Introduction

Systemic lupus erythematosus (SLE) is hetrogenous multi-system disease characterized by auto-antibody production and impaired immune complex clearance ***(Miah, 2008).***

SLE is more common in afro-caribbean and asian and more predominante in women (20 to 40 years), at a female to male ratio of 10:1 ***(Simon, 2006).***

SLE presented in youth and adulthood. 50% of patients will develop renal involvement within 3 years of diagnosis, and 10% progress to end stage renal disease and hemodialysis by 10 years ***(Amissah-Arthur & Gordon, 2009).***

The prevelance of SLE is increasing worldwide. SLE patients have no effective cures and treatment is often based on immune-suppressive regimens in the current therapeutic management ***(Waldman, 2009).***

Lupus itself is defined by combination of clinical and laboratory features according to American Collage of Rheumatology (ACR) for defining lupus ***(Apple, 2004).***

Diagnosis of lupus nephritis depends on clinical features which include: proteinuria, microscopic hematuria,

hypertension, reduced glomerular filtration rate and acute kidney injury ***(Ramesh, 2011).***

Anti-phospholipid syndrome is an auto-immune hypercoagulable state caused by anti-phospholipid antibodies which provoke thrombosis in both arteries and veins.

These antibodies are lupus anticoagulant and anti-cardiolipin antibodies ***(Charles & Wadi, 2011).***

In patients with SLE there are antibodies directed against the phospholipid components of coagulation factors which leads to recurrent arterial and venous thrombosis and often found with lupus anticoagulant ***(Shafi & Gupta, 2007).***

Patients with SLE on hemodialysis are found to have high incidence of arterio-venous fistula or graft thrombosis ***(Schick & Emmanuel, 2013).***

Aim of the work

To study the occurrence of vascular access thrombosis in patient with systemic lupus erythematosus on hemodialysis and its relation to SLE disease activity.

Systemic Lupus Erythematosus (SLE)

SLE is a chronic autoimmune illness characterized by auto antibodies directed at nuclear antigens and causing a variety of clinical and laboratory abnormalities, including rash, arthritis, leucokopenia, thrombocytopenia, alopecia, fever, nephritis and neurologic manifestations ***(Ruiz et al., 2007).***

Most or all of the symptoms of acute lupus are attributable to immunologic attack on the affected organs. Many complications of long-term disease are attributable both to the disease and to its treatment ***(Ringold, 2006).***

SLE may occur as an overlap syndrome that shares features with other autoimmune illnesses, such as mixed or undifferentiated connective tissue disease, dermatomyositis, sjogren syndrome, rheumatoid arthritis, and scleroderma. Also, organ-specific autoimmune diseases, such as thyroiditis, autoimmune hemolytic anemia, and idiopathic thrombocytopenia, frequently accompany and may be part of SLE ***(Gladman et al., 2005).***

Approximately one third of lupus patients have antiphospholipid antibodies, which induces blood clots and fetal death ***(McClain et al., 2004).***

Epidemiology:

Age and Sex:

There is a relationship between age and disease frequency observed in women with SLE ***(Danchenko et al., 2006).***

Disease incidence is higher among women between 14-55 years. Female children and postmenopausal women at equal rates to developed SLE. Males, in contrast to females, do not have an age-related peak incidence ***(Amador-Patarroyo et al., 2012).***

SLE is a disease of women, particularly during their reproductive period. Female to male ratio is 10:1 ***(Schwartzman-Morris & Putterman, 2012).*** This support the hypothesis that hormonal factors may be involved in the pathogenesis of the disease, these were supported by increase risk of development of SLE in men with klinfelter syndrome, menopausal women treated with hormonal replacement therapy and women exposed to estrogen containing oral contraceptives ***(Costenbader, 2007).***

Race:

Both geography and race affect the prevalence of SLE, its frequency and severity of clinical and laboratory

manifestations. The disease appears to be more common in urban than rural areas ***(Chakravarty et al., 2007).*** The prevalence of SLE has been estimated between 40-200 per 100,000 in Caucasian and Afro-Caribbean population, respectively ***(Danchenko et al., 2006).*** A higher prevalence of SLE occurs in African American women in United States than in white women.

Morbidity and mortality:

The unpredictable nature of the disease and wide spread potential harm lead to variation in the clinical course of the disease ranging from relatively benign to rapidly progressive or even fatal disease. A Cohort study done by ***Cervera et al., in 2003*** found that within 10 years of diagnosis, 48.1% patients presented 1 or more episodes of arthritis, 31.1% patients had malar rash, 27.9% had active nephropathy, 19.4% had neurologic involvement, 16.3% had Raynaud phenomenon, 16% had serositis, 13.4% had thrombocytopenia and 9.2% had thrombosis.

