INTRODUCTION

Systemic lupus erythematosus (SLE) is a worldwide multisystem autoimmune disease of unknown etiology ***(Essam et al., 2013)***. It usually affects adults as well as adolescences and affects ten times as many women as men. It characterized by production of autoantibodies, which result in widespread immunological abnormalities and immune complex formation. Symptoms range from rather mild manifestations such as rash or arthritis to life threatening conditions ***(Postal et al., 2012)***.

Juvenile systemic lupus erythematosus diagnosed as disease onset before 16 years of age. Patients younger than 5 years are rarely affected and the age of onset may contribute to the course of disease in terms of clinical presentation, organ involvement, and serological findings ***(Hedrich et al., 2011).***

Juvenile-onset systemic lupus erythematosus represents 15-20% of all SLE cases. Whilst features of this chronic complex multisystem autoimmune disorder are highly variable, children and adolescents generally present with a more severe illness than adults and accrue greater disease damage over time. Juvenile SLE has a less striking female preponderance and differs from the adult form in pattern of major organ manifestation (***Morgan et al., 2013).***

In childhood-onset SLE, there are several clinical symptoms more commonly found than in adults, including mucocutaneous involvement (malar rash, ulcers), renal involvement (proteinuria, urinary cellular casts), seizures, thrombocytopenia, hemolytic anemia, fever, and lymphadenopathy. In adults, Raynaud, pleuritis and sicca are twice as common as in children and adolescents ***(Livingston et al., 2011)***

Over recent decades, survival of patients with juvenile SLE has improved considerably, with 10-years survival rate being 90% now ***(Waston et al., 2012).***

Despite these advances, patients with juvenile SLE have a significantly lower life expectancy than the general population, with a 4-fold greater risk of death. Moreover, mortality rates are higher in patients with juvenile SLE than in patients with adult-onset SLE, and the mortality risk increases with longer disease duration ***(Hersh et al., 2010).***

AIM OF THE STUDY

This study aims to evaluate the differences in organ involvement, serological pattern, disease activity and damage indices between juvenile-onset and adult-onset systemic lupus erythematosus (SLE) patients at diagnosis and follow-up.

Chapter (1)

ADULT SYSTEMIC LUPUS ERYTHEMATOUS

Systemic lupus erythematosus (SLE) is is a chronic autoimmune disease affecting multiple organ systems. In the past 40 years, prognosis for patients with SLE has improved significantly because of advances in the understanding of molecular mechanisms involved in the pathogenesis of disease, which has translated into early diagnosis and novel therapeutic strategies. ***(Shankar and Behera, 2014)***

Epidemiology

The reported prevalence of SLE in the population is 20 to 150 cases per 100,000 ***(Pons-Estel et al., 2010).***

1- Geographic and Racial Distribution

Both geography and race affect the prevalence of SLE and 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 the highest rates among United Kingdom residents of Afro-Caribbean descent, and non-White populations elsewhere ***(Danchenko et al., 2006).***

2- Gender Distribution

The increased frequency of SLE among women have been attributed in part to an estrogen hormonal effect ***(Costenbader et al., 2007).***

Men with lupus tend to have higher frequencies of renal disease, skin manifestations, cytopenias, serositis, neurologic involvement, thrombosis, cardiovascular disease, hypertension, and vasculitis than women. In contrast, Raynaud phenomenon, photosensitivity, and mucosal ulceration are less frequent manifestations in men than women. Most, but not all studies suggest that men have a higher one-year mortality rate ***(Lu et al., 2010).***

Female preponderance remains, it less pronounced in JSLE (female to male ratio of approximately 5: 1 compared to 9: 1 in adult-onset SLE ***(Watson et al., 2012)***

There is also evidence for a gene dose effect, since the prevalence of XXY (Klinefelter's syndrome) is increased 14-fold in men with SLE when compared with the general population of men, whereas XO (Turner's syndrome) is underrepresented in women ***(Scofield et al., 2008).***

3- Age Prevalence

SLE can occur at any age, it is most common in childbearing age, which correlated with levels of female sex

hormones. Although it reported in both extremes of life, 65% of patients with SLE have disease onset between the ages of 16 and 55. Of the remaining cases, 20% present before age 16 and 15% after age 55 ***(Lam and* Petri, *2005).***

Etiopathogenesis:

The etiology of SLE remains unknown and is clearly multifactorial. Many observations suggest a role for genetic, hormonal, immunologic, and environmental factors **(Relle and Schwarting, 2012).**

1- Genetic Factors:

SLE is a multigenic disease. A genetic predisposition is upported by 40% concordance in monozygotic twins; if a mother has SLE; her daughter's risk of developing the disease estimated to be 1:40, and her son's risk, 1:250. These observations of familial aggregation and twin concordance rate prompted recent work towards a comprehensive genetic analysis of SLE ***(Sestak et al., 2011).***

