HIV INFECTION IN RHEUMATOLOGY CLINIC

STUDY OF DETECTION

OF HIV CIRCULATING ANTIBODIES

IN SLE PATIENTS

SUBMITTED FOR PARTIAL FULFILEMENT OF

MASTER DEGREE IN INTERNAL MEDICINE

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1993

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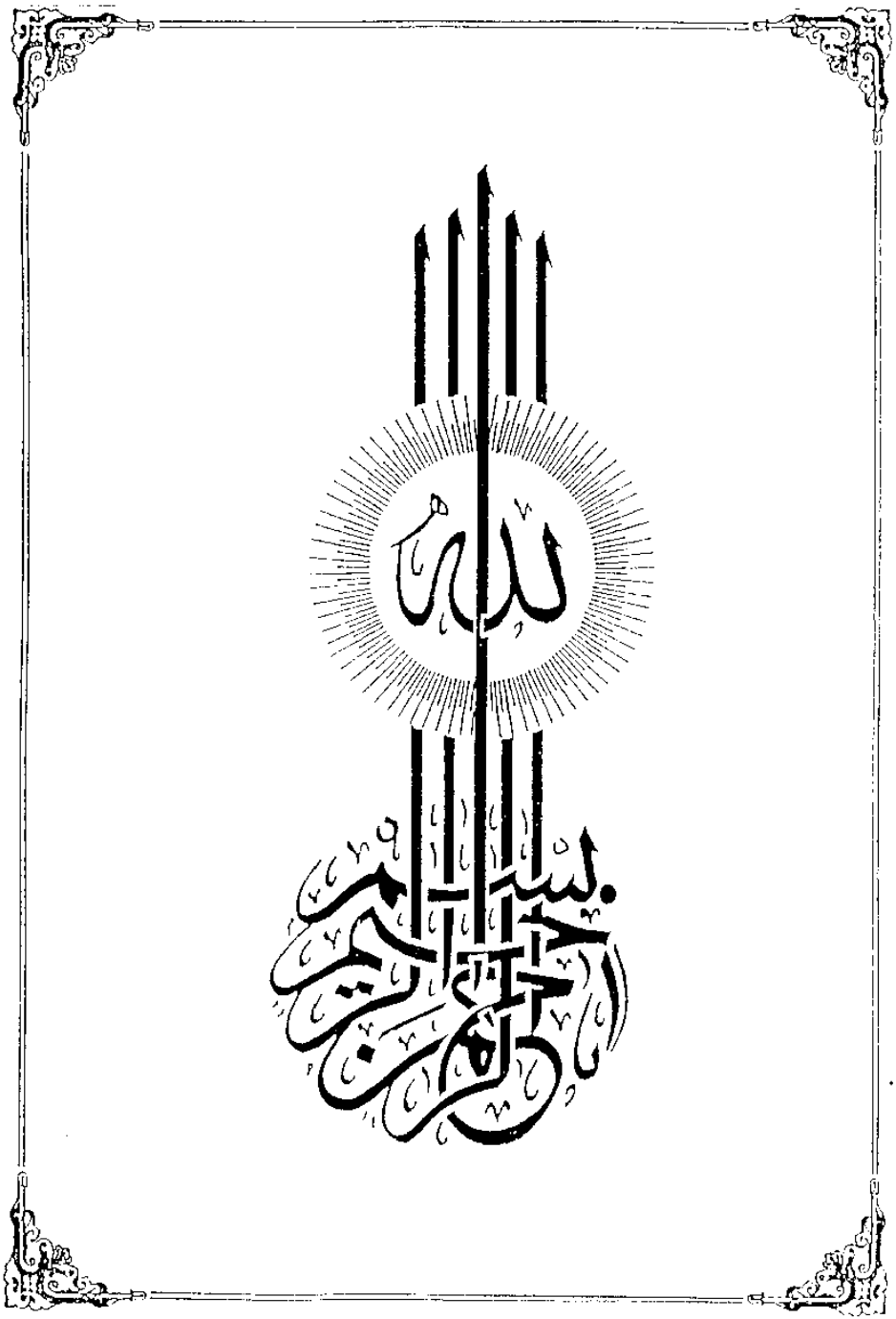

