A COMPARISON OF IMMUNOLOGICAL AND IMMUNOGENETIC CHARACTERISTICS IN SUBJECTS WITH SLE AND EXTRA-ARTICULAR RHEUMATIC DISEASE

Thesis

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M.D. Degree in Clinical and Chemical Pathology

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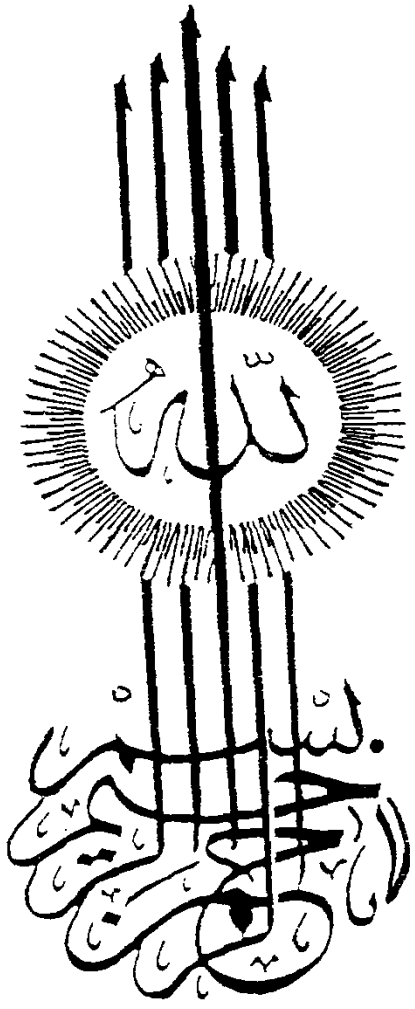

