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).***

Lupus nephritis (LN) is one of the most serious manifestations in SLE and it occurs in about 60% of patients. Patients with LN have increased risk of progressive deterioration of kidney function as well as increased mortality rates ***(Navaneethan et al., 2008).*** This poor outcome has occurred despite the availability of new therapeutic regimens ***(Ward, 2009).***

The most important feature in LN is immune complex deposition in renal glomeruli which produces glomerular inflammation. The site and the amount of these immune deposits determine the degree and class of LN ***(Mjelle et al., 2011).*** The standard treatment for LN is guided by histologic classification according to the American College of Rheumatology ***(Hahn et al., 2012).***

Management of LN consists of induction therapy to achieve remission and long-term maintenance therapy to prevent relapse, progression to end-stage renal disease, and

death. However, the options for long-term therapy remain controversial. Treatment options include glucocorticoids and the immunosuppressive agents e.g. cyclophosphamide, azathioprine, mycophenolate and others. These drugs have considerable toxicity and are not effective in all patients ***(Dooley et al., 2011).***

Introduction of agents such as rituximab and belimumab, which target specific components of the immune system, may be an improvement. A recent prospective observational study suggested that rituximab may be useful in treating patients with LN without using corticosteroids ***(Condon et al., 2013).***

LN has different and unpredictable clinical features. The risks associated with its management have challenged investigators to detect the factors influencing the survival rate of patients and to develop the rational approaches to therapy. Decades of intensive investigation at many centers worldwide had underscored the predictive value of demographic, clinical and laboratory data before treatment. Controversies still existed due to the difference in race, environment, and the selection criteria as well as the methods to evaluate the outcome. There are some factors with negative impact on the prognosis of LN still to be solved. Most of the articles on the prognosis of LN were reported from European and American patients. The prognosis of LN and its influence in Egyptian patients need more elucidation ***(Shen et al., 1997).***

AIM OF THE WORK

The aim of this study was to investigate the pattern, influencing factors and long-term outcome of lupus nephritis (LN) after different induction of remission and maintenance management modalities.

REVIEW OF LITERATURE

Etiology of SLE

The etiology of SLE and lupus nephritis is unknown but as with many autoimmune disorders, evidence suggests that multiple genetic, epigenetic, and environmental risk factors have been implicated in the development of both SLE and lupus nephritis. The inheritance of genes alone is not sufficient for developing SLE, suggesting the influence of environmental triggers on disease expression ***(Kamen, 2014)***.

It is known that SLE develops through multiple steps with the loss of self-tolerance and development of autoantibodies occurring sometimes several years prior to the onset of clinically symptomatic autoimmune disease ***(Kamen, 2014).***

Although first degree relatives of patients with SLE overall have a higher prevalence of autoantibodies and a higher risk of SLE and other autoimmune diseases ***(Kamen et al., 2008).*** Some develop SLE-specific autoantibodies but never develop clinical disease implying that there are protective factors as well ***(Bruner et al., 2012).***

The multifactorial nature of the genetic risk of SLE and the low disease penetrance emphasize the potential influence and complexity of environmental factors and gene-environment interactions on the etiology of SLE ***(Cooper et al., 1999).***

Genetic factors

As with many autoimmune disorders, evidence suggests that genetic predisposition plays an important role in the development of both SLE and lupus nephritis. Multiple genes, many of which are not yet identified, mediate this genetic predisposition as seen in table 1 ***(Kaiser and Criswell, 2010).***

Table (1): Genes associated with systemic lupus erythematosus

Gene Locus	Gene Name	Gene Product
1p13.2	*PTPN22*	Lymphoid-specific protein tyrosine phosphatase
1q21-q23	*CRP*	CRP
1q23	*FCGR2A, FCGR2B*	FcγRIIA (R131), FcγRIIB
1q23	*FCGR3A, FCGR3B*	FcγRIIIA (V176), FcγRIIIB
1q31-q32	*IL10*	IL-10
1q36.12	*C1QB*	C1q deficiency
2q32.2-q32.3	*STAT4*	Signal transducer and activator of transcription 4
2q33	*CTLA4*	Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
6p21.3	*HLA-DRB1*	HLA-DRB1: DR2/*1501, DR3/*0301C1q deficiency
6p21.3	*C2, C4A, C4B*	C2, C4 deficiencies
6p21.3	*TNF*	TNF-a (promoter, -308)
10q11.2-q21	*MBL2*	Mannose-binding lectin
CRP = C-reactive protein; HLA = human leukocyte antigen; IL = interleukin; TNF = tumor necrosis factor.		