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INTRODUCTION

It Has Been Known That "SLE", Is the protype-auto-immune disorder, characterised by the presence of circulating auto-antibodies, and variety of immunological abnormalities that participate in the mediation of tissue damage. Such antibodies include the non-organ speciffic type such as:Antiextractable nuclear gene "ANA"- antipho-spholipids such as : Cardiolipin -lupus anticoagulants-VDRL-Rheumatoid factor-cytotoxic antibiodies to lymphocytes, neutrophils and platelets. *[Maddison, et al., 1984]*.

So, patients with "SLE" are considered to be immuno-compromised, and liable to get infections including "HIV" infection *[Bennet, et al., 1990]*

Evidences appear to support the hypothesis of "AIDS" being an autoimmune disease. HIV infection most strikingly, is presented with various auto-antibodies including those directed against both R.B.Cs and W.B.Cs. Those antibodies appear to be in part, responsible of the auto-immune features of the disease. Several clinical and seriological similarities exist between"AIDS", and classic auto-immune disease of "SLE" *[Shoenfeld, et al., 1989]*. Researchers suggested the presence of a causal relation between "HIV" infection,and clinical presentation of the auto-immune phenomenon of patietns with "SLE", *[Arend, et al., 1992]*.

Such postulation depends on the similarity in the presenting faetures of "SLE" and "HIV" infected patients, which were noted to be correlated, and may lead to diagnostic difficulties. These include: Malar flush-proteinurea-focal and segmental glomerulosclerosis coomb's positive-haemolytic anemia-immunomediated thrombocytopenia. *[Arkelys, et al., 1991]* lymphopenia and constitutional features of fever and lymphadenopathy *[Kaye, et al., 1989]*

"HIV" infected patients may show positivity for antinuclear antibodies-lupus anticoagluants-anticardiolipn antibodies. *[Hasselar, et al., 1990]*. circulatory immune complexes hypogammaglobulinemia and Rheumatoid factor *[Delfoaissy, et al., 1990]*. It was found that "SLE" patients, make antibodies to P_{24} gag of "HIV-1", and thoes patients express human anti-sm-monoclonal antibodies, which can cross react with P_{24} gag of "HIV"-1 *[Alexander, et al., 1990]*.

In a prospective study searching for a retro-virus infection, is patients with "SLE" using freshly isolated prepheral blood t-cells, B-cells and monocyte as well as macrophages. The strategy used was cocultivation with susceptible cell lines, looking for syncitia formation-reverse transcriptase production and nucleic acid hybridisation with "HIV".CDNR probes. No evidence of infection was found. *[Smith-Burchnell, et al., 1988]*.

Previous studies were carried on for the detection of "HIV" antibodies in patients with "SLE" estimating the level of "HIV"111 outo-antibodies using enzyme immunoassay "Emzynont-anti-HTIV 111 method *[Korneeva, et al., 1987]*. Negative results were obtained. Since the isolation of HIV, researchers once again began to scratch for a viral aetiology of "SLE".

"SLE"

1. HISTORICAL ASPECT

"SLE" is considered to be the protype auto immune disorder. During the ninteenth century, the term lupus described a skin disease, that consisted of spreading ulcerations in the face. Acute and choronic types were distinguished by *[Kaposi]* in 1872. *[D.J. MacCarty, et al., 1989]*.

The concept of a systemic form of the disease was formulated by *Osler* in 1895 when he suggested that, the basis of the disease was vasculitis, he described a systemic disease with a variety of skin manifestations, and recognized the involvement of joints-intestinal tract, serosol surfaces and kidney. *"Osler"* also described the characteristic periods of Remessions and exacerbations. *[Schousboe, et al.,1989]*.

