A-15-year experience of Paediatric Systemic Lupus Erythematosus (pSLE) in Hospital Universiti Sains Malaysia

By

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A-15-YEAR EXPERIENCE OF PAEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS (pSLE) IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Introduction: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder, relatively rare and under-reported in paediatric age group, affecting females in the majority of cases. The disease manifestations and clinical outcomes vary depending on which system being involved and treatment response. Its etiology is complex and involves an interaction between genetic, hormonal and environmental factors. Diagnosis is made clinically based on certain clinical and laboratory criteria made by American College of Rheumatology (ACR).

Objectives: The aims of the study were to describe the demography, clinical and laboratory manifestations, and outcomes of children with SLE and to determine the risk factors associated with the development of renal failure and death among SLE children admitted to Hospital USM in the period between 1996 and 2010.

Patients and Methods: In this cross sectional study we retrospectively reviewed the folders of 51 children over a period of 15 years; all patients were below 18 years of age and fulfilled the SLE criteria outlined by American College of Rheumatology.

Results: The median age was 12 years with female predominance, male to female ratio was 1:10. Majority of our patients have positive family history and the commonest clinical manifestation was involvement of haematological and renal systems. One quarter of the cohort developed lupus nephritis some requiring acute dialysis but none necessitating long term dialysis or progressed to end stage renal disease (ESRD). Death complication was observed in almost 30% of the cases, majority due to sepsis.

Conclusion: The sociodemography, clinical profile, laboratory findings and outcome of childhood SLE in Kelantan are not much different from other studies done abroad. Lupus nephritis was found to be a risk factor for development of renal failure in this group of patients whereas infection was the leading cause of death; however, the other studied factors associated with these outcomes among our SLE children need further larger studies to be concluded.

Dr Mohamad Ikram Ilias: Supervisor

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ABBREVIATIONS

ACR	American College of Rheumatology
AIHA	Autoimmune hemolytic anemia
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
Anti-Sm	Anti-smooth muscle
ARF	Acute renal failure
aSLE	Adult systemic lupus erythematosus
AST	Aspartate aminotransferase
BP	Blood pressure
C3, C4	Complement 3, complement 4
CNS	Central nervous system
CRP	C-reactive protein
DCT	Direct Coombs test
DIL	Drug-induced lupus
dsDNA	Double-stranded DNA
EBV	Epstein Bar Virus
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
ESR	Erythrocyte sedimentation rate
ESRD	End stage renal disease
EULAR	European League Against Rheumatism
FBC	Full blood count
FBP	Full blood picture
GFR	Glomerular filtration rate

HD	Haemodialysis
Hib	Hemophilus influenza b
HLA	Human leukocyte antigen
HRPZ II	Hospital Raja Perempuan Zainab II
HUSM	Hospital Universiti Sains Malaysia
IQR	Interquartile range
KDIGO	Kidney Disease Improving Global Outcomes
JIA	Juvenile idiopathic arthritis
LFT	Liver function test
LN	Lupus nephritis
MCTD	Mixed connective tissue disease
PD	Peritoneal dialysis
pSLE	Paediatric systemic lupus erythematosus
RBCs	Red blood cells
RF	Rheumatoid factor
RFT	Renal function test
SD	Standard deviation
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
UK	United Kingdom
Urine PCI	Urine protein creatinine index
UV light	Ultraviolet light

ABSTRAK

Pengenalan

Systemic lupus erythematosus ialah penyakit autoimune yang jarang bagi peringkat umur kanak-kanak. Kebanyakan pesakit adalah dalam kalangan perempuan yang berumur 5 hingga 15 tahun. Namun penyakit ini sangat jarang bagi kanak-kanak berumur bawah dari 5 tahun. Nisbah bagi lelaki kepada perempuan adalah 1 kepada 10.

Objektif

Objektif kajian ini adalah untuk mengenalpasti faktor sosiodemografi, profil klinikal, keputusan makmal, komplikasi dan kesan terhadap kanak-kanak yang menghidap penyakit SLE di HUSM, Kelantan. Selain itu ia juga bertujuan untuk mengkaji faktor-faktor yang menyumbang kepada penyakit buah pinggang dan kematian di kalangan kanak-kanak.

Kaedah

Kajian telah dijalankan secara retrospektif di HUSM kelantan. Kajian ini melibatkan semua pesakit yang baru di sahkan menghidap penyakit SLE. Semua pesakit adalah berumur 18 tahun atau kebawah dari yang memenuhi kriteria kajian bermula dari Januari 1996 sehingga Disember 2010.