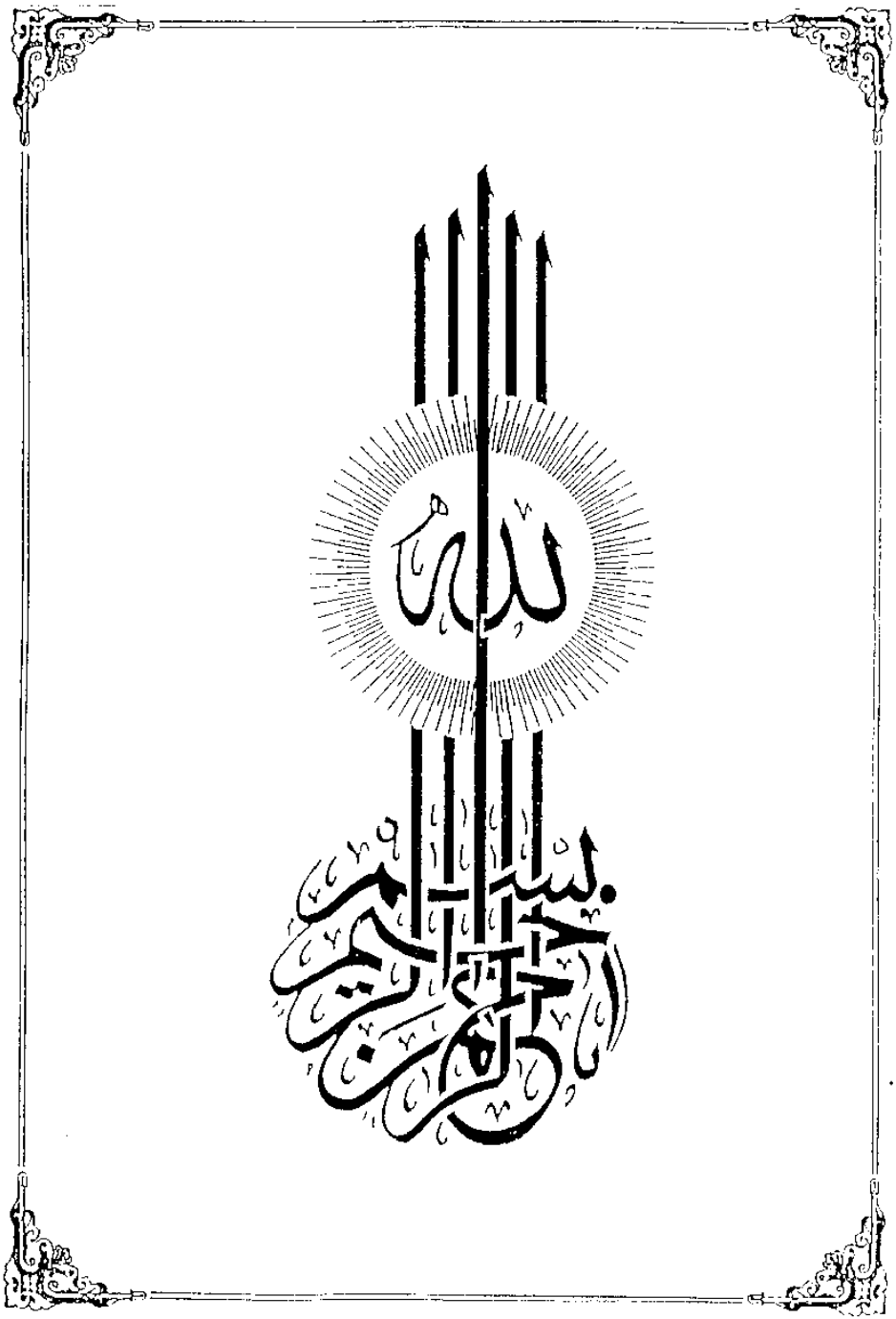

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LIST OF ABBREVIATIONS

- ACLA: Anticardiolipin antibody.
- ANA: Antinuclear antibody.
- AP: Alternative pathway.
- APA: Antiphospholipid antibody.
- ds: Double stranded.
- EA: Erythrocyte antibodies.
- EGTA: Ethylene glycol tetracetic acid.
- ELISA: Enzyme linked immunosorbent assay.
- ENA: Extractable nuclear antigen.
- F.S.: Felty's syndrome.
- HSE: Human spleen extract.
- IC: Immune complexes.
- Ig: Immunoglobulin.
- LA: Lupus anticoagulant.
- MAM: Mycoplasma arthritidis mitogen.
- MCTD: Mixed connective tissue disease.
- MHC: Major histocompatibility complex.
- O.D: Optical density.
- OHA: Hydroxylase locus A.
- OHB: Hydroxylase locus B.
- PBS: Phosphate buffered saline.
- PAP: Primary antiphospholipid.
- PMN: Polymorphonuclear.
- QO: Quantity zero.
- RA: Rheumatoid arthritis.

- RANA: Rheumatoid arthritis nuclear antigen.
- RAP: Rheumatoid arthritis precipitin.
- RA+V: Rheumatoid arthritis with vasculitis.
- RF: Rheumatoid factor.
- RIA: Radioimmunoassay.
- RNP: Ribonucleoprotein.
- RTE: Rabbit thymus extract.
- SLE: Systemic lupus erythematosus.
- ss: Single stranded.
- STS: Standard tests for syphilis.
- TCR: T-cell receptor.
- VDRL: Venereal disease research laboratory.

CONTENTS

INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

Autoimmune diseases are characterized by autoantibodies to self antigens. An unusual feature of certain diseases, such as SLE, is the presence of antibodies to normally inaccessible antigens. SLE in particular, is associated with the presence of multiple autoantibodies and their presence in high concentrations in many patients. Some of these antibodies are disease specific, such as anti ds-DNA and anti-Sm. Others, for instance anti-ss DNA, anti-histone, anti nuclear RNP, anti-SSA (anti-Ro), and anti-SS/B (anti-La) are not disease specific, and may be detected in other immunological diseases (Tan et al., 1988). Some of the antibodies in autoimmune diseases have been found among immunoglobulin classes. Rheumatoid factors have been found among IgM, IgG, and IgA classes. High titers of these classes are associated with severe forms of rheumatoid disease, and rheumatoid disease with extra-articular manifestations (Salusbury, 1986).