A combination of genome-wide association studies (GWAS) and candidate gene approaches has led to the identification of more than 30 robust genetic associations with SLE. They are genes, which induce the transcription of proteins involved in key pathogenetic pathways, including

apoptosis and clearance of apoptotic material or immune complexes, function of innate and adaptive immunity, production of cytokines, chemokines, or adhesion molecules. Both major histocompatibility complex (MHC) and non-MHC genes were found to be linked with SLE susceptibility. GWAS found that MHC region have the strongest association with SLE risk in comparison to any other investigated gene (Figure 1) ***(Gatto et al., 2013).***

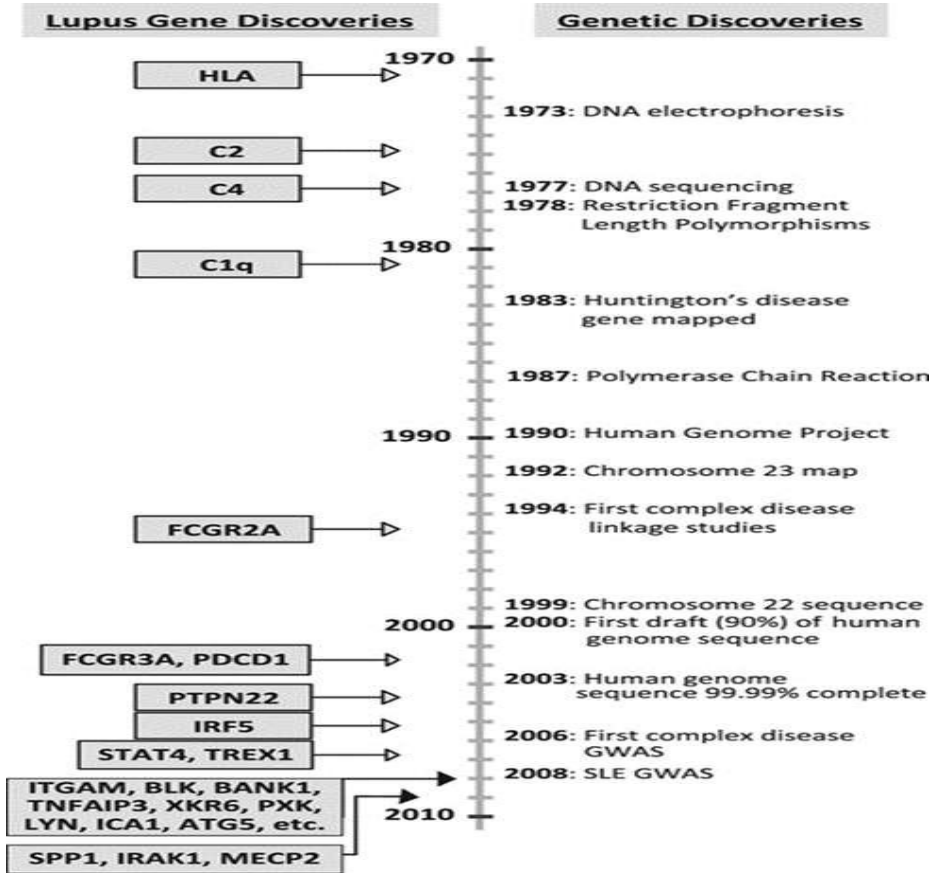

Fig. (1): A timeline of discoveries in human genetics (right) and confirmed genes discovered in lupus (left). Adapted from ***(Moser et al., 2009).***

2- Hormonal Factors:

Hormones contribute through unknown mechanisms to the increased prevalence of SLE among women ***(Duarte et al., 2011).***

Substantial evidence of the immunoregulatory function of estradiol, testosterone, progesterone, dehydroepiandrosterone (DHEA), and pituitary hormones, including prolactin, have supported the hypothesis that they modulate the incidence and severity of SLE ***(Li et al., 2005)***.

The use of estrogen-containing contraceptive agents is associated with a 50 % increase in risk of developing SLE; while either early onset of menarche (age ≤10 years) or administration of estrogen to postmenopausal women doubles their risk ***(Costenbader et al., 2007).***

3- Immunological factors: (figure 2)

SLE is primarily a disease with abnormalities in immune regulation ***(Hahn et al., 2005)***. The mediators of SLE are autoantibodies and immune complexes (ICs) they form with antigens; the autoantibodies may be present for years before the first symptom of disease appears ***(Arbuckle et al., 2003)***.

