INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease that results from the interaction of multiple environmental, immunological and genetic factors, causing inflammation and eventually damage in a wide range of organs and systems. Its prevalence ranges from approximately 40 cases per 100,000 individuals in Caucasians to more than 200 cases per 100,000 individuals among black people ***(Yazdany et al., 2009).***

Although mainly it's a disease of women in childbearing age, its prevalence is not confined within this population. A total of 15-20% of cases present in children under 16 years of age. Although there have been limited studies directly comparing adult-hood and childhood-onset SLE, it has been suggested that pediatric lupus patients have a more aggressive disease course and an increased rate of more unusual initial clinical presentations compared with their adult counterparts . Also differences in the serological and autoantibody profiles of children and adults with SLE have also been described ***(Hersh et al., 2009)***.

Overall, an increased male-to-female ratio, a higher prevalence of nephritis and CNS involvement necessitating a more sustained need for steroids and immunosuppressive drugs, and a higher prevalence of progression to end-stage renal disease are distinguishing features of childhood-onset lupus. In contrast, a higher prevalence of pulmonary involvement,

arthritis and discoid lupus are reported in adult-onset SLE patients ***(Papadimitraki and Isenberg, 2009).***

Despite widely variable estimates, fever and lymphadenopathy are more frequently described with pediatric SLE than aSLE in studies directly comparing both groups. When comparing prepubertal to post pubertal onset of pediatric SLE, the former group presents more often with hemolytic anemia whereas in the latter group cutaneous and musculoskeletal features are more common at disease onset approximately one-third of the children and adolescents with SLE present with anemia, thrombocytopenia, or lymphopenia at the time of SLE onset. Also leucopenia is more common in pediatric SLE than aSLE at onset ***(Hoffman 2009).***

Renal involvement in SLE carries a poor prognosis and significant morbidity and mortality. The 5- and 10-year renal survival rates of lupus nephritis in the 1990s range between 83%–92% and 74–84% respectively, up to 25% of patients still develop end stage renal failure 10 years after onset of renal disease ***(Bhinder et al., 2010).***

Lupus nephritis (LN) is often a presenting feature of pediatric SLE. In comparative studies of pediatric SLE and aSLE, the prevalence of LN in adults with SLE is at 34% to 48%.and most studies report LN to be present in 50% to 67% of the children, at a higher frequency than with aSLE. Consequently, proteinuria and urinary cell casts during the disease course are more common with pediatric SLE than aSLE ***(Bernard et al., 2008).***

Aim of the Work

The aim of the present study is to compare the clinical, immunological and laboratory profiles and treatment options in childhood and adulthood-onset lupus nephritis patients pointing out the differences in the two studied population.

Chapter (1)

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic, relapsing autoimmune disease that can affect various organs, such as the skin, joints, kidneys, and serosal membranes. Lupus disease is of unknown etiology but is thought to be a failure of the regulatory mechanisms of the autoimmune system. Lupus symptoms include swollen joints, extreme fatigue, skin rashes, and sensitivity to sunlight ***(Rahman et al., 2008).***

SLE is an autoimmune disorder characterized by multisystem microvascular inflammation with the generation of autoantibodies. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, racial, hormonal, and environmental factors ***(Rahman et al., 2008).***

Many immune disturbances, occur in SLE involves a defect in apoptosis and a disturbance in immune tolerance, the Recent genetic studies point to disruptions in lymphocyte signalling, interferon response, clearance of complement and immune complexes, apoptosis, and DNA methylation. Many clinical manifestations of SLE are mediated via circulating immune complexes in various tissues or the direct effects of antibodies to cell surface components ***(Sestak et al., 2011).***

Renal disease is the major cause of mortality and morbidity in 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 (LN), the diffuse proliferative type (WHO class IV) carries the worst prognosis ***(Lai et al., 2005).***

Epidemiology of SLE:

SLE is found worldwide with an estimated prevalence of 40/100,000 in northern European ***(Rahman and Isenberg, 2008).***

The disease occurs nine times more often in women than in men, especially in women in child-bearing years ages 15 to 35, and is also more common in those of non-European descent ***(Harrison's., 2011).***