A retrospective cohort study used data from the National Health Insurance Research Database of Taiwan on female patients newly diagnosed with SLE from 2001 to 2004 has found that female patients with late-onset SLE carried a higher risk of mortality than those with adult-

onset disease (15-50 years) in the presence of other co-morbidities. Juvenile-onset SLE patients were at greatest risk of mortality, which is probably due to disease severity ***(Chen et al., 2013).***

The frequency of lupus could be increasing because milder forms of the disease are being recognized and patients with lupus nowadays could have a milder form of the disease and a better chance of survival than patients described several decades ago, probably because of an earlier diagnosis of milder disease. However, despite these improvements in survival, fatigue and other quality of life measures might not have improved ***(Danchenko et al., 2006).***

Pathogenesis and Etiology:

Although the etiology of SLE is not yet well known, increasing evidence indicates that it is caused, or at least influenced by a combination of genetic, immunologic, hormonal and possibly environmental factors ***(Danchenko et al., 2006).***

1. The genetic and immunological factors:

The genetic contribution to SLE has been demonstrated in studies of specific ethnicities, families, twin cohorts, and other groups. Epidemiology data on the

sibling risk ratio, familial aggregation of SLE, and the disease concordance rate in twins all support a genetic component of the occurrence of SLE. A study has shown that a family history of autoimmune diseases may be a risk factor for SLE, and first degree relatives of female patients with SLE have four fold risk of having autoimmune diseases over first degree relatives of female subjects without an autoimmune disease ***(Vinuesa and Cook, 2007).***

Over the last decade, several studies using gene knockout technology have revealed that the disruption of several genes caused SLE-like syndrome in mice. Based on the function of these genes, the causes of SLE can be classified into two categories: impairment of immunological tolerance and defective clearance of auto-antigens. The impairment of immunological tolerance might induce SLE by two mechanisms. First, the threshold for lymphocyte activation becomes low by mutations in genes, which were critical for immunological tolerance. Second, auto reactive lymphocytes might not be deleted by mutations in genes related to apoptotic machinery. On the other hand, recent reports have shown that defects in the genes for clearance of auto-antigens have also been shown to cause SLE. For example, complement protein C1q ***(O'Flynn et al., 2011).*** C1q deficiency is a rare condition,

autosomal recessively inherited complement deficiency. Since the classical complement cascade is known to be involved in the clearance of immune complexes, failure of immune complex clearance in C1q deficiency has been the traditional explanation for the strong association of lupus in these patients ***(Marquart et al., 2009).***

To better understand the pathogenesis of SLE, the contributions of various cell types have been examined. There is evidence for contributions by B cells, dendritic cells, non lymphoid cells at sites of tissue injury, and T cells to the development of SLE. B cells are important in SLE as they produce antibodies against nuclear and cell surface antigens. B cell hyperactivity is present in SLE and this results in the production of a variety of autoantibodies including those against nuclear antigens that contain chromatin (DNA histone) and uridylate-rich (U) small nuclear ribonucleoproteins (U-RNP or U-snRNP) ***(Schwartz et al., 2010).***

Indeed, it is now accepted that B cells may play pathogenic roles not only through conventional autoantibody mediated mechanisms, but also by performing antibody-independent regulatory functions. At least 2 mechanisms could account for the antibody-independent activity of B cells. First, B cells may contribute to T cell

activation and influence T helper cell polarization through their autoantigen-presenting and co-stimulatory abilities. Second, B cells might induce tissue damage through their ability to regulate leukocytes and follicular dendiritic cells. Also human SLE is characterized by both quantitative and functional B cell abnormalities ***(Looney et al., 2004).***

Soluble factors, such as complement components, participate in local tissue injury; these may have additional importance in pathogenesis by their influence on the clearance of apoptotic debris. A variety of additional cells, including T-cells, could participate in inflammation and tissue injury either directly or through recruitment of other cells ***(Whittier et al., 2009).***

2-The hormonal factors:

Substantial evidence of the immune-regulatory function of estradiol, testosterone, progesterone, dehydroepiandrosterone (DHEA), and pituitary hormones, including prolactin has supported the hypothesis that they modulate the incidence and severity of SLE ***(Korbet et al., 2010).***

Sex hormone metabolism might contribute to gender differences in susceptibility to SLE. Men and women with SLE have accelerated metabolism of testosterone. Estrone is preferentially hydroxylated at C-16 position in men and

women with SLE and in their first degree relatives, resulting in accumulation of 16 hydroxylated metabolites which have sustained high estrogenic activity ***(Kelley et al., 2005).***

Menopausal women with hormone replacement therapy and women exposed to estrogen containing oral contraceptives also have increased risk for SLE and also observed in some males with Klinefelter's syndrome ***(Costenbader et al., 2007).***

