Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that can affect all organs, most commonly the skin, joints, blood and kidneys. The severity of the disease is highly variable spanning from mild symptoms to life-threatening manifestations. The main effectors of disease pathology are the diverse autoantibodies, immune complexes (ICs), complement activation and autoreactive cells ***(Katsiari and Tsokos, 2006).***

Renal disease is the major cause of mortality and morbidity in systemic lupus erythematosus (SLE). Up to 66% of patients with SLE have renal disease at some stage of their illness. Among the different histological classes of lupus nephritis, the diffuse proliferative type (WHO class IV) carries the worst prognosis ***(Lai et al., 2005).***

The renal survival (survival without dialysis) rates of lupus nephritis in the 1990s ranged from 83 to 92% in 5 years and 74 to 84% in 10 years. The risks of end-stage renal failure were particularly high in patients with diffuse proliferative glomerulonephritis, with figures ranging from 11 to 33% in 5 years. The prognosis of lupus nephritis is dependent on a large number of demographic, racial, genetic, histopathological,

immunological, and time-dependent factors. Despite the complex interplay of these factors in individual patients, glomerulo-nephritis that fails to remit with conventional immunosuppressive therapies is a major risk factor for subsequent renal function deterioration and poor long-term outcome ***(Mok, 2006).***

Aim of the Work

The aim of this work is to compare adult onset SLE patients and childhood onset SLE patients who received follow up care at Ain Shams University hospitals from January 1989 to December 2009 for differences in renal disease activity, differences in the type and amount of disease damage according to standardized disease indices.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease with a worldwide distribution. The immune system of the body, fights against the infectious agents by producing antibodies ***(Katsiari and Tsokos, 2006).*** Patients with SLE produce abnormal antibodies in their blood that target tissues within their own body rather than foreign infectious agents. Because the antibodies and accompanying cells of inflammation can involve tissues anywhere in the body, SLE has the potential to affect a variety of areas of the body. SLE can cause disease of the skin, heart, lungs, kidneys, joints, and/or nervous system. When the kidneys are involved it is called lupus nephritis (LN) ***(Uthman et al., 1999).***

Diagnosis of SLE:

SLE is notoriously difficult to diagnose. Many cases are not diagnosed until the patient has suffered irreversible kidney damage; For patients who do not have organ-threatening disease, diagnosis takes an average of two years of searching among physicians. The telltale erythematous skin lumps or rashes that give lupus erythematosus the latter half of its name eventually appear in 90% of systemic lupus patients and all discoid lupus patients, but may not appear early enough in the course of the disease to guarantee timely diagnosis. Additionally, no single laboratory test can confirm SLE,

although certain antibody tests can help to distinguish SLE from other diseases ***(Gilman, 2005)***.

The proposed classification is based on eleven criteria **(Table 1).** The American College of Rheumatology established eleven criteria in 1982, which were revised in 1997 as a classificatory instrument to operationalise the definition of SLE in clinical trials. For the purpose of identifying patients for clinical studies, a person has SLE if any 4 out of the 11 criteria are present simultaneously or serially on two separate occasions ***(Tan et al., 1982).***

Table (1): The American College Rheumatology Classification Criteria of Systemic Lupus Erythematosus

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR b) Pericarditis--documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 gram per day or greater than 3+ if quantitation is not performed OR b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9.Hematologic disorder	a) Hemolytic anemia--with reticulocytosis OR b) Leukopenia--less than 4,000/mm OR c) Lymphopenia--less than 1,500/mm OR d) Thrombocytopenia--less than 100,000/mm in the absence of offending drugs
10. Immunologic disorder	a) Positive LE cell preparation OR b) Anti-DNA: antibody to native DNA in abnormal titer OR c) Anti-Sm: presence of antibody to Sm nuclear antigen OR d) False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

(Tan et al., 1982)

Approximately 15% of cases of SLE may be misdiagnosed as other disorders, including fibromyalgia, seronegative spondylo-arthropathies such as ankylosing spondylitis or Reiters syndrome,autoimmune thyroiditis and multiple sclerosis ***(Gilman, 2005).***

Lupus Nephritis

Lupus nephritis (LN) is an inflammation of the kidney caused by systemic lupus erythematosus (SLE), a disease of the immune system. About 50-80% of patients with lupus suffer from lupus nephritis which is one of the major causes of morbidity and mortality ***(Weening et al., 2004)***.