Self-antigens that are recognized primarily on cell surfaces, particularly by cells that are activated or undergoing apoptosis, where intracellular antigens access cell surfaces where they can be recognized by the immune system ***(Graham and Utz, 2005)***.

Phagocytosis and clearing of ICs, of apoptotic cells, and of necrotic cell derived material are defective in SLE, allowing persistence of antigen and ICs ***(Munoz et al., 2009)***.

B cells/plasma cells that make autoantibodies are more persistently activated and driven to maturation by B cell activating factor (BAFF, also known as B lymphocyte stimulator, BLyS) and by persistently activated T helper cells making B-supporting cytokines such as IL-6 and IL-10. BAFF (BLyS), whose serum levels are elevated in some patients with SLE, promotes formation and survival of memory B cells and plasmablasts, this increased autoantibody persistence is not down regulated appropriately by anti-idiotypic antibodies, or by CD4+ regulatory T cells, or by CD8+ suppressor T cells ***(Gerl et al., 2010)***.

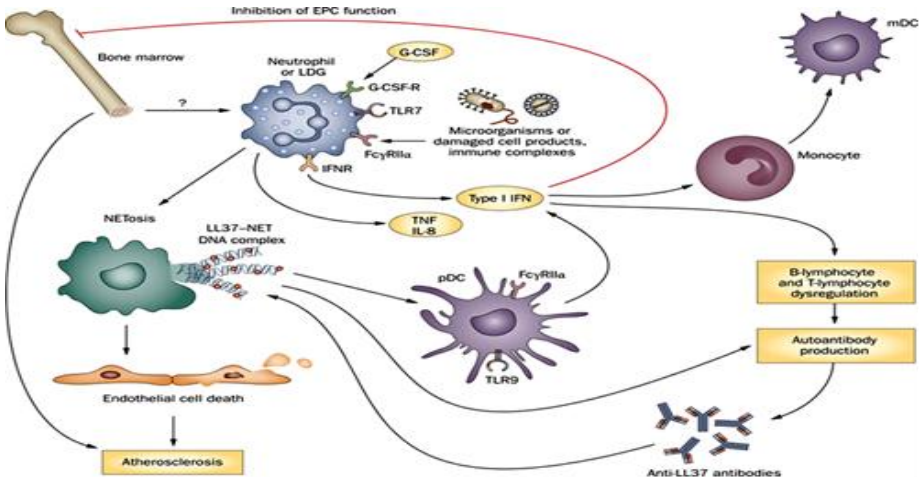

Fig. (2): Immunological abnormalities in SLE.
Adapted from ***(Caroll, 2004).***

A) T Lymphocytes in SLE:

Lupus T cells are likely to contribute to disease through contact dependent mechanisms (e.g., CD40L:CD40) as well as released cytokines ***(Pathak* and Mohan*, 2011)***.

B) B Lymphocytes in SLE

Among many potential immune aberrations, SLE is marked by uncontrolled B-cell activation that may be a result of genetic predisposition, the presence of aberrant help from CD4 T cells, or altered cytokine milieu ***(Crispin and Tsokos, 2011).***

In active SLE, a marked disease activity–dependent reduction in the number of naive B cells is observed, and the

number of plasma cells is increased in the peripheral blood. All B-cell subgroups (B1 and B2 cells in both the follicular and marginal zones) contribute to the production of autoantibodies ***(Tsokos, 2011)***.

C) Dendritic Cells in SLE

Dendritic cells (DCs) are a heterogeneous group of cells derived from the bone marrow, which participate in immunovigilance, antigen presentation and tolerance. There are two subtypes, conventional dendritic cells and Plasmacytoid DCs (pDCs), the latter playing a principal role in the pathogenesis of SLE ***(Sifuentes Giraldo et al., 2012***).

IFN-α, CD40 ligand, free nucleosomes and autoantibody–DNA complexes cause differentiation and activation of normal DCs and stimulate their cytokine production. DCs may promote or suppress the immune response ***(Tsokos, 2011).***

4- Environmental Factors

The environment probably has a role in the etiology of SLE via its effects on the immune system.

A) ***Infection:***

The possibility that viruses may trigger SLE has been considered during the past 40 years, viruses may stimulate specific cells in this immune network ***(Tsokos, 2011).***

Endogenous retroviruses have also been postulated to trigger lupus through structural and functional molecular mimicry ***(Perl et al., 2010)***.

B) Ultraviolet (UV) light:

It is the most obvious environmental factor that can exacerbate the disease ***(D'Cruz et al., 2007).*** The classic environmental precipitant of SLE is ultraviolet light (UV).

