INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune systemic disorder with unknown etio-pathogenesis. Upon the susceptible genetic, hormonal and abnormal immunologic background, the environmental factors especially ultraviolet rays may play role as trigger to permit disease development ***(Von Feldt, 1995).***

Auto-antibodies especially Antinuclear Antibodies (ANA), anti-double stranded DNA (anti-dsDNA), anti-smith antibody (anti-Sm), anti-phospholipid antibodies (aPLs), antibodies against RBC, WBC, platelets, anti-neuronal antibodies, consumption of complements and production of Immune-complexes can contribute to creation of all clinical and laboratory manifestations of SLE ***(Wallace and Hahn, 2013).***

Worldwide, the prevalence of SLE varies. The highest rates of prevalence have been reported in Italy, Spain, Martinique, and the United Kingdom Afro-Caribbean populations. Although the prevalence of SLE is high in black persons in the United Kingdom, the disease is rarely reported in blacks in Africa ***(Danchenko and Satia, 2006).***

It occurs predominantly among women of childbearing ages and involves all organs in the body ***(Dhar and Sokol, 2006).***

Aim of the Work

The purpose of this study was to evaluate the cardiovascular autonomic function in patients with Systemic lupus erythematosus, and to correlate it with SLE clinical features.

Systemic Lupus Erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous multi-system autoimmune disease ***(Molineros et al., 2014)*** with protean manifestations, which may range from relatively minor skin and joint manifestations to severe life-threatening major organ involvement ***(Navarra and Leynes, 2010).***

Pathophysiology of SLE

Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, epigenetic, ethnic, immuno-regulatory, hormonal, and environmental factors. Many immune disturbances, both innate and acquired, occur in SLE ***(Kohli et al., 2018).***

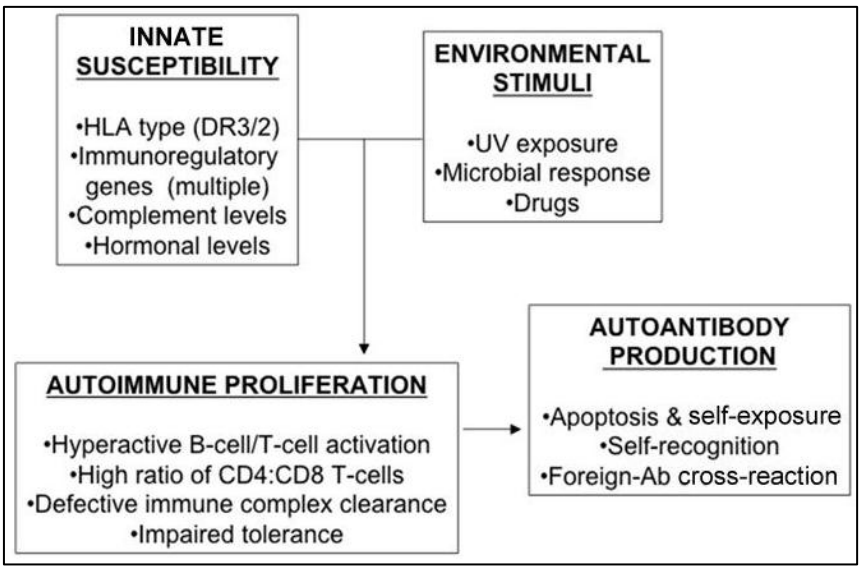

Fig. (1): Pathophysiology of SLE

HLA = human leukocyte antigen; UV = ultraviolet light.

Etiology of SLE

1. Genetic factors

The following observations are compatible with a genetic role in the pathogenesis of SLE:

- There is a high concordance rate (14 to 57 %) of SLE in monozygotic twins ***(Deapen et al., 1992).***
- 5 to 12% of relatives of patients with SLE have the disease, and there is an increased frequency of anti-C1q and anti-cardiolipin antibodies and C3 and C4 abnormalities in relatives ***(Hunnangkul et al., 2008).***
- 27% of children of mothers with lupus had a positive test for anti-nuclear antibodies ***(Murashima et al., 2004).***
- The most common genetic predisposition is found at the major histocompatibility locus (MHC). The MHC contains genes for antigen presenting molecules (class I human leukocyte antigens [HLA-A, -B, and -C] and class II HLA molecules [HLA-DR, -DQ, and DP]). The MHC also contains genes for some complement components, cytokines, and heat shock protein ***(lee et al., 2012).***

2. Hormonal factors

- Substantial evidence of the immunoregulatory function of estradiol, testosterone, progesterone, dehydro-epiandrosterone (DHEA), and pituitary hormones, including prolactin, has supported the hypothesis that they modulate the incidence and severity of SLE**.** As example:

- The use of estrogen-containing contraceptive agents is associated with a 50 percent 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. Immune abnormalities

SLE is primarily a disease with abnormalities in immune regulation. Antibodies may be present for many years before the onset of the first symptoms of SLE. The proposed mechanism for the development of autoantibodies involves a defect in apoptosis that causes increased cell death and a disturbance in immune tolerance. The redistribution of cellular antigens during apoptosis leads to a cell-surface display of plasma and nuclear antigens in the form of nucleosomes. Subsequently, dysregulated (intolerant) lymphocytes begin targeting normally protected intracellular antigens. The defective clearance of the apoptotic cell debris allows for the persistence of antigen and immune complex production ***(Muñoz et al., 2005).***

T cells have long been thought to play a central role in SLE pathogenesis, and T cells from patients with lupus show defects in both signaling and effector function ***(Choi et al., 2012).***

Many clinical manifestations of SLE are mediated by circulating immune complexes (IC) that form with antigens in various tissues or the direct effects of antibodies to cell surface components. Immune complexes in the microvasculature, leading to complement activation and inflammation ***(Tian et al., 2007).*** Moreover, antibody-

antigen complexes deposit on the basement membranes of skin and kidneys. In active SLE, this process has been confirmed by demonstration of complexes of nuclear antigens such as DNA, immunoglobulins, and complement proteins at these sites ***(Tian et al., 2007).***

Autoantibodies have been found to be biomarkers for future neuropsychiatric events in SLE, individuals who had evidence of lupus anticoagulant (LA) had an increased future risk of intracranial thrombosis and that those with anti-ribosomal P antibodies had an increased future risk of lupus psychosis ***(Hanly et al.,2011).***

Serum antinuclear antibodies (ANAs) are found in nearly all individuals with active SLE. Antibodies to native double-stranded DNA (dsDNA) are relatively specific for the diagnosis of SLE ***(Bosch 2011).***

4. Environmental factors

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

a. Viruses, for example, may stimulate specific cells in this 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., 2002).***

b. Ultraviolet (UV) light may stimulate keratinocytes to secrete more IL-1, IL-3, IL-6, GM-CSF, and TNF-alpha, thereby stimulating B cells to make more antibodies ***(Cooper et al., 2010).***

c. Silica dust, found in cleaning powders, soil, pottery materials, cement, and cigarette smoke may increase the risk of developing SLE, especially in African American women ***(Cooper et al., 2010).***

Epidemiology

Race, sex, and age related demographics

Worldwide, the prevalence of SLE appears to vary by race. However, there are different prevalence rates for people of the same race in different areas of the world. The contrast between low reported rates of SLE in black women in Africa and high rates in black women in the United Kingdom suggests that there are environmental influences ***(Patel et al., 2006).***

In general, black women have a higher rate of SLE than women of any other race, followed by Asian women and then white women. In the United States, black women are 4 times more likely to have SLE than white women ***(Danchenko et al., 2006).***

A review of SLE across Asia-Pacific countries revealed considerable variation in prevalence and survival rates. For example, overall prevalence rates ranged from 4.3 to 45.3 per 100,000, and the overall incidence ranged from 0.9 to 3.1 per 100,000 per year. Moreover, Asians with SLE had higher rates of renal involvement than whites did, and cardiovascular involvement was a leading cause of death in Asians ***(Jakes et al., 2012).***

More than 90% of cases of SLE occur in women, frequently starting at childbearing age ***(Crispin et al., 2010).*** The use of exogenous hormones has been associated with lupus onset and flares, suggesting a role for hormonal factors in the pathogenesis of the disease ***(Crispin et al., 2010)***.

The risk of SLE development in men is similar to that in prepubertal or postmenopausal women. Interestingly, in men, SLE is more common in those with Klinefelter syndrome (ie, genotype XXY), further supporting a hormonal hypothesis ***(Dillon et al., 2011).***

The female-to-male ratio peaks at 11:1 during the childbearing years ***(Manzi, 2001).***

Onset of SLE is usually after puberty, typically in the 20s and 30s, with 20% of all cases diagnosed during the first 2 decades of life ***(Klein-Gitelman et al., 2002).***

The prevalence of SLE is highest in women aged 14 to 64 years. SLE does not have an age predilection in males, although it should be noted that in older adults, the female-to-male ratio falls. This effect is likely due to loss of the estrogen effect in older females ***(Boddaert et al., 2004).***

Precipitating Factors

The onset of SLE is infrequently attributed to a single event, although most clinicians have seen patients in which the disease began shortly following some memorable occurrence.

- Exposure to the sun and other sources of ultraviolet light may cause exacerbations or may even induce the first

sign of lupus. The relapse is usually limited to a rash, although other symptoms can also develop. Infections can initiate lupus or can cause a relapse ***(Granholm and Cavallo, 1993).***

- Stress has been implicated in causing flares, particularly of mild disease ***(Pawlak et al., 2003).***
- Pregnancy can cause an exacerbation or can even trigger the first symptoms of lupus; a relapse is more likely to develop in the postpartum period (puerperium) ***(Ruiz-Irastorza et al., 1996).*** The hormonal adjuvants that are used during ovulation induction and during ovarian stimulation in preparation for in vitro fertilization may also cause exacerbations of SLE. Therapeutic abortions can also induce a relapse, perhaps via mechanisms related to pregnancy or to the surgery itself ***(Guballa et al., 2000).***
- Although it had been suggested that use of hair dye may be associated with SLE, a very large prospective cohort study found no evidence of such a relationship ***(Sánchez-Guerrero et al., 1996).***

Clinical Manifestations of Systemic Lupus Erythematosus

1. Constitutional Symptoms

Fatigue, fever, and weight loss are typically present at some time during the course of the disease, occurring in 50 to 100 percent of patients.

a) Fatigue is the most common complaint and is occasionally the most debilitating. It occurs in 80 to 100 percent of patients, and its presence is not clearly correlated with other measures of disease activity ***(Jump et al., 2005).*** However, fatigue may not be due to active SLE but to one or more of the following: increased work load, depression, unhealthful habits (smoking, fad diets, sedentary living, drug abuse), stress, anemia, hypothyroidism, use of certain medications (including prednisone, beta-blockers), any inflammatory and/or infectious disease, coexistent fibromyalgia, sleep disturbances, deconditioning, or a perception of poor social support ***(Iaboni et al., 2006).***

b) Weight changes are frequent in patients with SLE and may be related to the disease or to its treatment. Weight loss often occurs prior to the diagnosis of SLE. Unintentional weight loss may be due to decreased appetite, to the side effects of medications (particularly diuretics or antimalarials), and to gastrointestinal disease (e.g., gastroesophageal reflux, abdominal pain, peptic ulcer disease, or pancreatitis weight gain in SLE

is usually due to one of two factors: salt and water retention associated with hypo-albuminemia (e.g., due to nephrotic syndrome or protein losing enteropathy) or increased appetite associated with the use of glucocorticoids ***(Sultan et al., 1999).***

c) Fever

Fever due to active disease is seen in over 50 % of patients with SLE. Fever may also represent infection or a drug reaction. The history may be helpful in determining the cause of the fever. As an example, fever developing while on moderate or high doses of glucocorticoids should make one strongly suspect new infection, particular if other signs of active lupus have begun to remit ***(Hidalgo-Tenorio et al., 2004).*** The pattern of fever may be helpful diagnostically. Episodic fever is suggestive of active SLE or infection; in comparison, sustained fever may reflect central nervous system (CNS) involvement or an adverse effect to a drug ***(Cuchacovich and Gedalia, 2009).*** Serious infectious complications, especially of the skin, respiratory, and urinary systems, develop in up to 50 percent of SLE patients. A large majority (approximately 80 percent) is due to pathogenic bacteria. Opportunistic infections, including those due to fungi, related to immunosuppressive therapy are a common cause of death. Consequently, ascribing fever to SLE in an immunocompromised patient should be done only after reasonable efforts have been made to exclude infection ***(Barber and Barnabe, 2012).*** Fever that does not respond to nonsteroidal anti-inflammatory drugs

(NSAIDs), acetaminophen, and/or low to moderate doses of glucocorticoids further raises the suspicion of an infectious or drug-related etiology, since most fevers due to active SLE will remit with use of these agents ***(Rovin et al., 2005).***

2. Musculoskeletal manifestations.

a) Arthritis and arthralgias: Arthritis and arthralgias have been noted in up to 95 percent of patients with SLE. These symptoms may be mistaken for another type of inflammatory arthritis and can precede the diagnosis of SLE by months or years. Arthritis, with inflammation, occurs in 65 to 70 percent of patients and tends to be migratory and symmetrical. Only a few joints are usually affected, especially those of the hands. The arthritis is moderately painful and is rarely deforming ***(Greco et al., 2003).*** Synovial effusions are infrequent in patients with SLE. When they occur, they are usually small, and the fluid is clear or slightly cloudy with low protein levels and white blood cell counts (similar to a transudate) ***(Grossman, 2009).***

b) Subcutaneous nodules: Subcutaneous nodules that occur characteristically in patients with RA have been noted in 5 to 7 % of patients with SLE. Nodules are generally seen in association with active disease in patients with disease that resembles RA (e.g., rheumatoid factor positivity) ***(Cervera et al., 1993).***

c) **Osteonecrosis:** Osteonecrosis (also called avascular, aseptic, or ischemic necrosis) in patients with SLE is most common in the femoral head, although the humeral head, tibial plateau, and scaphoid navicular can also be affected. Osteonecrosis is usually bilateral and is often asymptomatic. When symptoms occur, femoral head involvement usually manifests as pain in the groin, especially with weight bearing ***(Calvo-Alén et al., 2006).***

d) **Osteoporosis:** Loss of trabecular bone density is a significant problem in patients with SLE. Trabecular bones (e.g., ribs, vertebrae) are more likely to be involved than long cortical bones there are no symptoms unless fractures occur ***(Kalla et al., 1993).***

e) **Muscle disease:** Myalgias, muscle tenderness, or muscle weakness occurs in up to 70 percent of patients with SLE and may be the reason that the patient initially seeks medical attention ***(Greco et al., 2003).***

3. Mucocutaneous manifestations

a) **Acute cutaneous lupus erythematosus (ACLE) (butterfly rash):** The classic acute cutaneous lupus erythematosus rash (butterfly rash), characterized by erythema in a malar distribution over the cheeks and bridge of the nose, appears in approximately one-half of patients, usually after ultraviolet (UV) light exposure, and is frequently mistaken for a sunburn (fig. 2). The rash may precede other symptoms of lupus by months or even years or may be accompanied by other symptoms and signs of acute SLE. The involved skin feels warm and appears slightly edematous, creating at times a "peaud'orange" appearance ***(Crowson and Magro, 2001).***

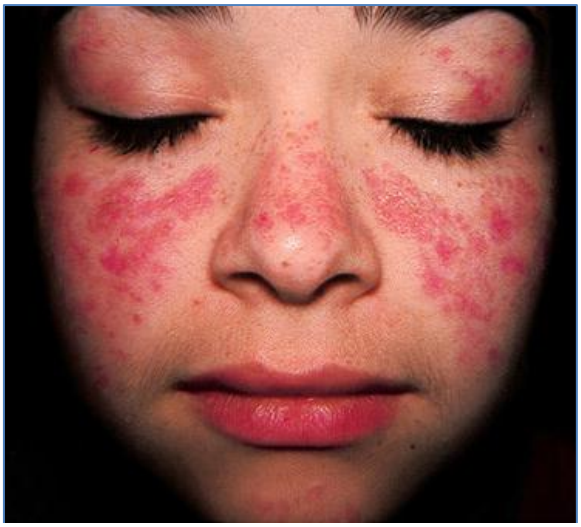

Fig. (2): Acute cutaneous lupus erythematosus rash (butterfly rash).

b) Disseminated (generalized) ACLE: Disseminated (generalized) ACLE presents as an erythematous maculo-urticarial to papular eruption involving primarily unexposed skin. Sometimes the inflammatory infiltrate can be severe enough to produce vesiculobullous skin lesions. Nonspecific lupus erythematosus skin changes, such as subungual erythema with cuticle changes, can be seen. Ulcers, pitting scars, and microinfarcts can be seen in the fingers and toes. Cheilitis, periorbital edema, diffuse telogen effluvium, and stubby hair (lupus hair) have also been described ***(CrowsonandMagro, 2001).***

c) Discoid lupus: Discoid lesions are characterized by discrete, erythematous, slightly infiltrated plaques covered by a well-formed adherent scale that extends into dilated hair follicles (follicular plugging). Lesions of DLE are most often present on the face, neck, and scalp but also occur on the ears and, infrequently, on the upper torso (fig 3, 4, 5). They tend to slowly expand with active

inflammation at the periphery and then to heal, leaving depressed central scars, atrophy, telangiectasias, and hyperpigmentation or hypo-pigmentation ***(Cervera et al., 1993).***

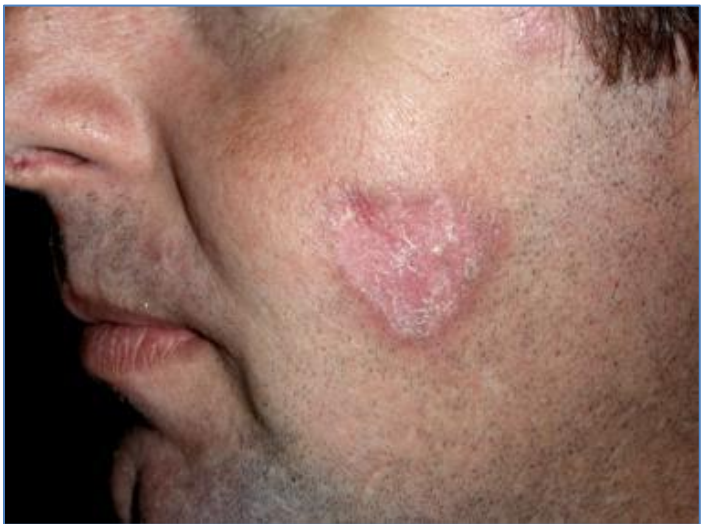

Fig. (3): Discoid lupus erythematosus on the face.

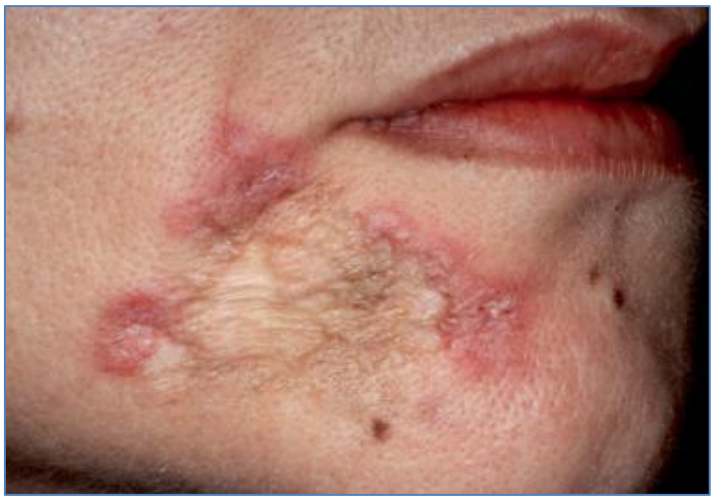

Fig. (4): Chronic scarred lesion of discoid lupus erythematosus