LN usually manifests within 5 years of diagnosis, but renal failure rarely presents in SLE prior to the patient fulfilling ACR classification criteria. The symptoms are generally related to hypertension, proteinuria, and renal failure ***(Brent et al., 2005).***

Epidemiology:

Systemic lupus erythematosus is more common in African-Americans, African-Caribbeans, and Asians, which accounts for a higher prevalence of lupus nephritis in these ethnic groups **(Ortega et al., 2010)**. SLE predominantly affects women of reproductive age, with the peak age of onset ranging between 20 and 40 years ***(Hahn, 2001).*** Published ratios of women to men vary from 9:1 to 15:1, and has a mean age at diagnosis of 30 to 39 years ***(Tamir and Brenner, 2003).***

LN is found worldwide, with an estimated prevalence between 12 and 64/100,000 populations ***(Kurien and Scofield, 2006)***. In the UK, the Caribbean and the USA, it is more common and more severe in black females than in white Caucasians.Disease onset before 8 years of age is unusual,although lupus has been diagnosed even in the first year of life ***(Li and Isenberg, 2006)***.

In Egypt, the female to male ratio was 2.7 to 1 and the mean age at presentation was10 ±2.7 years (range 2–16). The mean disease duration was 6.47 ± 3.74 years. At presentation, musculoskeletal, constitutional and mucocutaneous manifestations were the commonest features ***(Salah et al., 2009).***

Etiology and pathogenesis:

Autoimmunity plays a major role in the pathogenesis of lupus nephritis. The immunologic mechanisms involved include production of autoantibodies directed against nuclear elements. These autoantibodies form pathogenic immune complexes. Deposition of these immune deposits in the kidneys initiates an inflammatory response by activating the complement cascade and recruiting inflammatory cells that can subsequently be observed on biopsy specimens ***(D'Agati and Appel, 2007).*** Immune complex deposition in the kidney initiates an inflammatory cascade that causes glomerular disease but there are many modulating factors including genetic predisposition, products of the innate immune system, cytokines, complement

and activated cells (both renal and immune) ***(Davidson and Aranow, 2006).***

SLE typically presents itself as a chronic, relapsing and remitting disease. Not all organs may be affected in all patients at the same time. Immunologically, the disease is characterized by B cell hyperactivity, the production of (multiple) autoantibodies and the formation of (circulating) immune complexes. Autoantibodies against nuclear antigens, such as anti- dsDNA antibodies, are considered responsible for much of the kidney disease and renal manifestations that can occur in SLE.A strong correlation exists between renal disease activity and anti-dsDNA antibody titers and the development of lupus nephritis ***(Mok and Lau, 2003)***. Anti-dsDNA antibodies participate in the pathogenesis of lupus nephritis by binding directly or indirectly with renal antigens. The observation that a subset of anti-dsDNA antibodies can penetrate into living cells raises an additional intriguing possibility to explain the nephritogenic potential of these antibodies. Anti-dsDNA antibodies that bind to cell surface targets and/or penetrate into the cell may influence cell activation, proliferation and death, and induce expression of pro-inflammatory cytokines. Penetration into living cells, which is seen not only with anti-dsDNA antibodies but also with other lupus associated autoantibodies, suggests not only new approaches to understand autoantibody involvement in target organ damage, but may also lead to the development of a novel technique for intracellular delivery of therapeutic proteins ***(Putterman, 2004).***

Lupus nephritis results from a complex interplay of autoantibodies, inflammatory cells, stimulated resident cells, chemokines, cytokines, reactive oxygen species, reactive nitrogen species, vasoactive compounds, and eicosanoids ***(Oates and Gilkeson, 2002).***

Although knowledge of the etiology of SLE is incomplete, it is clear from the varied forms of tissue injury that a number of different effector mechanisms may act alone or in concert to produce the pleomorphic patterns of lupus nephritis. Autoantibodies may lead to cell and tissue injury by Fc receptor-mediated inflammation ***(Clynes et al., 1998)*** as well as by direct cytotoxicity, which is usually complement-dependent, as has been shown for antibody-mediated hemolytic anemia or thrombocytopenia. In the kidney, intrinsic antigens such as extracellular matrix components or cell surface glycoproteins may serve as targets for autoantibody binding. In addition, renal injury in lupus nephritis may result from autoantibodies that bind to circulating antigens, forming circulating preformed immune complexes, or autoantibodies that bind to antigens deposited from the circulation in glomerular and vessel walls, causing in situ immune complex formation, as has been shown for nucleosomes and anti-double-stranded DNA autoantibodies ***(Berden, 1997)***. Subsequent Fc receptor and complement binding then initiates an inflammatory and cytotoxic reaction. Such cytotoxicity may be directed toward podocytes in the setting of membranous nephropathy, where in situ immune

complex formation occurs along the subepithelial aspect of the glomerular basement membrane, or toward endocapillary cells in the case of the endocapillary proliferative and exudative inflammatory reaction that follows subendothelial immune complex formation ***(Weening et al., 2004).***

In addition to direct immune complex-mediated cell and tissue injury, autoantibodies with antiphospholipid or cryoglobulin activity may also promote thrombotic and inflammatory vascular lesions in SLE ***(Daugas et al., 2002).*** Antineutrophil cytoplasmic antibodies (ANCA) have been reported in a subgroup of lupus nephritis patients which may initiate vasculitis and glomerulonephritis by" pauci immune" neutrophil dependent mechanisms ***(Weening et al., 2004).***