(Kaiser and Criswell, 2010)

Interplay between environmental factors, genetics and epigenetics

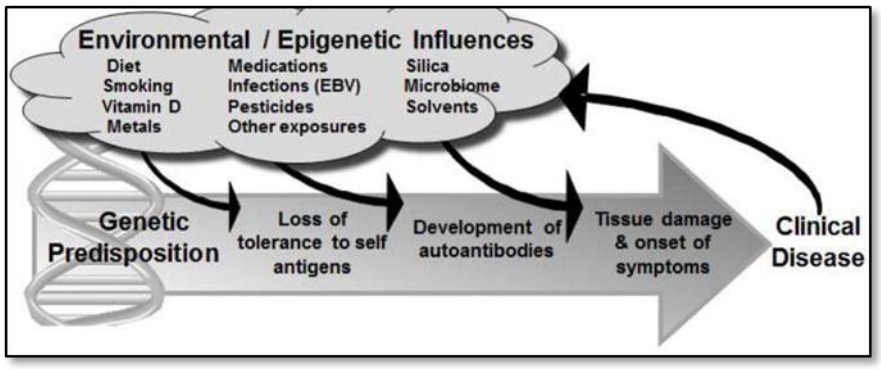

Fig. (1): Interplay between environmental factors, genetics and epigenetics. SLE develops through multiple steps with the loss of self-tolerance and development of autoantibodies occurring sometimes several years prior to the onset of clinically symptomatic autoimmune disease ***(Kamen, 2014).***

Knowledge of the genetic contributions to SLE risk has grown exponentially over the past decade, and has contributed to recent improvement in understanding the role of genetic risk factors for SLE. Each susceptibility gene present in an individual's genome contributes to that individual's relative risk of developing SLE and can influence age of disease onset and clinical manifestations ***(Webb et al., 2011).***

Non-encoded gene expression regulation provided by epigenetic mechanisms (DNA methylation, modifications of histone tails, and noncoding RNAs) plays a role in SLE susceptibility that is still being deciphered. These epigenetic modifications can result from both inherited DNA sequences and environmental exposures. Even monozygotic twins,

epigenetically nearly indistinguishable at birth, later develop important differences in their epigenomic landscape ***(Fraga et al., 2005)***.

Reduced DNA methylation, histone hypoacetylation and hyperacetylation and the overexpression of certain miRNAs, resulting in altered immune responses, have been associated with the onset and progression of SLE ***(Absher et al., 2013).*** Along these lines, it is interesting to note that procainamide and hydralazine can cause drug-induced lupus through epigenetic mechanisms by inhibiting DNA methylation in T cells ***(Hughes et al., 2011).***

Dietary influences on SLE

Although alterations in diet can reduce the risk of associated conditions such as atherosclerosis and metabolic syndrome, definitive evidence is lacking that dietary factors influence human SLE disease development or disease activity ***(Klack et al., 2012)***.

Epigenetic changes in response to diet and other environmental exposures have important implications for the development of SLE, including potential targets for prevention. Studies by *Strickland et al.,* have shown in a mouse model of SLE that manipulation of DNA methylation via changes in dietary methyl donor content can significantly influence disease susceptibility and severity little is known about the influence of diet on DNA methylation in human disease pathogenesis ***(Strickland et al., 2013)***.

Influence of vitamin D status on SLE

Vitamin D, an essential steroid hormone with well-established effects on mineral metabolism and skeletal health, also has important effects on the immune system ***(Kamen and Tangpricha, 2010).***

A high prevalence of vitamin D insufficiency has been found in SLE patient populations around the world, particularly among those with darker skin pigment, and observational studies suggest that insufficiency contributes to multiple comorbid conditions and potential complications of SLE. It is notable that the same ethnic disparities seen in the prevalence of vitamin D deficiency are seen in the prevalence of SLE, with African Americans and Hispanics having a disproportionately high risk for developing SLE and having severe disease manifestations ***(Kamen and Tangpricha, 2010).***

Established environmental risk factors for SLE

The triggers, mechanisms and timing of disease development in SLE remain largely unknown despite many lines of experimental and epidemiologic investigation. Many potential environmental triggers of SLE have been investigated, often as part of large-scale epidemiologic studies, but compelling evidence of a causative role has thus far only been reported with silica dust and to a lesser extent smoking and Epstein Barr virus (EBV) exposure ***(Miller et al., 2012).***

Cigarette smoking and SLE

Current cigarette smoking was considered "likely" contribute to the development of SLE based on multiple studies with variable results. A meta-analysis of smoking and SLE risk studies by Costenbader et al., found a modestly increased risk of SLE with current smoking compared to never smoking (OR 1.50, 95% CI of 1.09-2.08). Based on the 7 case-control and 2 cohort studies available for the meta-analysis, the risk with past smoking compared to never smoking was not elevated (OR 0.98, 95% CI of 0.75-1.27) ***(Costenbader et al., 2004).***

Smoking also appears to influence the course of disease among patients with SLE, particularly skin manifestations with current smoking associated with active SLE rashes and having ever smoked associated with discoid rash and photosensitivity ***(Bourré-Tessier et al., 2013)***.