High titers of anticardiolipin antibodies in systemic lupus erythematosus patients are usually associated with repeated episodes of arterial and venous thrombosis, thrombocytopenia, and recurrent fetal loss (Harris et al., 1986).

The recent development of immunoassays for the detection and quantitation of autoantibodies to Ro, La, Sm, RNP, and cardiolipin promises to provide new insight into the pathogenetic nature, molecular biology, and genetics of SLE and other autoimmune diseases with similar features, including extra-articular rheumatic diseases.

A role for genetic factors predisposing to the development of SLE was first suggested by observation of familial cases (Estes and Christian, 1971). In SLE the strongest disease susceptibility genes to be identified in humans are those encoding deficiencies of proteins of the classical pathway of complement, especially C1q, C2, and C4. These deficiencies stimulated detailed studies of complement proteins encoded within the MHC class III locus. They have led to the identification of null alleles of one of the two isotypic variants of C4, C4A as a putative disease susceptibility gene present in the majority of patients with SLE (Ng and Walport, 1988).

In rheumatoid arthritis, in contrast, the results of family and twin studies suggest that RA may result from interaction between an oligogenic susceptibility and unknown environmental factors. Studies of families of rheumatoid cases have also shown significant aggregation of autoimmune disorders which affects second degree as well as first

degree relatives suggesting that RA and thyroid autoimmunity have common autoimmune genes (Thomas et al., 1983).

Studies of DR and other MHC variants have also shown different associations with particular clinical subgroups. For instance, in Felty's syndrome there is a strong association with DR4, DQB and C4B null variants. This C4B null variant and DQB may characterize a single haplotype which is associated with extra-articular disease (Grennan and Sanders, 1988).

Selective IgA deficiency is associated with a strong familial predisposition to develop autoantibodies and autoimmune disease including SLE, and RA. It is also associated with particular combinations of the MHC alleles referred to as supratypes (Dawkins et al., 1987). One of these suprotypes (8.1) is common for both IgA deficiency and autoimmune diseases (French and Dawkins, 1990).

Aim of the work:

The aim of this work was to study and compare the immunological and immunogenetic characteristics of SLE with those of extra-articular rheumatic diseases.