The risk of SLE development in men is similar to that in prepubertal or postmenopausal women. Childhood systemic lupus erythematosus generally presents between age of 3 and 15, with girls outnumbering boys 4:1, and typical skin manifestations being butterfly eruption on the face and photosensitivity ***(James et al., 2005).***

The life expectancy of such patients is improved from an approximate 4 year survival rate of 50% in the 1950s to a 15-year survival rate of 80% in 2008 ***(Rahman et al., 2008).***

Even so, a patient in whom lupus is diagnosed at 20 years of age still has a 1 in 6 chance of dying by 35 years of age, most often from lupus or infection ***(Gladman et al., 2007).***

Later, myocardial infarction and stroke become important causes of death ***(Gladman et al., 2007).*** This bimodal pattern of mortality in lupus was recognized more than 30 years ago ***(Rahman et al., 2008).***

Pathogenesis:

The pathogenesis of lupus remains unclear, although the notion of apoptosis goes some way to explain how the immune system might recognize predominantly intracellular antigens. Autoantigens are released by both necrotic and apoptotic cells. Defects in the clearance of apoptotic cells have been described in this disorder and these defects could lead to aberrant uptake by macrophages, which then present the previously intracellular antigens to T and B cells, thus driving the autoimmune process. Further studies have expanded these ideas and examined possible defects in the clearance of apoptotic bodies, including complement deficiencies, defects in macrophage handling, and presentation of these antigens to the immune system ***(Munoz et al., 2005).***

Cytokine patterns might also be important in the pathogenesis of lupus. Investigations have drawn attention to the over expression of the type I interferon pathway in patients the so called interferon signature ***(Hau et al., 2006).***

Diagnosis:

The American College of Rheumatology (ACR) has defined criteria for the classification of SLE ***(Hochberg, 1997)***.

Table (1): American College of Rheumatology Criteria for the Classification of SLE ***(Hochberg, 1997).***

Criteria	Definition
Malar (Butterfly) Rash	Fixed erythema, flat or raised, over the malar eminencies, tending to spare the nasolabial fold.
Discoid Lupus	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sun light by patient history or physician observation.
Oral Ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	characterized by tenderness, swelling or effusion
Serositis	a) Pleuritis: convincing history of pleurtic pain or rub heard by a physician or evidence of pleural effusion Or b) Pericarditis: documented by ECG or rub or evidence of pericardial effusion
Renal Disorder	a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed Or b) Cellular casts: may be red cell, hemoglobin granular, tubular, or mixed
Neurologic Disorder	a) Seizures: in the absence of offending drugs or known metabolic derangements; eg., uremia, ketoacidosis, or electrolyte imbalance. Or b) Psychosis in the absence of offending drugs or known metabolic derangements; eg., uremia, ketoacidosis, or electrolyte imbalance.
Hematologic Disorder	a) Hemolytic anemia with reticulocytosis. Or b) Leukopenia: less than 4,000/microliter total on two or more occasions Or c) Lymphopenia: less than 1,500/ microliter on two or more occasions. Or d) Thrombocytopenia: less than 100,000/ microliter in the absence of offending drugs.
Immunologic Disorder	a) Anti-DNA: presence of antibody to native DNA in abnormal titer. Or b) Anti-SM: presence of antibody to Sm nuclear antigen. Or c) Positive finding of antiphospholipid antibodies based on: 1) An abnormal serurn level of IgG or IgM anticardiolipin antibodies, 2) A positive test result for lupus anticoagulant using a standard method, or 3) A false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidurn imrnobilization or fluorescent treponernal antibody absorption test
Antinuclear Antibody	An abnormal titer of antinuclear antibody for 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

SLE is diagnosed when four of the eleven criteria are documented at any time in the history (Hochberg, 1997).

In clinical practice; diagnosis of SLE is based on a combination of autoantibody assays, clinical manifestations, and laboratory studies of affected organ systems. Patients with lupus activity or damage may be asymptomatic or may present with findings that reflect the specific organ systems involved. Symptoms and signs accumulate over time in patients with SLE ***(Lahita, 2004).***

At any given time, especially at the onset of illness, most often only a few manifestations are present. Arthritis, malaise, cytopenias, and rashes are the most prominent early findings. Nephritis (with renal failure), arthritis, osteoporosis and osteonecrosis (corticosteroid complications), neurologic disease, accelerated atherosclerosis, and cardiac valvular disease dominate the late course. With disease activity and with its treatment, the risk of opportunistic infection is high. For conceptual purposes, it is easiest to consider disease activity and manifestations separately for each affected organ system ***(Lahita, 2004)***.