Silica exposure and SLE

Exposure to particulate silica (crystalline silica or quartz) most commonly comes from mining and "dusty trades" such as sandblasting, granite cutting, construction work, cement work, brick and tile laying. Exposure can also result from proximity to agricultural work in areas with high soil silica content. The studies of silica exposure and SLE provide evidence to support a dose-response with higher risk in those with higher exposure. Overall the estimated risk ratios for SLE ranged from 1.6 (any

silica exposure) to 4.9 (high silica exposure) within the general population and the risk ratio was >10 among highly exposed populations (i.e., people with silicosis) ***(Miller et al., 2012).***

EBV exposure and SLE

Many infectious agents, including viruses, bacteria, and parasites, have been proposed as triggers of autoimmune diseases, including SLE ***(Caza et al., 2014).*** The infectious agent with the most compelling evidence to date for contributing to the pathogenesis of SLE has been Epstein Barr virus (EBV). Epidemiologic data supports a connection between EBV infection and SLE ***(Parks et al., 2005)***.

Infectious mononucleosis shares clinical features with active SLE and results in antinuclear antibody (ANA) positivity and production of SLE-related autoantibodies such as anti-Sm. One of the initial epitopes for autoantibody generation in SLE is thought to be 60 kDa antigen Ro which is cross-reactive with EBV-nuclear antigen1 (EBNA1). The appearance of autoantibodies which cross-react with EBV proteins sometimes several years prior to the onset of clinical symptoms is hypothesized to be due to molecular mimicry of SLE-associated autoantigens (specifically anti-Sm and anti-Ro) ***(Hogan et al., 2001)***.

Differences in immunologic responses to EBV exposure being dependent on the genetic background of the exposed

individual serve as another example of gene-environment interaction. Several SLE susceptibility genes play a role in EBV replication and immune evasion**,** with an individual's immune response to EBV infection being a significant role in the development of early autoantibodies ***(Vaughn et al., 2012)***.

SLE Classification Criteria

The 1982 American College of Rheumatology (ACR) classification criteria for systemic lupus erythematosus (SLE) and their 1997 revision have shaped our understanding of SLE and have been used widely in lupus research for decades. However, novel information on the disease has emerged, such as the recognition of subacute cutaneous lupus erythematosus as an SLE manifestation, and the Systemic Lupus International Collaborating Clinics (SLICC) group has shown that the sensitivity of these criteria is suboptimal ***(Tedeschi et al.,2017)***.

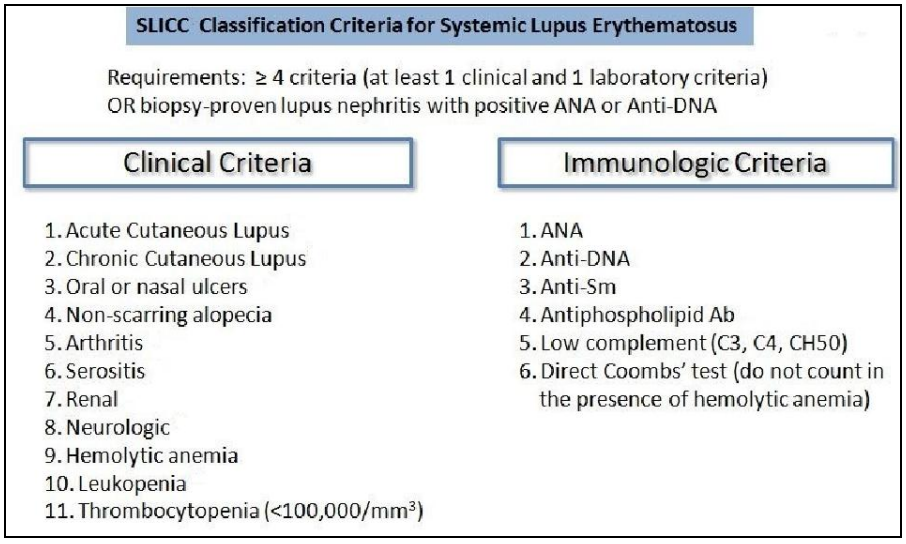

Fig. (2): SLICC classification Criteria for SLE ***(Petri et al., 2012).***

On the other hand, while introducing important new concepts, the SLICC 2012 criteria have only partially succeeded in better performance, in that they had increased sensitivity at the price of reduced specificity. This decrease in specificity is probably due to maintaining the overall structure of the ACR criteria, which assigns equal weights to each criterion. While SLICC criteria require the presence of at least 1 clinical and 1 immunologic criterion, both the ACR and SLICC criteria classify SLE based on a simple count of the number of criteria present ***(Tedeschi et al.,2017)***.

