak age of onset between the late teens and early 40s ***(Joseph et al., 2007)*** are more susceptible to SLE compared to men, with a gender ratio of SLE patients of 10:1 (female: male). It is thought that sex hormones (such as estrogens) have a potent role in disease development. Studies had shown that estrogen can protect auto-reactive T lymphocytes from apoptosis, thus leading to a hyperactive production of autoantibodies by auto-reactive B cells. The role of prolactin in SLE had also been studied. Hyperprolactinemia is present in SLE patients of both sexes, with a correlation between prolactin concentrations and lupus activity. It is