However, because lupus-like illnesses is also usually suspected, it is often efficient also to obtain at first visit the following tests: Erythrocyte sedimentation rate (ESR) or C-reactive protein level; assays for antibodies against dsDNA, Sm, RNP, SS-A, and SS-B; partial thromboplastin time (or

other screening test for lupus anticoagulant) and cardiolipin antibodies; and a chemistry profile that includes liver function tests and serum creatinine level ***(Marrack et al., 2001).***

SLE is treatable using immunosuppression, mainly with cyclophosphamide, corticosteroids and other immuno-suppressants; there is currently no cure. SLE can be fatal, although with recent medical advances, fatalities are becoming increasingly rare. Survival for people with SLE in the United States, Canada, and Europe has risen to approximately 95% at five years, 90% at 10 years, and 78% at 20 years ***(Harrison's Internal Medicine, 17th ed. Chapter 313, 2011).***

In November 2010, an FDA advisory panel recommended approving Benlysta (belimumab) as a treatment for the pain and flare-ups common in lupus. The drug was approved by the FDA in March 2011 FB ***(Morand et al., 2012).***

The disease course is milder and survival rate higher among persons with isolated skin and musculoskeletal involvement than in those with renal and CNS disease ***(Faurschou et al., 2010)***

Prognosis is normally worse for men and children than for women; however, if symptoms are present after age 60, the disease tends to run a more benign course. Early mortality, within 5 years, is due to organ failure or overwhelming infections, both of which can be modified by early diagnosis and treatment ***(Vasudevan et al., 2009).***

Chapter (II)

CLINICAL INDICES IN THE ASSESSMENT OF LUPUS

Disease activity can be defined as the reversible manifestations of the underlying inflammatory process. It is a reflection of the type and severity of organ involvement at each point in time. Although the physician's opinion is the gold standard for the evaluation of disease activity, it is evident that there is bias based on personal experience and different opinions on the relative merits of disease activity in different systems ***(Yee et al., 2009).***

Many used measures, in order of date of publication, include the British Isles Lupus Assessment Group index (BILAG), the Systemic Lupus Activity Measure (SLAM), the Lupus Activity Index (LAI), the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the European Consensus Lupus Activity Measure (ECLAM). A key feature of all of these instruments in addition to the focus of active SLE as opposed to damage is the attribution of the manifestations to SLE. Although they are all valid, reliable, responsive indices that have been shown to correlate with each other, there are significant differences ***(Grossman and Gordon, 2007).***

British Lupus Isles Assessment Group index (BILAG) was developed using a nominal consensus approach by a group

of investigators from five centers in the United Kingdom and was first published in 1988 ***(Symmons et al., 1988).***

The instrument scores the activity in eight organ-based systems occurring in the preceding month. It is based on an intent to treat principle and uses the following ratings:

A: Active (severe disease that would warrant increased prednisone at more than 20 mg a day or the addition of other immunosuppressants)

B: Beware (less active disease that would be treated with low-dose prednisone, nonsteroidal anti-inflammatories or antimalarials)

C: Contentment (mild stable disease with no change in therapy or simple analgesics)

D: (system unaffected)

The organ-based systems include general features, mucocutaneous, neurologic, musculoskeletal, cardiorespiratory, vasculopathy, renal, and hematologic. Immunologic abnormalities are not included in this index. Although not originally derived to be a global score, a weighted system where an A =9, B =4, C =1, and D =0, was devised to yield a total score of all the organ systems ranging from 0 to 72 ***(Ehrenstein et al., 1995).***

This was later revised to A =9, B =3, C =1, D =0, and E =0 (version 3).

Modifications to this version included clarification of ambiguous terms, the addition of a glossary, definition of a time scale, the standardization of the calculation of the BILAG score, and the change of D to Discount (previously unaffected) and the addition of a category E, never affected. The positive predictive value (ppv) of a BILAG A, that is the likelihood that a patient with an A score would receive prednisone at greater than or equal to 20 mg a day or additional immunosuppressant therapy was excellent at 80%. The only individual systems that did not have at least an 80% ppv were the nervous system (ppv 30%) and hematologic (ppv 50%) ***(Grossman and Gordon, 2007).***

Over time, members of the British Isles Lupus Assessment Group have found certain aspects of the BILAG index unsatisfactory and modifications have been made. As a result BILAG 2004 was developed ***(Isenberg et al., 2004).***

This version has nine organ-based systems rather than eight adding lupus-related ophthalmologic problems, re-organizing and expanding the gastrointestinal and hepatic manifestations into its own category and removing the vasculitis category and distributing its components to the appropriate organ system. Furthermore, BILAG 2004 deletes some items from the current BILAG that are really more

damage than activity such as avascular necrosis. Also, BILAG 2004 states that an A score that is improving becomes a B score, rather than a C as it is currently measured to try to more accurately reflect change in activity. In two real patient exercises, the instrument demonstrated good reliability and agreement in all organ systems except musculoskeletal. Further improvement of the glossary as well as additional validation studies are underway ***(Grossman and Gordon, 2007).***

Systemic Lupus Activity Measure: The SLAM was developed at the Brigham and Women's Hospital and published in 1989 ***(Liang et al., 1989).***

Like the SLEDAI, it is a global score assessing overall disease activity occurring in the month preceding the assessment with a score ranging from 0 to 84. It consists of 24 clinical and 7 laboratory manifestations of lupus. The manifestations are graded as active or inactive, with activity scores varying from mild to moderate to severe. A revised version, SLAM-R, which drops the pneumonitis and "other" manifestations and rewords some of the definitions has been more commonly used ***(Bae et al., 2001).***

There are a few important differences between SLEDAI and SLAM. SLE manifestations in SLAM are not weighted giving equal importance to features, such as fatigue and urinary sediment. It does, however, allow for severity to be taken into account such that a severe rash scores more than a mild rash. It

also captures subjective features in SLE such as fatigue and myalgias, which are not part of SLEDAI. This may be a problem in studies of disease activity as the SLAM scores fibromyalgia, which frequently does not correlate with active lupus ***(Grossman and Gordon, 2007).***

The Lupus Activity Index

The LAI was developed at Johns Hopkins University and the University of California, San Francisco ***(Petri et al., 1992).***

It is a global scale with five parts that assesses disease activity occurring up to 14 days before the visit. Part one is the physician's global assessment (PGA) scored on a 0 to 3 point Visual Analogue Scale (VAS) where 3 represents the most severe disease. Part two is an assessment of fatigue, rash, arthritis, and serositis again on a 0 to 3(VAS). Part three scores the activity of the neurologic, renal, pulmonary, and hematologic organ systems of a 0 to 3 (VAS). Part four scores medications with higher doses of prednisone and cytotoxic agents receiving higher scores. Part five scores three laboratory parameters of urinary sediment, anti-DNA levels, and complement levels. The LAI summary score is calculated as the mean of part one score plus the mean of the four values in part 2 plus the maximum value in part 3 plus the mean of the scores in part 4 plus the mean of the three laboratory values. The summary score ranges from 0 to 3. The modified LAI (modified to exclude part 1, the PGA) it is correlated well with

the PGA and with SLEDAI, has also been shown to be sensitive to change ***(Ward et al., 2000).***

Systemic Lupus Erythematosus Disease Activity Index:

The SLEDAI was developed at the University of Toronto in 1992 ***(Bombardier et al., 1992).***

It is a one-page weighted scale for 24 items. The weighting system was derived by multiple regression analysis from expert clinicians' judgment about the features' contribution to the overall disease activity. The manifestations felt to be most commonly contributing to disease activity are included and are scored based on presence or absence within 10 days of the evaluation and are more objective rather than subjective in nature. The score can range from 0 to 105 and is a global score reflecting all aspects of disease activity. The SLEDAI does include immunologic laboratory results. It has been shown to be a valid, reliable instrument that is sensitive to change ***(Gladman et al., 1994).***

MEX-SLEDAI was developed by Guzman et al. for use in countries where immunologic tests are not routinely available ***(Guzman et al., 1992).***

The MEX-SLEDAI does not include complement levels, anti-DNA antibodies, visual disturbances, lupus headache, and pyuria ***(Guzman et al., 1992).***