Prolactin levels are elevated in some individuals with SLE and may increase disease activity; some studies revealed that oral bromocriptine for 2 weeks in postpartum patients with SLE may relieve the disease from hyperprolactinemia and hyperestrogenemia, and may be beneficial in protecting the patients from disease relapse and in reducing the usage of steroid and immunosuppressant ***(Saha et al., 2011).***

Abnormalities of hypothalamus-pituitary-adrenal axis may also exist among those with SLE patients appear to have an abnormal reaction to stress characterized by an increased response to human corticotrophin releasing hormone (hCRH) ***(Wasef, 2004).***

Recent studies revealed that elevations in the levels of estrogen or prolactin can promote the survival and activation of high affinity autoreactive B cells. These hormones engage different B cell pathways to interfere with B cell tolerance. The identification of SLE patients with either an estrogen responsive disease will influence the development of therapeutics that can specifically modulate hormonal responses ***(Grimaldi, 2009).***

3-The environmental factors:

Infection:

Viruses may stimulate specific cells in the immune network. In addition, trypanosomiasis or mycobacterial infections may induce anti-DNA antibodies or even lupus like symptoms, and lupus flares may follow bacterial infections ***(Cooper et al., 2011).***

Serological studies of serum antiviral antibodies in SLE reveal that although elevated levels are often found, they are directed at a number of apparently unrelated viruses including measles, rubella, mumps and Epstein Barr virus (EBV). Many findings suggest that repeated or reactivated EBV infection, which results in increased EBV IgA seroprevelance and higher IgG antibody titres, may be associated with SLE, and influences immune responsiveness to EBV in SLE patients ***(Parks et al., 2005).***

Ultraviolet light:

Seventy percent of SLE patients have disease flared by exposure to ultraviolet (UV) light. The B spectrum may be more important than a spectrum in activating disease in humans. Some data suggest that exposure to UVA might benefit SLE. UV light may stimulate keratinocytes to express more (SnRNP) on their cell surface and to secrete more interlukin-1 (IL-1), IL-3, IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF) and tissue necrosis factor alpha (TNF), thereby stimulating B cells to make more antibody. In addition to the local effects in skin, UV light may also increase the degree of systemic autoimmunity by interfering with antigen processing, activation of macrophages, and increasing number of autoantibody formation ***(Ramos and Brown, 2010).***

Diet:

Study in human SLE suggested that 20g of fish oil daily may be steroid sparing. The role of these dietary observations in human disease is uncertain, but we recommend that patients with SLE minimize their dietary intake of excessive calories, and saturated fat ***(Weckerle et al., 2011).***

Drugs:

Drug-induced lupus:

Before making a diagnosis of SLE, rolling out drugs as the cause of the condition is important. Drug induced lupus is a syndrome which share symptoms and laboratory characteristics with idiopathic systemic lupus erythematosus. The first case of drug induced lupus was reported in 1945 and associated with sulfadiazine. In 1953, it was reported that drug induced lupus was related to use of hydralazine. More than 80 drugs have been associated with drug induced lupus (e.g.: Hydralazine, Procainamide, Isoniazid, Chlorpromazine, Methyl-dopa, Statins) ***(Vasoo, 2006).***

Similarly to idiopathic lupus, drug induced lupus can be divided into systemic, subacute cutaneous and chronic cutaneous lupus. The syndrome is characterized by arthralgia, myalgia, pleurisy, rash and fever in association with antinuclear antibodies in the serum. The clinical and laboratory manifestations are similar but central nervous system and renal involvement are rare in drug induced lupus. Recognition of drug induced lupus is important because it usually disappear within a few weeks after stopping the drug ***(Alonso et al., 2011).***

Others:

Silica dust (especially among men) and cigarette smoking may increase the risk of developing SLE ***(Freemer et al., 2006).*** There is no apparent association between SLE and the use of hair dyes, occupational solvent exposure and the use of pesticides ***(Cooper and Parks, 2004).***

Clinical features of SLE:

Systemic lupus erythematosus (SLE) can affect the skin, joints, kidneys, lungs, nervous system, serous membranes and other organs of the body. The clinical course of SLE is variable and may be characterized by periods of remissions and relapses ***(Isenberg et al., 2008).***

Non specific features:

Patients may present with fever, fatigue, anorexia and weight loss or lymphadenopathy, and often undergo a series of investigations including biopsy to exclude malignancy or infection such as tuberculosis ***(Cervera et al., 2003).***

Fever is associated with active disease and must be differentiated from infection. SLE patients are immune-suppressed as a result of the disease and its treatment. C-reactive protein (CRP) is usually not raised in active SLE