Keputusan

Terdapat seramai 51 kanak-kanak yang memenuhi kriteria kajian dengan median umur adalah pada umur 12 tahun. Kanak-kanak perempuan adalah paling ramai disahkan menghidap SLE dengan nisbah 1 dalam 10. Majoriti pesakit adalah berasal dari kawasan bandar dan lebih dari separuh pesakit (78 %) mempunyai sejarah keluarga yang menghidap penyakit autoimun. Tanda-tanda klinikal yang paling banyak ditemui iaitu 60 peratus dalam kalangan pesakit adalah manifestasi buah pinggang dan haematologi. Manakala 56 peratus lagi adalah manifestasi immunologi. Antinuclear antibody (ANA) adalah positif bagi 96 peratus pesakit. Komplikasi yang biasa dikalangan pesakit adalah Lupus Nephritis (LN) dimana ia melibatkan 60.8 peratus dan separuh dari mereka menghidap Lupus Nephritis Class IV. Lupus Nephritis yang teruk boleh menyebabkan pesakit menghidap Acute Renal Failure (ARF) dan 27% pesakit memerlukan dialisis kerana uraemia dan fluid overload. 14 pesakit iaitu 27.5 peratus telah meninggal dunia dan kebanyakannya adalah disebabkan kerana jangkitan kuman.

Konklusi

Sosiodemografi, profil klinikal, keputusan makmal dan kesan-kesan SLE di kalangan kanak-kanak di Kelantan adalah hampir sama dengan kajian-kajian yang dilakukan di luar negara. Walaubagaimnapun faktor-faktor penting yang menyebabkan pesakit-pesakit SLE mendapat penyakit buah pinggang dan meningal dunia adalah tidak dapat disahkan di dalam kajian ini.

ABSTRACT

Introduction

Systemic lupus erythematosus is an uncommon multisystemic autoimmune disorder, relatively rare in paediatric age group. It is predominantly affecting females in the age group 5 to 15 years. It is very rare in children below 5 years old. The male to female ratio is 1 in 10.

Objectives

The objectives of this study were to evaluate the sociodemographic, clinical profiles, laboratory findings, complications and outcome of children with SLE in Hospital USM (HUSM), Kelantan and to explore the factors associated with development of renal failure and death among those patients.

Methodology

This study was conducted via retrospective (cross sectional) record review in HUSM, Kelantan. It involved all newly diagnosed SLE cases aged 18 years or less who met all the study criteria from January 1996 till December 2010.

Results

There were 51 children included in this study with the median age at diagnosis of 12 years old with female predominance, male to female ratio of 1:10. The majority of

patients came from urban areas and family history of autoimmune diseases was seen in more than half of the patients (78%). The most common clinical findings in our patients were renal and haematological manifestations (60% of patients) followed by immunological findings (56%). Antinuclear antibodies (ANA) were positive in 96% of patients. The most common encountered complication was lupus nephritis (LN) in 60.8% of patients; half of them have lupus nephritis class IV. Lupus nephritis was complicated by ARF in some patients; 27% needed acute dialysis for their uraemia and fluid overload. Fourteen patients in this study (27.5%) passed away. Infection was the most common cause of death in pSLE.

Conclusion

The sociodemography, clinical profile, laboratory findings and outcome of childhood SLE in Kelantan are not much different from other studies done abroad. Lupus nephritis was found to be a risk factor for development of renal failure in this group of patients whereas infection was the leading cause of death; however, the other studied factors associated with these outcomes among our SLE children need further larger studies to be concluded.

CHAPTER 1

INTRODUCTION

1.1 Systemic Lupus Eyrthematosus (SLE)

Systematic Lupus Erythematosus (SLE) is the commonest autoimmune disorder with renal involvement. About 10-15% of all SLE patients are diagnosed in childhood (Stichweh et al 2004). Childhood-onset SLE patients have been reported to differ from their adult-onset counterparts in that they have more nephritis, more central nervous system involvements, and have been reported to have a poorer outcome. There have also been reports of ethnic differences in the incidence and severity of pediatric SLE (pSLE) patients, indicating that African Americans and Hispanic patients are more prone to the disorder and have more severe symptoms than Caucasian patients(Tucker LB et al 1995, and Alareon GS 2001). However, most of these reports were small case-series and limited by referral bias as they came from tertiary pediatric centers.

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease characterized by widespread inflammation of blood vessels and connective tissues and by the presence of antinuclear antibodies (ANAs), especially antibodies to the native double stranded DNA (Anti-dsDNA). Its clinical manifestation is variable and its natural history is unpredictable. Incidence of juvenile SLE varies by location and ethnicity. There is a wide range of variation in the natural history of SLE among different ethnic and geographical groups.

Studies in juvenile SLE have estimated the incidence at 0.28 to 0.9/100,000 per year (Malleson P et al 1996, Kaipiainen-Seppanen 1996, and Fujikawa S et al 1997).

The course of SLE disease is characterized by periods of flare and remission, and inflammation that can result in irreversible tissue damage, as well as premature death (Brunner HI et al 2002). Despite numerous reports of SLE in adults, in the recent years there have been few reports on the clinical and laboratory features of pediatric SLE at presentation (Hiraki et al 2008). Although adult and pediatric SLE share clinical features, it has been suggested that children have a more severe and aggressive disease course and may present different signs and symptoms at onset; in fact about one third of patients with pSLE may have non classical manifestations at presentation that may be responsible for the major diagnostic delay in this age group (Brunner HI et al 2008).

Most of the studies of pSLE reported to date have been limited by the relatively small sample sizes compared with studies of adult SLE (aSLE). There has been no large comprehensive, single-center cohort study in pSLE examining the clinical presentation, laboratory features, autoantibody profile, disease progression, and accrual of damage. Most studies have been limited by sample size or have focused on only one or two aspects of pSLE, with the majority of studies focusing on either renal or CNS disease (Levy DM et al 2003, Alsaeid K et al 2004, Balkaran BN et al 2004, Beresford et al 2005, and Houghton KM et al 2006).

Worldwide estimated incidence of SLE in children under 18 years old is 15-17%, with a peak incidence at 10-14 years with female predominance; the disease is rare in children below 5 years old (White P 1994).

1.2 Aetiology and Pathogenesis of SLE

The aetiology of SLE is largely unknown, but it involves *genetic*, *hormonal*, and *environmental* factors.

Genetic factors – the evidence of genetic susceptibility to SLE in humans is based on familial aggregation. The prevalence of SLE is estimated to be 2.6-3.5% in first-degree relatives of SLE probands compared with 0.3-0.4% in relatives of match controls. Moreover, an increase in concordance rate is observed in monozygotic twins (24-56%) compared to dizygotic twins (2-5%). The risk of developing the disease in siblings of SLE patients is 10-40 times higher than that in the general population.

Hormonal factors – the female predominance in SLE is particularly strong during childbearing age, suggesting that hormonal differences may contribute to the increased risk of the disease. Reduced androgen levels, increased estradiol and prolactin levels have been reported in SLE patients.

Environmental factors – beside genetic and hormonal factors studies have shown that other factors such as toxic and infectious factors are suspected to induce SLE. The fact that seroconversion against EBV was observed in 99% of children with SLE as

compared to only 70% of their controls is consistent with but does not in itself establishes EBV as a causative factor in SLE. Photosensitivity is a common feature of SLE since specific lupus lesions occur on sun-exposed areas and the disease is aggravated by sun exposure in 40-70% of patients. The current theory is that the UV light induces apoptosis of keratinocytes, which develop small surface blebs containing lupus auto- antigens such as Ro particle. Similarly drugs such as chlorpromazine or environmental toxins such as silica dust have been shown capable of inducing apoptosis.

SLE is an autoimmune disease characterized by B cell hyperreactivity, producing multitude of different auto- antibodies against self antigens such as dsDNA, nucleosome, anticardiolipin etc. The complement system plays an important role in the onset as well as the effect phase of SLE. The autoantibodies and self antigens form immune complexes which over activate complement, causing inflammation and multi-organ damage, including skin, joints, CNS, kidney etc (Siegert et al 1997, and Fremeaux Bacchi et al 2002).

The aetiology of SLE is complex and relates to interactions between environmental, genetic, and endocrine influences. It is more common in certain ethnic groups (Asian, Hispanic, South -East Asian, African, and African American), and strongly associated with HLA haplotypes. Lupus occurs much more commonly after puberty and in females, this suggests an important role of estrogens, which is supported by animal models. Known environmental influences include sun exposure and certain medications.

The end result to these interactions is the production of multiple auto-antibodies that is both organ-specific and directed against a host of nuclear and cytoplasmic antigens.

The pathogenesis and etiology of SLE remains unclear. It is well recognized that SLE predominantly affects females, especially in the reproductive age. An increase in frequency of SLE among females is believed to be related to the effect of endogenous sex hormones. In fact, supporting evidence is provided by the literature showing the ratio of female to male s much lower in prepubertal children and after menopause, although a female predominance remains (Ho CT et al 1998, and Alsaeid K et al 2004). An administration of exogenous estrogens exacerbates SLE, while androgens have a protective role (Roubinian et al 1997, and Carlsten H et al 1993).

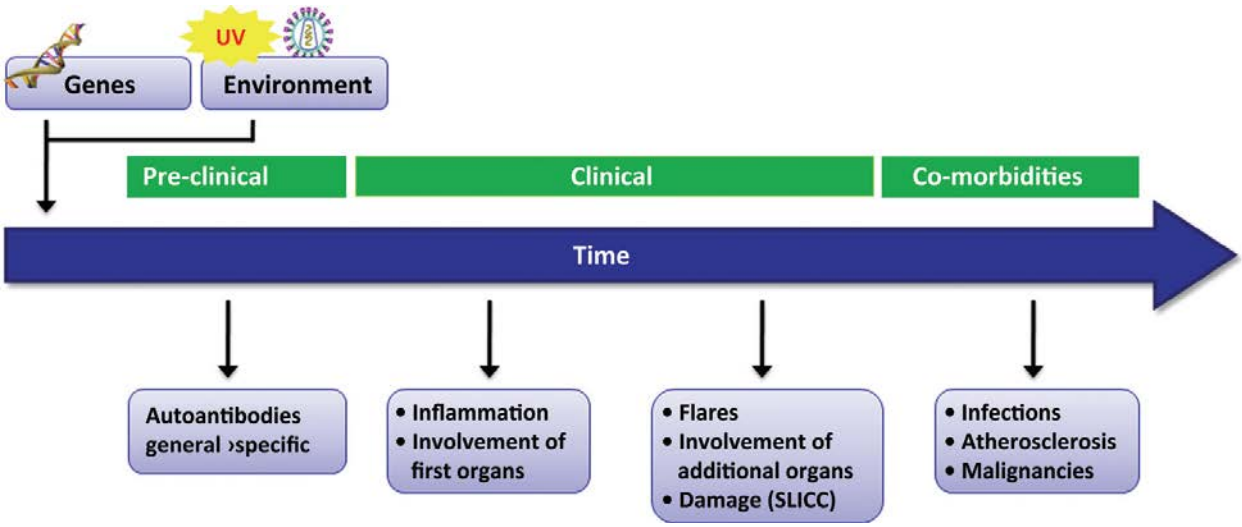

Figure 1 Natural history of systemic lupus erythematosus. SLICC, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index.

[a]Reprinted from systemic lupus erythematosus. Pathogenesis and clinical features. *Ann Rheum* Dis 2010;69:1603–11.

1.3 Clinical manifestations and diagnosis

The clinical manifestations of SLE reflect the degree of systemic inflammation as well as the organ system (s) affected. Systemic manifestations, both at the time of diagnosis as well as a time of disease exacerbations, frequently include fever, anorexia, lethargy, weight loss and fatigue. The diagnosis is based on the presence of multisystem involvement with compatible laboratory abnormalities. The presence of 4 of 11 classification criteria for SLE has both a very high sensitivity and specificity for the diagnosis of pediatric SLE. (Steinlin et al 1995)

According to American College of Rheumatology (ACR) revised SLE criteria in 1997, there are 11 criteria for SLE; presence of 4 out of these 11 criteria is diagnostic. These criteria are:

1) Malar rash
2) Discoid rash
3) Photosensitivity
4) Oral ulcers
5) Arthritis: nonerosive, involvement of 2 or more joints characterized by tenderness, swelling and effusion
6) Serositis: pleuritis or pericarditis
7) Renal disorder: persistent proteinuria or cellular casts in the urine
8) Neurologic disorder: seizures or psychosis
9) Haematological disorder: haemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
10) Immunologic disorder: positive LE preparation; anti-DNA antibody or antibodies to sm nuclear antigen, or false positive serologic tests for syphilis
11) Antinuclear antibody

Clinical manifestations at onset are diverse; it may range from isolated mild skin rash to severe multi-organ involvement. Initial symptoms may be insidious; however, it may present as an acute and even fatal disease. The disease course is progressive and may lead to significant morbidity and mortality if left untreated. A high level of suspicion and the proper use of laboratory tests may aid the treating physician in reaching an early diagnosis and proper management. (Lehman T 1995).

The Systemic Lupus International Collaborating Clinics (SLICC) Classification 2012 criteria were derived using the technique of "recursive partitioning" to derive a relatively simple classification rule. The diagnosis of SLE is as following:

Classify a patient as having SLE if

- The patient satisfies four of the criteria listed in table 1 including at least one clinical criterion and one immunologic criterion; or
- The patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies. (Petri M et al 2012).

Table 1 SLICC classification criteria

Clinical and immunologic criteria used in the SLICC classification criteria	
Clinical criteria	
Acute cutaneous lupus	Including lupus malar rash (do not count if malar discoid); bullous lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash in the absence of dermatomyositis; or subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory depigmentation or telangiectasia).
Chronic cutaneous lupus	Including classical discoid rash; localized (above the neck); generalized (above and below the neck); hypertrophic (verrucous) lupus; lupus panniculitis (profundus); mucosal lupus; lupus erythematosus tumidus; chillblains lupus; discoid lupus/lichen planus overlap.
Oral ulcers	Palate, buccal, tongue or nasal ulcers in the absence of other causes, such as vasculitis, Behçet's, infection (herpes), inflammatory bowel disease, reactive arthritis and acidic foods.
Nonscarring alopecia	Diffuse thinning or hair fragility with visible broken hairs in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia.
Synovitis	Involving two or more joints, characterized by swelling, effusion or tenderness in two or more joints, and 30 minutes or more of morning stiffness.
Serositis	Typical pleurisy for more than 1 day or pleural effusions or pleural rub; typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day or pericardial effusion or pericardial rub or pericarditis by electrocardiography in the absence of other causes, such as infection, uremia and Dressler's pericarditis.
Renal	Urine protein/creatinine (or 24-hour urine protein) representing 500 mg of protein/24 hour or red blood cell casts.
Neurologic	Seizures; psychosis; mononeuritis multiplex in the absence of other known causes such as primary vasculitis; myelitis; peripheral or cranial neuropathy in the absence of other known causes such as primary vasculitis, infection and diabetes mellitus; acute confusional state in the absence of other causes, including toxic-metabolic, uremia, drugs

Hemolytic anemia	
Leukopenia	< 4,000/mm3 at least once (in the absence of other known causes such as Felty's, drugs and portal hypertension); or Lymphopenia (< 1,000/mm3 at least once) in the absence of other known causes such as corticosteroids, drugs and infection.
Thrombocytopenia	(< 100,000/mm3) at least once (in the absence of other known causes such as drugs, portal hypertension, and TTP)
Immunologic criteria	
ANA	Above laboratory reference range.
Anti-dsDNA	Above laboratory reference range, except ELISA: twice above laboratory reference range.
Anti-Sm	
Antiphospholipid antibody	Any of the following lupus anticoagulant false-positive RPR medium or high titer anticardiolipin (IgA, IgG or IgM) anti-β2 glycoprotein I (IgA, IgG or IgM).
Low complement	Low C3, low C4, low CH50.
Direct Coombs test	In the absence of hemolytic anemia

Criteria are cumulative and need not be present concurrently.
Abbreviations: SLE, Systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics Classification; ANA, Antinuclear antibody; ELISA, Enzyme linked immunosorbent assay; RPR, Rapid plasma regain

[b]Printed from Systemic Lupus Erythematosus.*Ann Rheum* Dis 2012; 69:1603–11

Since the original criteria for lupus, first proposed in 1971, three significant revisions have taken place. The 1982 criteria (revised in 1997) continue to be the most widely used. Although developed as "classification criteria", they have been extensively used as diagnostic criteria. Over a period of time, many pitfalls became evident and the current revision in 2012 by SLICC using the methodology of recursive partitioning has attempted to overcome the same. The new criteria retain the specificity while being more sensitive. As with original ACR criteria they have not been tested for purposes of diagnosis. SLICC concludes that the new criteria retain the goal of simplicity of use, yet reflect current knowledge of SLE obtained in 29 years since the initial ACR criteria.

1.4 Complications of SLE

The morbidity and mortality associated with SLE is still considerable despite improvement in initial immunosuppressive therapy of active disease. There is still much to learn about the long term complications of this disease. Patients require lifelong follow up by physicians aware of the broad range of conditions that may ensue. The lupus patients and their families need to understand why this is important and their own role in modifying lifestyle factors that increase the risk of complications.

The common comorbidities of SLE include renal toxicity, infection, neuropsychiatric issues, ophthalmic complications and drug side effects. Other complications are rare in paediatric age group such as coronary artery disease, osteoporosis, and malignancies. Because of paucity of data in paediatric SLE, a little is known about its long term outcome, and optimal management.

Studies published around 1980 found that about 80% of patients survived 5 year and about 60% of patients survived 10 year. More recent studies have shown that 5year survival is now nearer 90–95% and that 70–85% of patients survives 10 year (Trager et al 2001). In most studies, patients with renal involvement have had a poorer prognosis than those without renal disease. Nevertheless, survival has shown improvement in those with renal disease presenting to a UK centre between 1976 and 1986 (81% 10 year survival), compared with those presenting between 1963 and 1975 (56% 10 year survival) [(Bono et al 1999)].

In one adult SLE study it was observed that the commonest cause of death has been infection, both in early and late deaths. Active SLE contributes to about a third of early deaths but less commonly to late deaths. However, deaths related to acute and chronic vascular disease including sudden death are more common in those dying more than 5 years after diagnosis. However, there is more to prognosis than just death. There is considerable morbidity associated with more prolonged survival after the diagnosis of SLE (Abu Shakra et al 1995).

Having improved therapy for active lupus disease, the challenge is now to understand and prevent the long-term complications of this disease, whether they are due to effects of the disease itself, the therapies used, or co-morbid disease (perhaps with associated underlying disease mechanisms or linked genetic predisposition).

1.5 Management of SLE

The treatment of SLE is mainly based on the use of traditional drugs, such as corticosteroids, antimalarials, azathioprine, and cyclophosphamide. Because of paucity of data in paediatric SLE, a little is known about its optimal management, however, it has the same principles as for adult SLE.

1.5.1 General measures

All SLE patients need education, counseling, and support due to complexity and unpredictability of the disease process. Patient education programs for SLE patients and their families are designed to provide information, knowledge, and social support with an emphasis on enhancing self-management skills (Robbins et al 1997).

Patients need advice regarding physical measures, including minimizing sun exposure, using sunscreen, and exercising regularly. Diet management for prevention of obesity, osteoporosis, and hyperlipidemia is of particular importance. Routine health maintenance, including regular ophthalmologic examinations and dental care (especially for those on corticosteroids and antimalarials), is very important in this chronic systemic disease. Preventive measures such as immunizations (e.g., Hepatitis B, hemophilus influenza (Hib), and pneumococcal vaccine) or use of hormone replacement therapy (in adolescent girls) should be also considered (American College of Rheumatology (ACR) guidelines 1999).

1.5.2 Medications

The first line treatment of SLE is the use of steroids. As our knowledge on the mechanisms of immune response increases, new drugs that can interfere with T and B cell interaction, immune-complex deposition and cytokine activation have been developed and some of these drugs are still under investigation in SLE. Although initial data regarding efficacy are encouraging, caution must be taken before these drugs are considered as the treatment of choice for specific SLE manifestations (Marta Moska et al 2001).

1.5.2.1 Glucocorticoids

Glucocorticoids are used for refractory manifestations of SLE, as well as for severe organ-threatening disease. High-dose daily therapy (40-60mg/day) improves survival

among patients with severe forms of SLE nephritis , but is associated with virtually universal undesirable side effects.

The treatment of active SLE nephritis, cerebritis, or thrombocytopenia may require high doses of prednisolone, or intravenous pulses up to 1 gm of methylprednisolone per day for 3 consecutive days. Studies of monthly high-dose intravenous methylprednisolone (in addition to daily oral glucocorticoids) have shown a positive effect on severe SLE nephritis, although the therapy is not as effective as intermittent intravenous cyclophosphamide added to oral glucocorticoids (Gourley MF et al 1996).

Even with aggressive therapy, some patients with proliferative lupus nephritis (LN) will have a progressive decline in renal function leading to end-stage renal disease (ESRD). Clinical risk factors for progression, evident at the time of initial presentation, include an elevated serum creatinine, hypertension, nephrotic range proteinuria, anemia with a hematocrit below 26 percent, and black and Hispanic race and ethnicity (Contreras et al 2005 and Siso et al 2010).

The likelihood of a successful initial outcome is greater if therapy for LN is initiated relatively early in the course of the disease. Delaying therapy because of presumed mild disease can be associated with increased glomerular injury, progressive tubulointerstitial fibrosis, glomerulosclerosis, and therefore a lesser response to immunosuppressive drugs (Faurschou et al 2006).

1.5.2.2 Immunosuppresive/Cytotoxic agents

Immunosuppressive therapy for proliferative lupus nephritis (LN) consists of Induction and maintenance phases. A number of immunosuppressive/cytotoxic medications have been used to treat SLE, this includes azathioprine, cyclophosphamide, methotrexate, cyclosporine, etc. the choice of the drug will depend on the nature and severity of the condition, as well as individual preference. For example, for patients with particularly severe arthritis, methotrexate may be preferred as the first cytotoxic medication, whereas for SLE nephritis, azathioprine or cyclophosphamide may be chosen first.

For initial induction therapy in patients with diffuse or moderate to severe focal proliferative lupus nephritis (LN), it is recommended to use immunosuppressive therapy with either an intravenous cyclophosphamide- or MMF-based regimen. Glucocorticoids are also given as part of the induction regimen. This recommendation is in agreement with both the KDIGO and EULAR/ERA-EDTA guidelines (Bertasias GK et al 2012).

In a series of long-term studies (more than 20 years follow up) in patients with SLE nephritis, treatment with glucocorticoids plus cyclophosphamide for > 2 years appears to be superior than glucocorticoids and azathioprine, and both seem superior to glucocorticoid alone in preventing renal failure in these patients (Boumpas DT et al 1995).

Some patients with severe disease (renal or extra renal) respond well over both the short term and long term to glucocorticoid alone, or they require only a few months of treatment with cytotoxic agents plus glucocorticoids to achieve long term improvement. There is evidence that cytotoxic agents plus low-dose steroids prevent scarring in the kidney better than do glucocortecoids alone (Hahn BH et al 2012).

1.5.2.3 Antimalarial agents (e.g., Hydroxychloroquine)

Antimalarial agents are useful for skin and joint manifestations of SLE, for preventing flares, and for other constitutional symptoms of the disease (Wallace DJ et al 1994, Petri M et al 1994, and Drake LA et al 1996). They may also reduce fatigue and decrease levels of low density lipoproteins.

1.5.3 Follow up and monitoring

Lifelong follow up is required for all patients. It is the cornerstone of managing SLE to detect flares of disease early and to institute prompt, appropriate therapy. The frequency of these evaluations will depend on the activity, severity, and extent of the SLE, the response to treatment, and the type of treatment, including the need for toxicity monitoring. SLE disease activity can be monitored by specific clinical features (such as arthritis, serositis, etc.) or laboratory features (e.g., anti-dsDNA antibodies and complement level), or by using other disease activity indices.

At routine follow up visits, full blood count (FBC), renal function test (RFT), and urinalysis should be obtained. Patients with lupus nephritis should have a urinalysis, 24-hour urine protein,serum electrolytes and creatinine measurements on regular basis till stable (Bootsma H et al 1995).

Renal biopsy is indicated for diagnostic purposes in patients in whom nephritis is suspected. Thus, patients with persistent urinary sediment abnormalities such as hematuria and pyuria without adequate explanation (infection, menstrual period, stone), patients who have urinary casts, or patients who have increased serum creatinine levels should have a renal biopsy. The prognostic value of renal biopsy, although controversial, has been demonstrated, particularly for patients with normal serum creatinine levels (Boompas DT et al 1995, and Gladman DD et al 1996). Patients with proliferative glomerular lesions and chronic changes found on renal biopsy are at a higher risk for end-stage renal disease and death than patients who do not demonstrate these changes. Patients with deteriorating renal function, or patients not responding to conventional therapy, may need a renal biopsy to outline a course of treatment (Esdaile et al 1998 and Markowitz et al 2007).

International Society of Nephrology/Renal Pathology Society 2003 has categorized lupus nephritis (LN) into 6 main classes as follows:

- Class I Minimal mesangial LN
- Class II Mesangial proliferative LN

- Class III Focal LN (<50% of glomeruli)

  III (A): active lesions

  III (A/C): active and chronic lesions

  III (C): chronic lesions

- Class IV Diffuse LN (≥50% glomeruli)

  Diffuse segmental (IV-S) or global (IV-G) LN

  IV (A): active lesions

  IV (A/C): active and chronic lesions

  IV (C): chronic lesions

- Class V Membranous LN
- Class VI Advanced sclerosing LN (90% globally sclerosed glomeruli

  Without residual activity)

1.6 PLACE OF STUDY

Hospital Universiti Sains Malaysia (HUSM) in Kubang Kerian is the tertiary care centre in Kelantan. Hospital USM is also one of the main teaching hospitals for the undergraduates and postgraduate students in Malaysia. It offers 723 beds for inpatients. This hospital provides multiple clinical sub-specialities, together with clinical and non-clinical support services.

The weather in Kelantan in general is hot and dry. Over the East Coast states including Kelantan, the months with maximum rainfall are November, December and January while June and July are the driest months in most districts (http://www.met.gov.my).

The population here are predominantly Malays (95%), followed by other races like Chinese, Indian, Siamese and Orang Asli. The population estimates based on the adjusted population and housing census of Malaysia in 2010 was around 1.6 million.

1.7 RATIONALE OF STUDY

At present very limited studies have been published on paediatric SLE worldwide. This study aimed to provide local data for paediatric SLE and it was conducted to serve as a baseline for subsequent similar studies on SLE in Malaysia. Even though the cohort was derived from only one state and may not represent the whole population size, the data and results in this study will help to focus on specific risk factors and at risk groups, hence provide early intervention and hopefully better prognosis.

CHAPTER TWO

OBJECTIVES AND HYPOTHESIS

2.1 OBJECTIVES

2.1.1 General objective:

To study the demographic characteristics, clinical and laboratory manifestations, and outcome of children with SLE admitted to HUSM between 1996 and 2010.

2.1.2 Specific objectives:

1. To describe the demographic characteristics, clinical manifestations, laboratory characteristics and the outcome of all children with SLE admitted to HUSM from 1996 to 2010
2. To determine the factors associated with renal failure in that group of children with SLE.
3. To explore the risk factors associated with death among paediatric SLE patients admitted to HUSM at that period of time.

2.3 Study hypotheses

Certain factors are associated with the development of renal failure and death among patients with SLE such as age at presentation, gender, positive family history, number of relapses, and hypertension at presentation, lupus nephritis, cerebral lupus, and proteinuria at presentation.

CHAPTER THREE

METHODOLOGY

3.1 STUDY DESIGN

This was a cross sectional study conducted retrospectively via hospital record review. This study was done in Hospital USM in Kubang Kerian. This hospital is the main referral center for other district hospitals in Kelantan as well as bordering district, Besut in Terengganu.

3.2 STUDY POPULATION

The reference population was pediatric patients in Kelantan admitted to HUSM and diagnosed as having SLE, whereas the source population was the newly diagnosed paediatric SLE patients who were diagnosed and treated in Hospital USM in the period between 1996 and 2010.

3.3 INCLUSION CRITERIA

All children aged 18 years and below who were diagnosed to have SLE (diagnosis based on revised SLE criteria made by ACR, 1997) and were admitted to Paediatric Medical wards in the period from January/1st/1996 to December/31st/2010.

3.4 EXCLUSION CRITERIA

The exclusion criteria were those with missing or untraceable case note. Patients who had the following conditions were also excluded:

- Drug-induced lupus
- Mixed connective tissue disease
- Overlap syndrome

3.5 SAMPLING FRAME

All children aged 18 years and below who were diagnosed to have SLE (diagnosis on discharge) and were admitted to Paediatric medical wards in the period from January/1996 to December/2010 who fulfilled the inclusion and exclusion criteria.

3.6 SAMPLE SIZE CALCULATION

For specific objectives 1 sample size was calculated using single proportion formula based on previous study is as follows:

Calculation of sample size:

Single proportion formula,

$n = (Z/\Delta)^2 P (1 - P)$

$Z = 1.96$

Precision value (Δ) = 0.05

P = the Prevalence

For specific objective 1 we used proportion of SLE patients with nephritis = 0.86 (Supavekin et al 2005).

The sample size calculation for objectives 1 was as following:

- $n = (1.96) /0.05)^2 \times 0.86(1-0.86) = 185$

Note: adding 20% missing rate for the calculated sample size, the actual sample size for objective 1 will be 222.

For specific objective 2, sample size was calculated for the variable sex using PS software as follows:

α= level of significant = 0.05

m= the ratio between SLE patients with and without renal failure = 1

Po = percentage of males among SLE patients = 8.9% (Carein et al 2011)

P_1 = expected percentage of males with renal failure = 70%

From the calculation, the sample size for objective 2 (n) was 9

For patients with and without renal failure as a total 9+9 = 18, adding 20% missing rate (n) was 22

For specific objective 3, sample size was calculated for infection as a risk factor for death using PS software as follows:

α= level of significant = 0.05

m= the ratio between SLE patients who alive and those died = 2 (those who alive are twice more than those who died)

Po = percentage of infection among SLE patients = 34.5% (Carein et al 2011)

P_1 = expected percentage of infection among those who died = 77%

From the calculation, the sample size for objective 3 (n) was 15; adding 20% missing, the total sample size was (15 X 2 of alive sample) + (15 of dead sample) + 20% = 54

The sample size chosen for this study was the sample size for objective 1 = 222

3.7 SAMPLING METHOD

All patients who fulfilled the inclusion and exclusion criteria were included in the study.

3.8 ETHICAL APPROVAL

Approval for the study was obtained from the Human Research Ethics Committee USM on 29th January 2012 [(reference: USMKK/PPP/JEPeM [244.4.(1.2)]. Confidentiality was maintained during data collection whereby each case was given a code number. The name and the code number were recorded in a separate list to avoid identification of patient's name. Permission from Hospital Director was obtained as well (appendix II).

3.9 RESEARCH TOOL

Patient's proforma consisting of demographic data, diagnostic criteria of SLE at the time of presentation, other clinical manifestations at the time of diagnosis, laboratory investigations at the time of diagnosis, complications that had occurred throughout the course of the disease, renal biopsy details and the specific management given based on the classes of lupus nephritis, medications given with their total duration and side effects were included, as well as other management modalities such as dialysis.