REVIEW OF LITERATURE

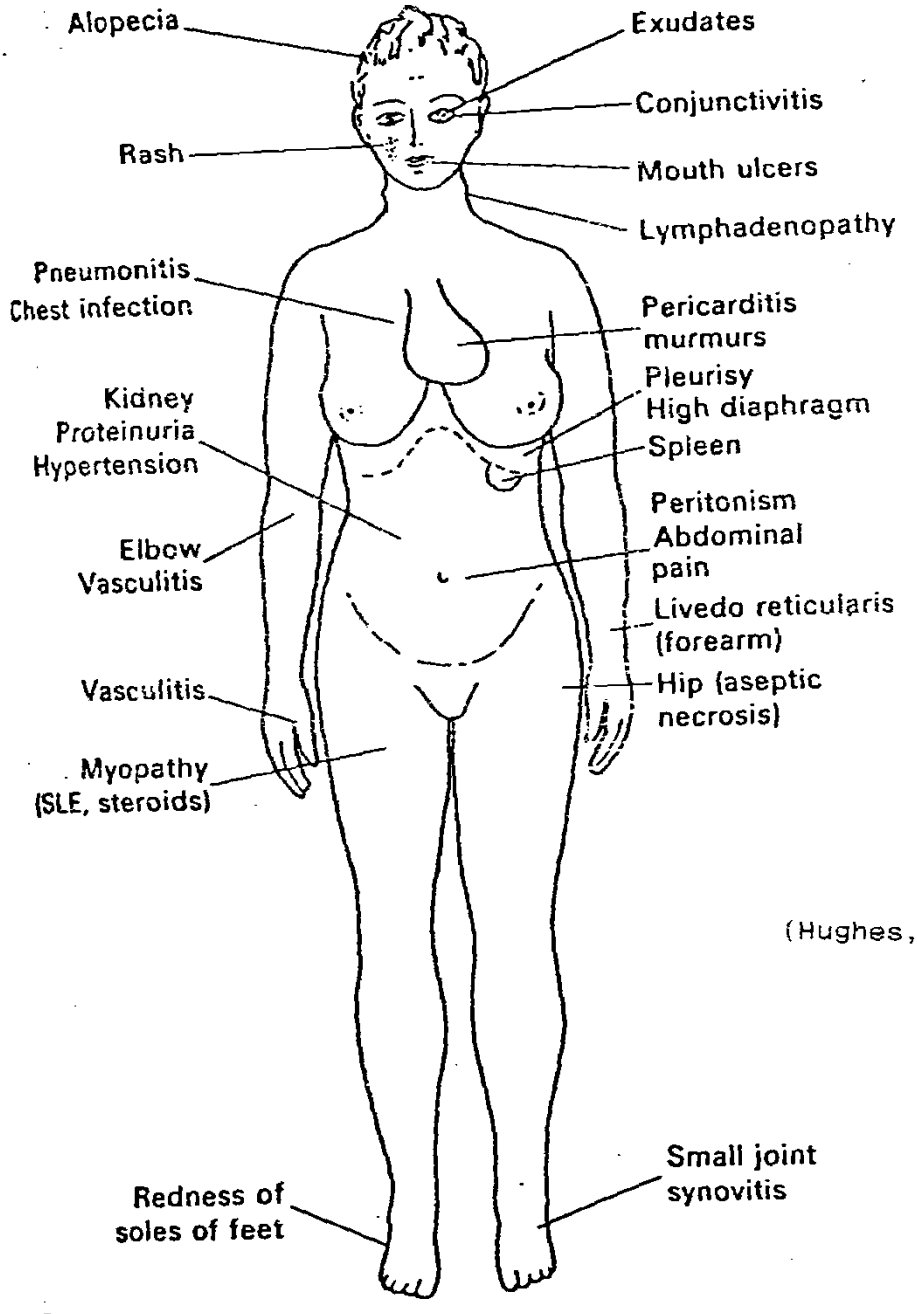
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Systemic lupus erythematosus is a chronic inflammatory disease of unknown cause that may affect the skin, joints, kidneys, lungs, nervous system, serous membranes, and or other organs of the body. Patients with SLE develop distinct immunologic abnormalities especially antinuclear antibodies. The clinical course of SLE is characterized by periods of remission and chronic or acute relapses (Schur.1989).

Clinical features:

SLE occurs in children and elderly, but the peak age at onset is the third decade. The prevalence of SLE has been estimated to be between 4 and 250 cases per 100,000 population. The figure 250 is based on data provided to the Lupus Foundation of America by the National Institute of Health. It appears to be more common in urban than in rural areas. There is also increased frequency of SLE among females which may be due to some hormonal effects (Wallace and Dubois, 1987).

The frequent findings of SLE are shown in figure (1) and their prevalencesare in table (1) (Hughes, 1982).



(Hughes, 1982).

Figure (1)

Table (1): Shows the prevalences of major clinical manifestations in SLE:

Manifestation	Percentage
Musculo-articular	95
Cutaneous	81
Fever	77
Neuropsychiatric	59
Renal	53
Pulmonary	48
Cardiac	38

(Quoted from Hughes, 1982).

Diagnosis:

The revised 1982 criteria for the classification of SLE (Table 2) is used as basis for the diagnosis of patients in many clinical reports. It is widely accepted and has a broad impact (Tan et al., 1982).

Table (2): The 1982 revised criteria for classification of systemic lupus erythematosus:

Criterion	Definition
1- Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.
2- Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.
3- Photosensitivity	Skin rash as a result of unusual reaction to sunlight by patient history or physician observation.
4- Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician.