Correlation Between Pathological And Serological Determinants Of Renal Activity In Patients With Lupus Nephritis

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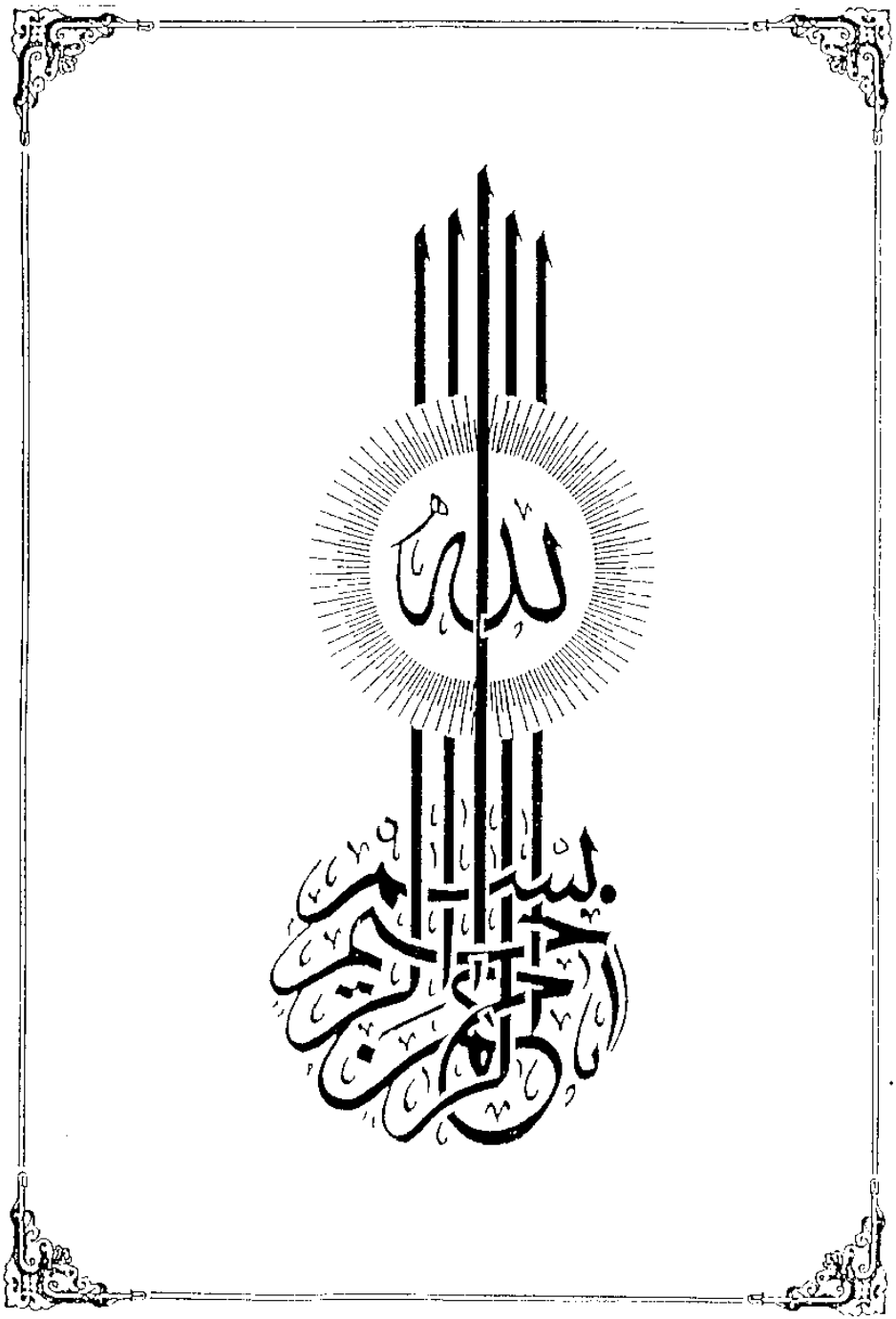

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INTRODUCTION:-

Lupus nephritis is one of the most serious organ involvement and a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE) *(Terai et al., 1987 & Glassock et al., 1991).*

Several distinct histological patterns of renal involvement in SLE have been recognized, the severity of these lesions determines the prognosis of patients with SLE *(Mclaughlin et al., 1991).*

Some investigators have suggested that all patients with SLE should undergo an initial renal biopsy for the purpose of staging the nature and extent of renal disease, in hope of guiding therapy and estimating the prognosis *(Glassock, 1986).* However, the value of renal biopsy in SLE as a prognostic tool and therapeutic guide is greatly diminished by the tendency for exacerbation and transformation of the disease from one category to another *(Baldwin et al., 1977 & Lee et al., 1984).* Moreover, the glomerular lesions do not always fit nicely into the discrete histologic categories *(Glassock et al., 1991).*

Renal biopsy can provide data on the extent and severity of the disease at a single point in time and the value of information decreases

with time since the initial observation *(Fries et al., 1978& Glassock et al., 1991)*. Thus, serial renal biopsies are required to evaluate accurately the severity of lupus nephritis *(Iwano et al., 1993)*.