The pathological abnormalities were later on described by *[Baher, Klennperer and Schrifrin]*, who emphasized that changes in many organs occurred, even in the absence of typical skin lesions. *[D.J.MacCarty, et al., 1989]*.

In *[1948, Hargraves at al.]* described lupus Erythematosus cell. "LE" cell. This major advance soon led to an increased interest in the disease,frequency of diagnosis, and eventually to the understanding of the mechanism of the "LE" cell phenomenon, and to the concept that antibodies were directed agaisnt nuclear antigens. *[Comez-Reino, et al., 1989]*.

Soon after the discovery of "L.E" cell, Corticosteroids and antimalarial drugs were used for treatment of the disease.

The discovery of antinuclear antibodies by means of fluorescent technique, led to the recognition of a wide variety of antibodies and, to the understanding of their clinical significance. *[Baldwin, et al., 1989]*

The concept of "SLE" as an immune complex-mediated disease evolved, and the role of complement in producing tissue damage was elucidated. More recently,various abnormal B cell, T cell and macrophage fucntions have been noted, in patients with active "SLE".

Yet, no single abnormality can explaine the origin of the disease. *[Federgreen, et al., 1989]*.

DEFFINITION

"SLE" is defined as a multisystem disease, characterised by the presence of multiple auto-antibody immune complexes that participate in immunologicaly mediated tissue injury. *[Schousboe, et al., 1989]*.

"SLE" is a syndrome commonly affecting young women. The clinical manifestations are extremely varied, and any major organ of the body may be involved. Misdiagnosis is not uncommon in early "SLE" where symptoms and signs may be few. Auto-Antibodies to DNA, RNA and other cell nuclear antigens are frequently present. Circulating immune complexes may deposite in major organs, causing inflamation and tissue damage by a number of mechanisms. The lupus disease is

marked by exacerbations and remissions. Management is dependant on accurate assessement of clinical activity, and severity. Pateint education and co-operation in management, affect the outcome of the disease.

With good management, the ten year survival may exceed 90% *[Boey, et al., 1992]*.

INCIDENCE AND PREVELANE

"SLE" affects individuals of all races, but its prevelance varies in different countries. The average annual incidence in U.S.A., has been estimated to be 27.5 per million population for white females, and 75.4 per million popualtion for Black females. The incidence of "SLE" among hospitalized patients was 4.6 per 100,000 per year in a baltimore, mareland study. *[Shornick, et al., 1991]*.

"SLE" occurs in children and in the eldery, but the peak age at the onset of the first symptom between 15 and 25 years. The mean age at diagnosis is 30 years. 90% of patients at such age are usually females *[Fronek, et al., 1991]*.

A higher percentage of males with "SLE", are particularly found among children and eldery individauls. *[Froneck, et al.,1991]*.

AETIOLOGY OF "SLE"

"SLE" is considered to be a multifactorial disease having several factors contributing to the elaboration of the disease.

GENETIC FACTORS

Results of clinical, serological, and histological studies, have doucumented the association between the hereditary complement [C_6] deficiency, and increased incidence of "SLE" among families.The propositus had SLE with prominant discoid features. Serum [C_6] was undetectable by radial immunodiffusion, and haemolytic . Assays.Serologic and typing studies suggested an autosomal codominant transmission. No correlation with a speciffic HLA phenotype was established. ***[Moone, et al.,1989].***

In a familial survey study of "SLE"., It was found that discoid lupus erythematosus was diagnosed in (0.61%) of SLE and 3.5% of discoid families, compared with 0.5% of controls. The data gave the best fit for a polygenic inheritance with a heritability of 66+/11/for "SLE", and 44 +/-10% for discoid lupus erythematosus. ***[Laurrence, et al., 1989].***

Systemic lupus erythematosus has shown association with the major histocompitability complex [MHC] class II DR antigens and class III complement components C_2 and C_4. In a study to detect C_4A and C_4B distribution among SLE patients, a statistically significant increase in C_4A QO allels when compared with ethnically matched controls. It was concluded that complete or partial deficiency of C_4 A is a genetic determinant of "SLE". ***[Dunckley, et al., 1988].***

C_3 genetic polymorphism was examined by immunefixation electrophoresis in controles and SLE pateints, no pateint group had frequencies which differ significantly from controles as regard C_3S, C_3 SF, C_3F. ***[Welch, et al.,1988]***.