Lupus nephritis in children:

The natural history of lupus nephritis in children is controversial. Study results have varied from the course of disease in children being described as better in some instances and worse in others than comparable classes of lupus nephritis in adults. Indeed, one study showed a dismal renal survival of 29% at 10 years in a cohort of 56 pediatric patients with lupus nephritis ***(Bakir et al., 1994).***

The high risk of renal failure may have been affected by racial factors; more than 64% of patients were Black and less than 10% were White. The natural histories, indications for treatment, and outcomes are similar in children and adults with

lupus nephritis, though most studies have not analyzed the confounding issue of race on the outcomes of pediatric aged patients ***(Niaudet, 2000).***

It is apparent that children have greater capacity to compensate for glomerular damage than do adults. Thus, children compared to adults with comparable proportions of obsolescent glomeruli have greater potential, for compensatory hypertrophy in less involved glomeruli (presumably with increased single nephron hyperfiltration) and in overall preservation of renal function ***(Balow et al., 2003).***

Children with SLE are at a higher risk of renal disease than adults and tend to sustain more disease damage secondary to more aggressive disease and treatment-associated toxicity ***(Salah et al., 2009)***.

Renal biopsy findings associated with pediatric lupus nephritis show a higher rate of focal and diffuse lupus nephritis compared with findings associated with adult lupus nephritis, and the prevalence of progression to renal failure is increased. Renal involvement occurs in two thirds of children and adolescents with SLE. Since the advent of immunosuppressive therapy, survival rates have improved; however, this improvement has occurred at the expense of long-term morbidity and complications of therapy, with profound consequences. ***Bogdanovic et al (2004)*** found a 5-year survival rate of 98% and a renal survival rate of 89% (without end-stage renal disease) in children with lupus nephritis.

In the treatment of patients with pediatric lupus nephritis, early therapy to control the disease should be balanced with long-term follow-up to minimize the adverse effects of therapy and the disease complications. Poor prognostic features include a renal biopsy specimen that shows diffuse lupus nephritis, persistent hypertension, persistent elevated anti-dsDNA, and hypocomplemen-temia.

Clinical manifestations of lupus nephritis:

Features of lupus nephritis range from the presence of proteinuria and mild hypertension to acute or chronic renal failure. Signs and symptoms of lupus nephritis include haematuria, proteinuria, fatigue, fever, edema, hypertension, and swelling around the eyes, legs, ankles and fingers ***(Moore, 2007).***

Table (2): Clinical features of patients with evident lupus nephritis

Feature	%
Proteinuria	100
Nephrotic syndrome	45-65
Granular casts	30
red-cell casts	10
Microscopic hematuria	80
Macroscopic hematuria	1-2
Reduced renal function	40-80
Rapidly declining renal function	30
Acute renal failure	1-2
Hypertension	15-50
Hyperkalemia	15
Tubular abnormalities *	60-80

** usually without symptoms* ***(Cameron, 2003)***

Active lupus nephritis can be defined clinically and patho-logically. Clinical evaluation for lupus nephritis includes microscopic urine analysis, 24 hour urinary protein and creatinine excretion, serum creatinine determinations, and serologic studies (anti-dsDNA titers and serum complement components C3 and C4**)**. Lupus renal disease is also defined immunohistopathologically. Tissue obtained by renal biopsy should be evaluated by light microscopy, immunofluorescence, and electron microscopy. There is a correlation between the pathologic class of lupus nephritis and the clinical features ***(Donadio et al., 1995).***

Diagnosis of lupus nephritis:

1. Laboratory Studies;

Renal function tests: Evaluating renal function in patients with systemic lupus erythematosus (SLE) to detect any renal involvement early is important because early detection and treatment can significantly improve renal outcome.

- Serum Creatinine.
- Blood urea nitrogen (BUN) testing.
- Urine analysis:

Table (3): Abnormal Urinary Findings

	%
Albuminuria	46.1
WBCs in urine (more than 6/HPF in clean specimen)	35.5
Hematuria	32.6
Granular casts	31.5
Hyaline casts	28.4
RBC casts	7.5
Fatty casts	6.1
Oval fat bodies	4.4
Double refractile bodies	1.9
Waxy casts	1.7
Mixed fatty casts	1.2

(Wallace and Hahn, 2008)

Spot urine test for creatinine and protein concentration. Clinically relevant lupus nephritis is associated with a 30% decrease in creatinine clearance, proteinuria of greater than 1000 mg/d, and renal biopsy findings indicating active lupus nephritis ***(Brent, 2009).*** (Normal creatinine excretion is 1000 mg/24 h/1.75 m^2; normal protein excretion is 150-200 mg/24 h/1.75 m^2; normal urinary protein-to-creatinine ratio is <0.2) ***(Dooley et al., 2008).***