Renal biopsy is a relatively invasive procedure, is not entirely without risk and performing serial biopsies in all patients with SLE is neither desirable nor practical *(Fries et al., 1978, Terai et al., 1987 & Iwano et al., 1993)*.

Therefore, serial studies of some more readily available non-invasive indices seem likely to be valuable. These indices would enable the physicians to predict outcome for patients with lupus nephritis and would minimize the need for repeated renal biopsies *(Hill et al., 1978, Terai et al., 1978 & Iwano et al., 1993)*.

AIM OF WORK :-

The aim of this work is to study the correlation between clinico-pathological changes and serological markers as determinants of renal activity in patients with lupus nephritis.

REVIEW OF LITERATURE

Systemic Lupus Erythematosus

DEFINITION :-

Systemic lupus erythematosus (SLE) is defined as a chronic inflammatory disease of unknown etiology which usually affects multiple organs but occasionally can clinically involve only one organ, for example the skin or kidney *(Tuffanelli, 1985).*

More precisely and concisely, *Nuki, (1987)* defined SLE as a multi-system connective tissue disease characterized by the presence of numerous auto-antibodies, circulating immune complexes, and wide spread immunologically determined tissue damage.

Berva, (1991) defined SLE as a disease of unknown etiology in which tissues and cells are damaged by deposition of pathogenic auto-antibodies and immune complexes.

EPIDEMIOLOGY :-

Age & Sex;

A female : male ratio of 9 : 1 is seen in most series of adults. Systemic lupus erythematosus can affect any age but more than 60% of patients experience the onset of disease between the age of 13 to 40 years. Among children, SLE occurs 2 times more commonly in females than in males. In patients in their teens, twenties, and thirties, 90% to 95% are

females. Thereafter, the female predominance again falls to that observed before puberty. Systemic lupus erythematosus occasionally occurs in the elderly, accounting for about 10% of all cases. The striking age and sex distribution of SLE has suggested an important role for the hormonal milieu in disease pathogenesis *(Han, 1980). Steinberg, (1988)* and *Berva, (1991)* noticed that the prevalence of SLE in Urban areas varies from 15 - 50 per 100,000 on which 90% of cases are women in the childbearing age.

Incidence and Prevalence :-

The disease is more common in Orientals than among whites. The disease has only recently been described in black Africans and appears to be more prevalent in China than in the United States *(Rothfield, 1991).*

The overall annual incidence of SLE is about 6 new cases per 100,000 population per year for relatively low risk populations. The incidence of a black female to develop SLE in her life is approximately 1 in 250. If a female member has SLE, the incidence increases approximately 30% for identical twins and 5% for other first degree relatives *(Steinberg, 1988).*

Blacks are more likely to have anti-Sm, anti-ribonucleoprotein (RNP), discoid skin lesions, proteinuria, psychosis, and serositis and have a poorer prognosis than whites *(Ward and Studenski, 1990).*

ETIOLOGY :-

I- Genetics :-

A hereditary component has also been ascertained, SLE appears more in certain racial and ethnic groups, such as blacks, and occurs at a greater frequency among relatives of patients with SLE. Hispanic and Asian populations are also susceptible *(Berva, 1991)*. The presence of genetic components in SLE are supported by family studies of the clinical disease, immunological and histocompatibility studies *(Nuki, 1987)*.

- **Clinical studies;**

Family members of SLE patients are more likely to have lupus or another connective tissue disease. The incidence is high among mono-zygotic than di-zygotic twin pairs *(Kimberly, 1981 & Berva, 1991)*.

- **Immunological studies;**

Family members are more likely to have a false positive test for syphilis, anti-nuclear antibodies (ANA), anti-lymphocyte antibodies, and hyper-gammaglobulinemia. Six percent of SLE patients have inherited deficiency of complement component especially C_2 *(Kimberly, 1981)*. Also, there is impaired interleukin-2 (IL2) activities in relatives *(Sakane et al., 1989)*.

• Histocompatibility studies;

The prevalence of HLA-B_7 and B_8 is increasing in SLE, and the HLA-B_8 antigen may be associated with a more severe form of renal involvement. There is increased frequency of HLA-B_8 and HLA-DR_3 in both males and females with later onset of the disease, while those with early onset of SLE, showed significant increase in any HLA-antigens *(Bell et al., 1984).*

HLA-B_8 and HLA-DR_3 are commonly associated with cutaneous lupus erythematosus *(Alvarellos et al., 1983).*

Systemic lupus erythematosus patients with anti-Ro / SS-A activity have a high incidence of HLA-DR_3. HLA-A_{10}, B_{18} and DR_2 tend to be associated with SLE-like syndromes in C_2-deficient patients. Familial cases have been described especially in association with complement deficiencies and IgA deficiency. Null alleles at C_2 and C_4 loci in the major histocompatibility complex are frequently found in patient with SLE *(Richard et al., 1991).*

These studies also show that in recent years, the incidence of SLE has increased in association with less severe disease course. This transformation is not well understood and may reflect new approaches to diagnosis. Thus, more sensitive and extensive serologic testings may allow recognition of milder disease forms. Alternatively, more effective and aggressive treatment may be promoting the more favorable prognosis.

Despite the general improvement in survival, there nevertheless remain patients at risk for life-threatening disease, particularly from renal failure and neurologic involvement. The factors distinguishing those with more benign course are unknown, and are important foci of investigations into the pathogenesis of SLE *(Steinberg, 1988).*

II- Hormonal Factors :-

Both male and female SLE patients have increased hydroxylation of estrone to 16-hydroxyestrone, a metabolite that is a potent estrogenic hormone. The ultimate outcome of all these factors is β cell hyperactivity accompanied by multiple abnormalities of immunoglobulins *(Berva, 1991).*

The onset of SLE frequency occurs at menarche, during pregnancy, during the post-partum period, or with the use of oral contraceptives containing estrogen. Testosterone metabolism also is different in women with SLE. The association of Klinefelter's syndrome with SLE has been well documented and suggests that X chromosomes may be predisposing factor for human SLE as well as for murine lupus *(Rothfield, 1991).*

III- Environmental Factors :-

A history of sun exposure before onset of the disease is obtained in about 36% of patients. The number of new cases of SLE usually increases

during the late spring and summer months in Southern New England and in New York. In other parts of the country with persistent year-round sunny weather, the incidence of new cases may not vary in this fashion. The relative lack of sun light in England has been postulated as an explanation of the rarity of SLE in that country *(Rothfield, 1991).*

IV- Infection :-

For many years, it has been thought that there might be a "lupus virus" that induces the disease. Patients with SLE have the endothelial cells of their kidneys and in their lymphocytes, structures that resemble viral nucleocapside *(Steinberg, 1988).*

Also, phospholipids in the cell walls of enteric bacteria may act as a polyclonal-B-cell activators or antigens to elicit antibody cross-reactive with the ribose phosphate backbone in DNA. Retrovirus has been implicated in the immune complex renal diseases of animals with SLE-like disorders *(Steinberg, 1985 & Berva, 1991).*

V- Ultraviolet Light :-

Some individuals with SLE have disease exacerbations following exposure to ultraviolet light. It induces keratinocytes to secrete IL-1, which in turn, stimulates B-cells and induces T-cells to produce growth

factors (IL-1, B-cell differentiation factor "BcDF", and B-cell growth factor "BcGF") which stimulate the immune system *(Steinberg, 1988).*

Berva, (1991) found that, in SLE patients, exposure to ultraviolet light causes disease flares probably by altering the antigenicity of DNA or the composition of dermal-epidermal junction.

Ultraviolet light damages the DNA or proteins in the skin and the patient makes antibodies to these altered molecules. Also, ultraviolet light increases binding of anti-Ro, anti-La, and anti-RNP to keratinocytes. It causes significant alterations in cellular membrane phospholipid metabolism, which may affect inflammation, also increase in production and release of cytokines including Il-1, and increase numbers of suppressor T-cells *(Furukawa and Kashihara-Sawani, 1990).*

VI- Diet:-

Alfalfa seeds cause SLE-like syndrome in monkey *(Podell, 1984).* L-Canavine alfalfa tablets ingestion was associated with a flare-up of previously quiescent SLE *(Roberts and Hyashi, 1983).*