"SLE" being a complex disease which is partly determined by genetic factors that influence susceptibility to the disease phenotype, an association study was made in a trial to define the haplotypes responsible for the disease, through applying the haplotype frequency difference [HFD]method which constructs its internal control group from those haplotypes transmitted to the affected individuals. Results showed that, haplotypes B_7 DR_3 as well as B_7 DR_2 have a high association with "SLE". When DR. locus was analysed alone, It was found that, allels DR_1-DR_5-DR_6 are having negative association for "SLE". ***[Seuchter, et al., 1988]***.

Families with "SLE" were investigated for anticardiolipin antibodies [CL] by global coagulation tests a well as one method based on dilute thromboplastine. Results revealed that, although anticardioplin levels are raised in subjects with (LA) lupus activity, there was no close correlation between length of KPTT and anticardiolipin titre. These findings support the hypothesis of transmissible agents, or other environmental factors being involved in lupus like disorder. ***[Mackie, et al., 1987]***.

There is deficiency in complement receptor type I [CR_1] on the erythrocytes of patients with SLE. This receptor is involved with processing of immune complexes. A restriction fragment length polymorphism [RFLP] identified, using a complementary DNA probe for CR_1 has been correlated with the numeric expression of CR_1 on normal erythrocytes. The gene frequeny for the 2 allels defined by this RFLP, was compared in patients with SLE-their consanguineous relatives, and non related normal subjects. The gene frequency was not significantly different in "SLE" patients. Such patients. Expressed fewer CR_1 mollecules per erythrocyte within each genotype, compared with normal and consanguineous relatives. SO, the inherited deficiency of erythrocyte complement receptor type I, does not cause susceptibility to systemic lupus erythematosus. *[Hyms, et al., 1987].*

Family members of "SLE" patients have isolated lab. abnormalities, such as false positive tests for syphilis, antinuclear antibodies, hypogammaglobulinemia, antiphospholipid antibodies and deposits of immunoglobulines in their skin *[Mackie, et al.,1987].*

Relatives of "SLE" patients have increased frequency of the disease (5%). The frequency of HLA-DR_2 and DR_3 in white patients is increased. HLA DR_2 & DQWL and specialy a rare allele DQBI, AZH confer a high risk of lupus nephritis. The association with DR_3, may be due to C_4A null allel, because the C_4A gene deletion is linked to B_8-DR_3 haplotype. C_4A

deficiency is associated with poor clearance of immune complexes *[Hymes, et al.,1987]*.

CHORONIC VIRAL INFECTION

A role for viruses in the aetiopathogenesis of human autoimmune diseases has long been suspected, but has not yet been proven.Their is continuing experimental support for the possible involvement of Epstein-Barr virus *[Mikkelson, et al.,1989]*.

Since the advent of "AIDS", there is great interest on linking retrovirus infection with the emergence of "SLE". It was reported that, (36%) of patients with systemic lupus erythematosus have serum antibodies to P_{24} gag protein of "HTIV.I" and that, two mechanisms classic for retrovirus "molecular mimicry and immunosupression" are operative in "SLE".

The P_{24} gag protein shares a proline -rich epitope with the Sm nucleoprotein, to whcih many "SLE" patients have antibodies. The imapired lymphocyte activation seen in prepheral blood T-cells in "SLE" pateints, is also seen in a human T-cell line infected with an A-type retroviral particle linked to "SLE". Studies suggest that, endogenous retroviral sequences are important in immunoregulation, etiology and pathogenesis of "SLE". *[Flescher, et al., 1992]*.

Spontaneous regression occured in some patietns of "SLE" presented with leukopnia, thrombocytopenia and hypocomplementemia . Such patients were serongative for