Prevalence of Microalbuminuria in Clinically Healthy Siblings of patients of SLE with and without Lupus Nephritis

Thesis

Submitted for Partial Fulfillment of Master Degree
In Internal Medicine

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Heba Mostafa

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List of Abbreviations

A.G.D.S.....Acute Gastro-Intestinal Distress Syndrome

ACR.....American College of Rheumatology

Alb.....Albumin/Creatinine Ratio

ANA.....Anti-Nuclear Antibody

AZA.....Azathioprine

BUN.....Blood Urea Nitrogen

CNV.....Copy Number Variation

CNS.....Central Nervous System

CRP.....C-Reactive Protein

CYC.....Cyclophosphamide

DAMPs.....Damage Associated Molecular Patterns

DCs.....Dendritic Cells

DHEA.....DehydroEpiandrosterone

DNA.....Deoxy Ribonucleic Acid

EBV.....Epstien Barr Virus

ECLAM.....European Community Lupus Activity Measure

ESR.....Erythrocyte Sedimentation Rate

F/M.....Female/Male Ratio

FDR.....First Degree Relatives

GBM.....Glomerular Basement Membrane

GM-CSF.....Granulocyte Macrophage Colony Stimulating Factor

GN.....Glomerulonephritis

GWAS.....Genome Wide Association Studies

hCRH.....Human CorticoTropin Releasing Hormone

List of Abbreviations

HLA .....Human Leucocytic Antigen

I.L.....Interleukin

IgA.....Immunoglobulin A

IgG.....Immunoglobulin G

L.N.....Lupus Nephritis

MHC .....Major Histocompatibility Complex

MMF .....MycophenolateMofetil

mRNA.....Micro-Ribonucleic Acid

N.P SLE .....Neuro-Psychiatric Lupus

NRH.....Nodular Regenerative Hyperplasia

NSAIDs .....Non-Steroidal Anti-Inflammatory Drugs

PAMPs .....Pathogen Associated Molecular Patterns

PLN.....Proliferative Lupus Nephritis

RNA .....Ribo Nucleic Acid

JDM.....Juvenile Diabetes Mellitus

JIA.....Juvenile Idiopathic Arthritis

SELENA.....Safety of Estrogen in Lupus Erythematosus National Assessment

SLAM.....Systemic Lupus Activity Measure

SLEDAI.....Systemic Lupus Erythematosus Disease Activity Index

SLE.....Systemic Lupus Erythematosus

SNAP .....Single Nucleotide Polymorphisms

TLR .....Toll-Like Receptor

TNF-α .....Tumornecsosis Factor Alpha

U.S.....United States

U.V .....Ultraviolet Light

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Prevalence of Microalbuminuria in Clinically Healthy Siblings of Patients of SLE with and without Lupus Nephritis

Abstract: Systemic lupus erythematosus (SLE) is a chronic, relapsing, inflammatory, and often multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidney and serosal membranes. Microalbuminuria is defined as excretion of between 30 and 300 mg of albumin a day in the urine of 20-200 ug/min of albumin. Possible familial tendency of SLE is still a mysterious question which has not been properly answered in the literature till now, yet there's growing evidence that possible genetic aberration in families may play a significant pathogenic role.

Results: We found that siblings of patients with nephritis had a relatively higher rate of microalbuminuria though no statistical significance could be obtained.

Keywords: SLE, microalbuminuria, siblings.

INTRODUCTION

Systemic Lupus Erythematosus is a systemic autoimmune disease affects any part of the body, as occurs in other autoimmune diseases, the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage, it is a type iii hypersensitivity reaction caused by antibody- immune complex ***(James et al., 2005).***

SLE most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system, The course of the disease is unpredictable, with periods of illness (called flares) alternating with remission, The disease occurs nine times more often in women than in men, especially in women in child- bearing years ages 15 to 35, and is more common in those also of non- European descent ***(Anisur et al., 2008).***

SLE is treatable through addressing its symptoms, mainly with cyelophosphamide, corticosteroids and immunosuppressants, there is currently no cure, SLE can be fatal, although with recent medical advances fatalities are becoming increasingly rare, Survival for people with SLE in the United States, Canada, and Europe is approximately 95% at five years, 9% at 10 years, and 78% at 20 years ***(Harrison's Internal Medicine).***

Family studies have revealed a higher than expected prevalence among the relatives of patients with SLE, Although the precise prevalence of familial SLE is not known, approximately 1% of patients with SLE have a first- degree relative, as compared to 1% of patients in control families, In familial SLE, the most frequent mode of familial intra-aggregation is affected sibling pairs and females predominate, with mother- daughter and sister-sister pairs being the most common and father- son pairs occurring relatively rarely ***(Petty et al., 2005).***

SLE is more common in first-degree relatives of patients with SLE (familial prevalence of 10%-12%), Concordance rates are higher in monozygotic twins (24-58%) than in dizygotic twins (2-5%), supporting an important role for genetics in the development of SLE ***(Harley et al., 2008).***

First- degree relatives (mother, father, brother, sister) of people with lupus have an eightfold to nine fold increased risk of having lupus compared with the general public ***(William, 2009).***

The first mechanism may arise genetically, Research indicates that SLE may have a genetic link, SLE does run in families, but no single, causal, gene has been identified. Instead, multiple genes appear to influence a person's

chance of developing lupus when triggered by environmental factors, the most important genes are located in the HLA region on chromosome 6, where mutations may occur randomly (de novo) or may be inherited, HLA class I, class II, and class III are associated with SLE, but only class I and class II contribute independently to increased risk of SLE ***(Martens et al., 2009).***

The inheritance of SLE does not follow simple Mendelian rules as we would expect for a single major gene effect, instead a polygenic model of susceptibility provides the best explanation for the familial clustering ***(Han et al., 2009).***

Microalbuminuria is defined as excretion of between 30 and 300 mg of albumin a day in the urine of 20-200 ug/min of albumin, Less than 30 mg is insignificant, Albumin levels below 300 mg a day is too small to be detected by standard protein dipstick testing, so any positive result is more severe than microalbuminuria ***(Herbet et al., 2009).***

Lupus nephritis, one of the most serious manifestations of systemic lupus erythematosus (SLE), usually arises within 5 years of diagnosis.

Autoimmunity plays a major role in the pathogenesis of lupus nephritis; the immunologic mechanisms include

production of autoantibodies directed against nuclear elements.

These autoantibodies form pathogenic immune complexes; Deposition of these immune deposits in the kidneys initiates an inflammatory response by activating the complement cascade and recruiting inflammatory cells that can subsequently be observed on biopsy specimens ***(D'Agati et al., 2007).***

Around 50% of patients with SLE are affected by lupus nephritis, with 10-20% having evidence of lupus nephritis at presentation ***(Brent et al., 2008).***

Systemic lupus erythematosus is a chronic autoimmune disease, the role of various pathogenic factors, leading to excessive activation of lymphocytes, leading to immune complex deposition in the kidneys and kidney damage affecting the renal filtration and reabsorption, resulting in increased urinary protein excretion ***(Wang et al., 2006).***

In patients with systemic lupus erythematosus microalbuminuria did not correlate with renal histology or predict the subsequent development of clinical nephritis ***(Velante de Almeida et al., 1999).***