INTRODUCTION

SLE is an autoimmune disorder characterized by the production of pathogenic autoantibodies, primarily to nuclear antigens, as well as dysregulation of both T and B cells ***(Namjou et al., 2009).***

SLE has a female predominance of 9:1. Although there are X-chromosome abnormalities associated with SLE ***(Zandman-Goddard et al., 2007)***, estrogen itself is strongly implicated in SLE autoimmunity ***(Gameiro et al., 2010).***

SLE is associated with a disrupted sex hormone balance characterized by lower amounts of androgens and dramatically higher levels of the estrogen metabolite, 16-hydroxyestrone ***(Cutolo, 2004).*** Pregnancy worsens the disease; incidence of SLE diminishes after menopause ***(González et al., 2010).*** Administration of an estrogen receptor (ER) blocker (fulvestrant) to human female SLE patients produces clinical improvement ***(Abdou et al., 2008)*** as does treatment with testosterone ***(Dinesh et al., 2010).***

Natural menopause is defined as the permanent cessation of menstruation caused by the loss of ovarian follicular activity. It corresponds to the last menstrual period (LMP) and is recognized to have occurred after 12

consecutive months of amenorrhoea for which there is no other obvious pathological or physiological cause ***(World Health Organization, 1996).***

The age at natural menopause seems to be determined primarily by genetic factors, but some variability should be observed ***(Murabito et al., 2005).*** It has long been believed that the menopause is presented at a younger age in women suffering from autoimmune diseases, including SLE ***(Bove, 2013).***

During menopause, women experience a variety of predictable symptoms and conditions related to changes in sex hormone levels and aging. The menopausal transition precedes menopause by several years and is usually characterized by irregularity of the menstrual cycle and by hot flashes and night sweats ***(Takahashi et al., 2015).*** After menopause, genitourinary symptoms predominate, including vulvovaginal atrophy and dryness and lower urinary tract symptoms, including urinary frequency, urgency, and nocturia ***(Takahashi et al., 2015).***

Although SLE generally emerges during reproductive ages, it was found that the age at menopause in lupus patients is lower than that observed in the general population; however, whether the occurrence of menopause at a younger age in lupus patients results from the

gonadotoxic effects of Cyclophosphamide treatment or from an autoimmune-mediated ovarian injury is debated ***(Sammaritano, 2012).***

Besides its reproductive implications, the timing of menopause is important since it is thought that it correlates with the risk of cardiovascular disease, some gynaecological cancers, bone health and overall mortality. In women with lupus, the increased risk of cardiovascular disease and osteoporosis after menopause adds to the risk associated with chronic inflammatory conditions ***(Romero-Díaz et al., 2012).*** On the other hand, menopause has been related to both lower lupus activity and greater damage accrual of organs affected by individual flares ***(Alpízar-Rodríguez et al., 2014).***

Aim of the Study

To identify menopause characteristics in an Egyptian cohort of women with SLE with effect of the disease on menopausal symptoms and the characteristics of disease activity and disease damage in peri- and post-menopausal patients.

Chapter (1): Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a prototype of systemic autoimmunity affecting many systems. Both antibodies and auto reactive T cells play significant roles in its pathogenesis. Experimental evidence has been obtained to support the hypothesis that auto antibodies and auto reactive T effector cells may be initiated by environmental factors through molecular mimicry and the inherent polyreactive nature of antigen receptors. A unified hypothesis has been postulated for the pathogenesis of SLE that has practical implications ***(Lewis et al., 2013).***

Sex:

SLE is a disease of women, particularly during their reproductive period. Female to male ratio 12:1, between menarche and menopause is 3:1 in younger and older ***(Schwartzman-Morris & Putterman, 2012)***. This ratio 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 Klinefelter Syndrome, menopausal women treated with hormonal replacement therapy and women exposed to estrogen containing oral contraceptives ***(Costenbader et al., 2007).***

Age:

More than 90% of cases of SLE occur in women, frequently starting at childbearing age ***(Ginzler and Tayar, 2012)***. 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 ***(Costenbader et al., 2007).***

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

Pregnancy:

There is increased in SLE disease activity during pregnancy which increases the risk of spontaneous abortion, intrauterine fetal death, preeclampsia, intrauterine growth retardation and preterm birth because of increased levels of estrogen, prolactin and T–helper cell 2 cytokines ***(Chen & Parker, 2004).*** SLE Prognosis for both mother and child are best when SLE is quiescent for at least 6 months before the pregnancy and when the mother's underlying renal function is stable and normal or near normal. Lupus nephritis can get worse during pregnancy ***(Gladman et al., 2010).***

The incidence of exacerbations during pregnancy and the postpartum period, especially in women in remission at the beginning of pregnancy, has been progressively diminishing in the last 30 years. Possible causes for flare-ups during the postpartum period include decreased levels of anti-inflammatory steroid, elevated levels of prolactin (which is a proinflammatory hormone) and changes in the neuroendocrine axis ***(Stojan & Baer, 2012).***

Mortality / Morbidity:

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 had found that female patients with late-onset (>50years) SLE carried a higher risk of mortality than those with adult-onset disease (18-50 years) in the presence of co-morbidities. Juvenile-onset SLE patients (<18 years) were at greatest risk of mortality, which is probably due to disease severity ***(Chen et al., 2014).***

Etiology:

The etiology of SLE remains unknown and is clearly multifactorial. Many observations suggest a role for genetic, hormonal, immunologic, and environmental factors (exposure to ultraviolet rays, viral infections, chemicals, and sexual hormones) ***(Relle and Schwarting, 2012).***

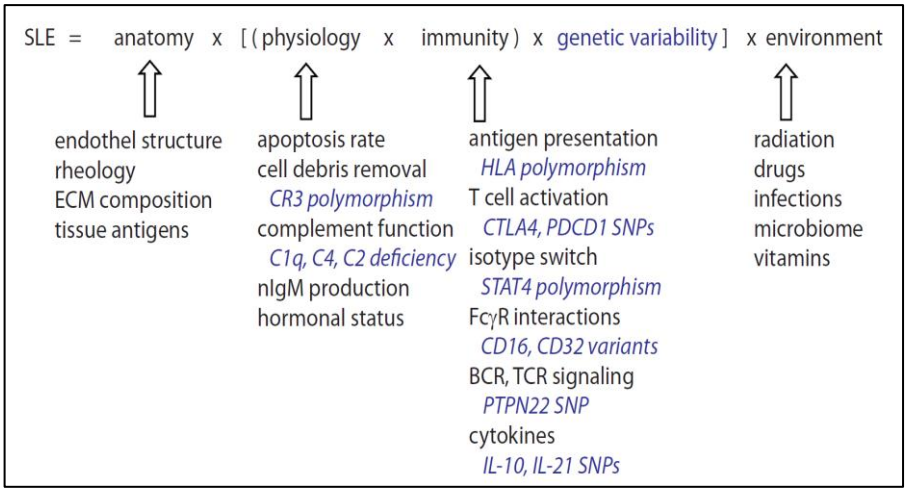

Fig. (1): Systemic lupus erythematosus is a heterogeneous group of multifactorial diseases ***(Prechl & Czirják, 2015).***

1- Genetic factors:

At least 35 genes are known to increase the risk of SLE. A genetic predisposition is supported by 40% concordance in monozygotic twins; if a mother has SLE, her daughter's risk of developing the disease has been estimated to be 1:40, and her son's risk, 1:250 ***(Sestak et al., 2010)***.

2- Hormonal factors:

Estradiol, testosterone, progesterone, dehydro-epiandrosterone (DHEA), and pituitary hormones, including prolactin has supported the hypothesis that they modulate the incidence and severity of SLE ***(Hahn et al., 2005).***

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 the 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 ***(Hahn et al., 2005).***

3- Immune abnormalities:

There are numerous immune defects in patients with SLE. However, the etiology of these abnormalities remains unclear, it is not known which defects are primary, and which are secondarily induced. In certain cases these immune defects are episodic, and some correlate with disease activity ***(Hahn et al., 2005)***.

4- Environmental factors:

a- Infection:

Multiple infections have been involved as potential triggers of SLE, including Epstein-Barr virus (EBV), hepatitis C virus, Cytomegalovirus (CMV) and parvovirus ***(Petri, 2005).***

b- Ultraviolet (UV) light:

Exposure to ultraviolet (UV) light causes flares of SLE in approximately 70% of patients, possibly by

increasing apoptosis in skin cells or by altering DNA and intracellular proteins to make them antigenic ***(Hahn, 2010).***

c- Drugs: Drug-induced lupus erythermatosus (DILE):

Similarly to idiopathic lupus, DILE e.g. (Procainamide, Hydralazine, Quinidine and Isoniazid) can be divided into systemic, sub-acute cutaneous and chronic cutaneous lupus. Recognition of DILE is important because it usually reverts within a few weeks after stopping the drug ***(Sarzi-Puttini et al., 2005).***

Pathogenesis:

Central to the immune dysfunction seen in SLE is the existence of overactive B cells, which produce auto antibodies, associated with inappropriate T cell suppression (high ratio of $CD4^+$ to $CD8^+$ T cells), defects in immune cell tolerance, and dysfunctional signaling by immune cells ***(Nagy et al., 2005).*** B cell activators, such as protein B-lymphocyte stimulator (BLyS), appear to be unregulated in lupus, further encouraging B-cell survival ***(Gerl et al., 2009).***

Disturbance of the immune response:

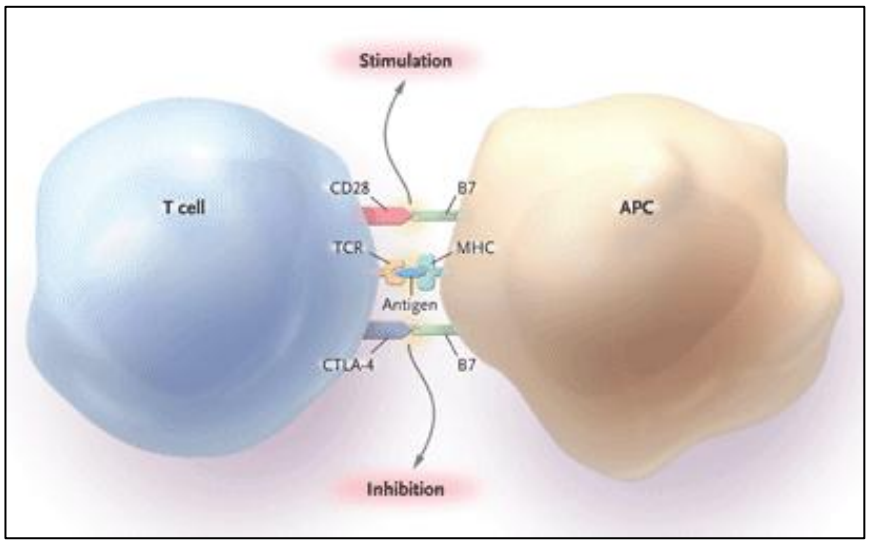

Fig. (2): Interaction between a T cell and an Antigen-Presenting Cell (APC) ***(Rahman & Isenberg, 2008):***

The antigen-presenting cell binds antigen in a complex with a molecule from the major histocompatibility complex (MHC) on its surface. This complex interacts with the T-cell receptor (TCR). The effect on the T cell depends on the interaction between other molecules on the surfaces of the two cells ***(Rahman & Isenberg, 2008).***

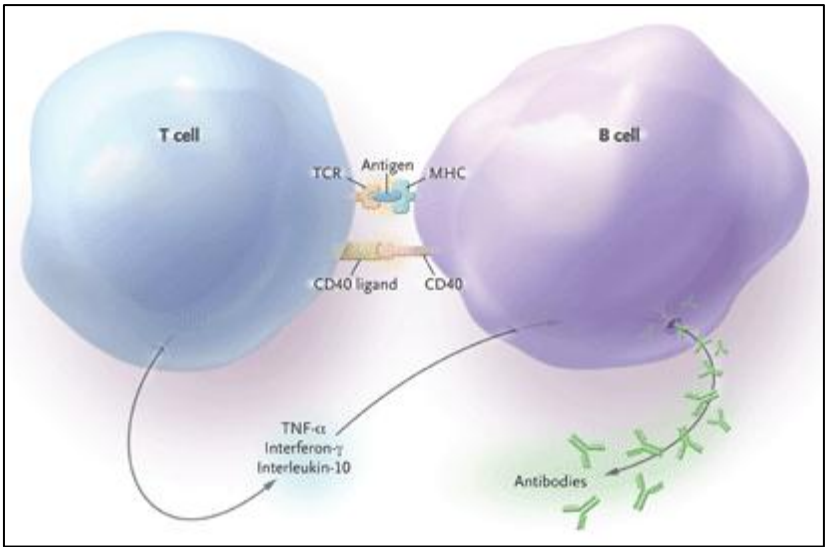

Fig. (3): T cell -B cell Interaction ***(Rahman & Isenberg, 2008).***

B cell and a T cell interacting and stimulating each other. T-cell cytokines affect B cells by stimulating cell division, switching antibody production from IgM to IgG and promoting a change in the molecular sequence of the secreted antibody so that it binds more strongly to the driving antigen. Thus, T-cell help makes possible the production of high-affinity IgG auto antibodies. These kinds of antibodies are closely linked to tissue damage in lupus ***(Rahman, 2004).***

B cell activation is abnormal in patients with SLE. The number of B cells at all stages of activation is increased in the peripheral blood of patients with active SLE**.** These B cell abnormalities can precede the development of SLE **(*Nagy et al., 2005).***

Clinical picture:

While common manifestations from joints, skin, mucous membranes, bone marrow and kidneys are usually rather easily identified, more subtle manifestations, such as neurological symptoms, may remain unrecognized or not judged related to SLE ***(Yu et al., 2014).***

1- Constitutional symptoms:

Fatigue, the most prevalent complaint in approximately 50–90% of patients with SLE ***(Schmeding & Schneider, 2013),*** with more than 50% of patients rating fatigue as the most debilitating symptom they experience. Fatigue manifests as an overwhelming sense of extraordinary tiredness or exhaustion that is not completely relieved by rest or sleep ***(Ahn & Ramsey-Goldman, 2012).*** SLE-related fatigue is a complex phenomenon and a broad array of factors is commonly associated with fatigue ***(Yuen and Cunningham, 2014).***

Fever that is thought to be due to active disease is seen in over 50 percent of patients with SLE. Intermittent fever is suggestive of active SLE or infection; in comparison, sustained fever may reflect CNS involvement or an adverse effect to a drug ***(Zhou and Yang, 2009).***

2- Mucocutaneous manifestations:

A- Acute Cutaneous LE (ACLE):

The most typical form of ACLE consists of flattened areas of red skin on the face that resemble persistent sunburn ***(Werth, 2005).***

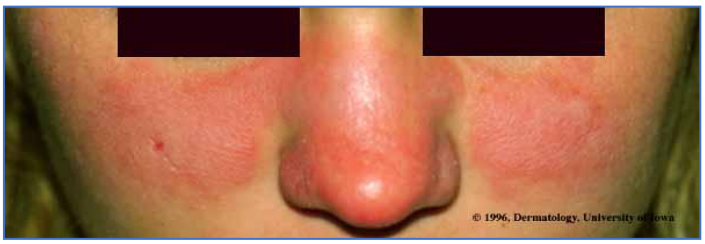

Fig. (4): Malar rash

B- Sub-acute Cutaneous LE (SCLE):

SCLE tend to occur on sun-exposed areas of the body but can have a generalized distribution**.** They are nonfixed and nonscarring, follow a waxing and waning course, and may occur with few other SLE features except for musculoskeletal symptoms and laboratory abnormalities, including ANA and antibodies to SSA/Ro ***(Stavropoulos et al., 2008).***

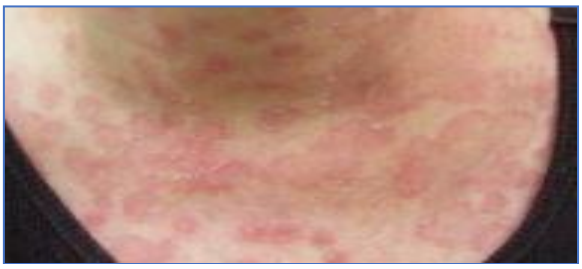

Fig. (5): Subacute cutaneous lupus erythematosus.

C- Chronic cutaneous lupus: Discoid lupus is the most common form of CCLE.

The coin-shaped (i.e., "discoid") lesions of DLE are most commonly seen on the scalp and face, but can be seen on other parts of the body as well. As the lesions get older they can produce scarring and discoloration of skin (darkly colored and/or lightly colored areas) ***(Panjwani, 2009).***

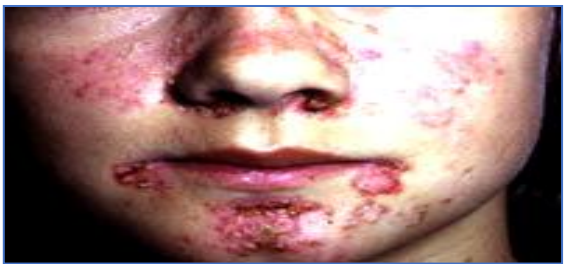

Fig. (6): Discoid lupus.

Fig. (7): Discoid alopecia.

D- Photosensitivity:

Approximately 40-70% of people with LE note that their cutaneous and/or systemic disease is aggravated by sun exposure. It is the sun burning UV-B rays in sunlight that are particularly bad for LE patients. Longer wavelength UV-A rays can also aggravate cutaneous LE,