Due to the heterogeneity of SLE, ranging from mild to severe symptoms with a variety of organ manifestations, the overall performance of SLE classification criteria could be further increased by developing a weighted scoring system. This fact is particularly true regarding early phases of the disease, where both ACR and SLICC criteria perform worse than in established SLE ***(Tedeschi et al.,2017)***.

Since 2014, a steering committee consisting of 12 members, equally appointed by the ACR and the European League Against Rheumatism (EULAR), has been working on developing new classification criteria for SLE for clinical research purposes. This effort involves hundreds of SLE experts worldwide. The overarching goal is to develop a system to identify potential participants for clinical research studies, which requires some degree of homogeneity across subjects, while simultaneously dealing with the extreme heterogeneity of

SLE. As with previously established classification criteria, the goal is to arrive at a system with the maximum combination of sensitivity and specificity for SLE ***(Tedeschi et al.,2017)***.

Clinical Domains and Criteria	Weight	Immunologic Domain and Criteria	Weight
Constitutional domain		*Antiphospholipid antibodies domain*	
Fever >38.3 °C	2	Anticardiolipin IgG >40 GPL units or anti-β2GP1 IgG >40 units or lupus anticoagulant positive	2
Cutaneous domain		*Complement proteins domain*	
Non-scarring alopecia	2	Low C3 or low C4	3
Oral ulcers	2	Low C3 and low C4 at same time	4
Subacute cutaneous or discoid lupus	4	*Highly specific antibodies domain*	
Acute cutaneous lupus	6	Anti-dsDNA antibody	6
Arthritis domain		Anti-Smith antibody	6
Synovitis in ≥2 joints or tenderness in ≥2 joints and ≥30 minutes of morning stiffness	6		
Neurologic domain			
Delirium	2		
Psychosis	3		
Seizure	5		
Serositis domain			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Hematologic domain			
Leukopenia (< 4000/mm^3)	3		
Thrombocytopenia	4		
Autoimmune hemolysis	4		
Renal domain			
Proteinuria >0.5g/24h	4		
Renal biopsy with Class II or V lupus nephritis	8		
Renal biopsy with Class III or IV lupus nephritis	10		
Classify as SLE if total score ≥10 points			

Fig. (3): The Upcoming EULAR/ACR Criteria for Classification of SLE

Lupus Nephritis

Lupus nephritis (LN) is one of the most serious SLE complications, it usually develops early in the course of the disease that it is why it is a major predictor of poor prognosis. However, in about 5% of the cases, LN may appear several years after the onset of the disease (i.e., delayed LN). The incidence and prevalence of LN varies depending on the studied population. The cumulative incidence is higher in people of Asian (55%) compared with, the Africans (51%), Hispanic (43%) ancestry and finally with Caucasians (14%) ***(Ceccarelli et al., 2015).***

Generally, survival in lupus patients is roughly 92% at 10 years after diagnosis. Proliferative renal involvement is among the most severe manifestations of lupus and without proper treatment it can lead to significant morbidity and mortality ***(Hahn et al., 2012).***

Pathogenesis of Lupus Nephritis

Lupus nephritis is an immune complex GN that develops as a frequent complication of SLE. The pathogenesis of lupus nephritis involves a variety of pathogenic mechanisms. The extrarenal etiology of systemic lupus is based on multiple combinations of genetic variants that compromise those mechanisms normally assuring immune tolerance to nuclear autoantigens ***(Lech and Anders, 2013).***

This loss of tolerance becomes clinically detectable by the presence of antinuclear antibodies. In addition, nucleic acids released from netting or apoptotic neutrophils activate innate and adaptive immunity via viral nucleic acid-specific Toll-like receptors ***(Lech and Anders, 2013).***

Therefore, many clinical manifestations of systemic lupus resemble those of viral infection. In lupus, endogenous nuclear particles trigger IFN-α signaling just like viral particles during viral infection. As such, dendritic cells, T helper cells, B cells, and plasma cells all contribute to the aberrant polyclonal autoimmunity ***(Lech and Anders, 2013).***

The intrarenal etiology of lupus nephritis involves antibody binding to multiple intrarenal autoantigens rather than the deposition of circulating immune complexes. Tertiary lymphoid tissue formation and local antibody production add to intrarenal complement activation as renal immunopathology progresses ***(Lech and Anders, 2013).***

Here we provide an update on the pathogenic mechanisms that lead to lupus nephritis and provide the rationale for the latest and novel treatment strategies ***(Lech and Anders, 2013).***

In recent years, we have learned a great deal about activation of B cells and their contribution to the maintenance of autoantibody production, as well as the importance of local