UV-B can be blocked by sunblocks and UV-A from computer and television screens can be blocked by plastic ***(Petri, 2006).***

C) *Drugs: Drug-induced lupus erythermatosus (DILE):*

(DILE) is a syndrome, which share symptoms and laboratory characteristics with idiopathic systemic lupus erythematosus. The first case of DILE was reported in 1945 and associated with sulfsalasine. In 1953, it was reported that DILE was related to the use of hydralazine. More than 80 drugs have been associated with DILE (e.g., Hydralazine, Procainamide, Isoniazid, Chlorpromazine, Methyldopa, Minocyclene and Statins), so before making a diagnosis of SLE, ruling out drugs as the cause of the condition is important. ***(Vasoo, 2006).***

Similarly, to idiopathic lupus, DILE divided into systemic, sub acute 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 DILE. Recognition of DILE is important because it usually reverts within a few weeks after stopping the drug ***(Sarzi-Puttini et al., 2005).***

D) Others:

Allergies to medications, particularly to antibiotics, reported more frequently in patients with newly diagnosed SLE than healthy controls ***(Schur& Hahn, 2012).***

Clinical Features of SLE:

SLE is a chronic autoimmune disease that can affect almost any organ system. Its presentation and course are highly variable, ranging from indolent to fulminant. The triad of fever, joint pain, and rash in a woman of childbearing age should suggest the diagnosis as a classic presentation of SLE ***(Bartels et al., 2012)*** (figure 3).

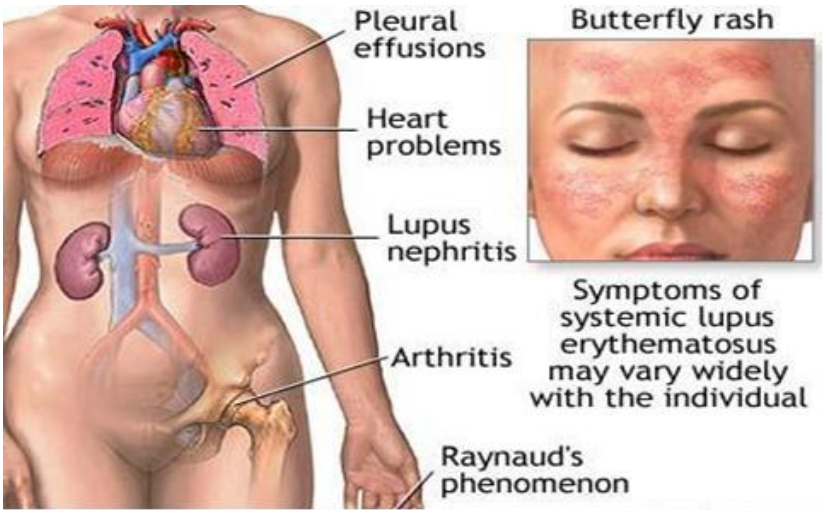

Fig. (3): Clinical picture of SLE. Adapted from ***(Caroll, 2004)***

Constitutional symptoms:

The patients with SLE may present with various systemic manifestations. The general symptoms include fever, malaise, arthralgias, myalgias, headache, and loss of appetite and weight. Nonspecific fatigue, fever, arthralgia, and weight changes are the most common symptoms in new cases or recurrent active SLE flares ***(Cojocaru et al., 2011).***

Fatigue is the most common constitutional symptom associated with SLE; it can be due to active SLE, medications, lifestyle habits, or concomitant fibromyalgia or affective disorders ***(Jump et al., 2005).***

Fever, another common yet non-specific symptom of SLE, may also result from many causes, the most common of

which include active SLE, infection, and drug fever. Careful history taking may help to differentiate these. ***(Pteri, 2007).***

Weight changes can related to SLE either directly or to its treatment. Weight loss can result from diminished appetite, gastrointestinal disease, or adverse effects of diuretic. Weight gain most frequently occurs due to corticosteroid-induced increase in appetite and to fluid retention in the nephritic syndrome **(Schur, 2006).**

Musculoskeletal symptoms:

Musculoskeletal symptoms particularly arthralgia, myalgia, fibromyalgia, tenosynovitis, bursitis and arthritis, represent the most common complaints in SLE. Arthritis tends to be migratory and asymmetrical. It can affect any joint, but the small joints of the hands, wrists and knees are involved most frequently. Arthritis classically is nonerosive, usually nondeforming**,** morning stiffness is usually measured in minutes and the degree of pain often exceeds objective physical findings ***(Kakumanu et al., 2009).***

Soft tissue swelling is common and effusions, when they occur, usually are mildly inflammatory. However, 10% developed hand deformities due to chronic arthritis and tendonitis, called Jaccoud's arthropathy, which mimic the changes observed in rheumatoid arthritis ***(Julie and Daniel, 2005).***