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Review Article

Paediatric Systemic Lupus Erythematosus. An Overview and Current Management

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Abstract

Pediatric Systemic Lupus Erythematosus (SLE) is a rare but severe autoimmune disease with multisystem involvement and wide heterogeneity of disease manifestations. Approximately 15% of patients with SLE will have the onset of their disease in childhood or adolescence. The mean age at pSLE diagnosis is approximately 12 to 13 years.

The common symptoms of SLE in children and adolescents include fever, fatigue, weight loss, arthritis, rash and renal disease. Making the diagnosis of SLE can be difficult, but early recognition of the disease is important to limit adverse outcomes which often involves the kidneys. Approximately 50% of pSLE patients have evidence of renal involvement, 80% to 90% within the first year of diagnosis. Routine laboratory investigations are of benefit in measuring overall disease activity. It is important to categorize the Antinuclear antibody (ANA) pattern, as ANA patterns are of varying sensitivity for SLE versus other auto-immune disorders.

Various measures of global disease activity have been developed for SLE in adults and subsequent validation confirmed these indices have concurrent validity for measuring disease activity with pediatric SLE.

The use of the New Zealand black/white mouse model, which manifested spontaneous Coombs-positive anemia and many other manifestations of lupus, has allowed intensive study of SLE's mechanisms and the importance of immunosuppressive therapy. Advances in treatment using targeted biological therapies may further improve treatment outcomes.

Disability associated with many rheumatic diseases has been minimized, and the quality of life has been enhanced. Nonetheless, major challenges remain. Although diminished, morbidity and mortality remain serious threats to the child with SLE even today.

Keywords: *Pediatric; SLE; Classification; Diagnosis; Renal; Management; Activity Index*

Introduction

Systemic lupus erythematosus (SLE) is a severe, chronic autoimmune disease, which results in inflammation and eventual damage in a broad range of organ systems. SLE is a relatively rare disease in childhood, with estimated incidence ranging from 10 to 20 per 100,000 children, depending on the ethnic population [1]. Pediatric SLE is a rare but severe autoimmune disease with multisystem involvement and wide heterogeneity of disease manifestations. Making the diagnosis of SLE can be difficult, but early recognition of the disease is important to limit adverse outcomes. This disorder predominantly affects adults (80% - 90%), predominantly females (‡90%), and is most common above age 10 years, but there are tremendous differences in prevalence and severity among different groups. On average it tends to be more common and more severe in its manifestations for nonwhite groups, including people of African, Asian, and Hispanic ancestry, and it is not unusual for there to be a family history of SLE.

Methodology of Review

Conducted a review of all relevant published literature on PubMed and Hinari search engines and standard textbooks of Pediatric Rheumatology and Allergic disorders between January 2012 and December 2017.

Background

Historical overview

Medical literature described the dermatitis of SLE as early as the 13th century. The butterfly rash was recognized in 1845, and in 1852 the term lupus erythemateux was coined. Osler described the clinical features, and in 1924 Libman and Sacks reported the characteristic endocarditis. In 1948 Hargraves and colleagues described the lupus erythematosus (LE) cell and one year later cortisone was first used. In 1957 the association of a positive ANA and SLE was made. The use of the New Zealand black/white mouse model, which manifested spontaneous Coombs-positive anemia and many other manifestations of lupus, has allowed intensive study of SLE's mechanisms and the importance of immunosuppressive therapy. Advances in treatment using targeted biological therapies may further improve treatment outcomes. As patients continue to improve and survive, physicians now must assess patients for long-term disease sequelae, such as atherosclerosis, and develop prevention strategies. Strategies using genomics and proteomics give hope for identification of biomarkers that can be used for early disease detection and treatment [2].

Mortality from diseases, such as chronic arthritis complicated by amyloidosis, dermatomyositis, and SLE, has been dramatically reduced since the 1970s. Disability associated with many rheumatic diseases has been minimized, and the quality of life has been enhanced. Nonetheless, major challenges remain. Although diminished, morbidity and mortality remain serious threats to the child with SLE even today.

Case Presentation

A 14-year-old, RVD negative, girl seen while working at the Pediatric Rheumatology Clinic, Gaborone, Botswana. She was referred to the clinic with arthritis as well as having become Cushingoid and developing glucose intolerance while on Prednisone.

Laboratory work up:

1. ANA: 1:640.
2. dsDNA: Positive (Titer 1:40).
3. Complement levels. C3: 34 mg/dl (80 - 170), C4: 4 mg/dl (14 - 44).

Her prednisone was tapered and eventually discontinued. A kidney biopsy done at Lenmed Bokamoso Private Hospital, Gaborone, revealed focal proliferative nephritis (WHO Lupus Class III Nephritis.)

She was started on Naproxen, Chloroquine, Methotrexate as well as receiving pulse steroids and i/v cyclophosphamide with resolution of her Cushingoid features. She developed recurrent episodes of chest pain. Chest X-ray findings as well as CT Scan of the chest were normal. She was diagnosed with a pericardial effusion, confirmed on echocardiography, without evidence of pulsus paradoxus or a pericardial friction rub, and received tuberculosis treatment, as is it was difficult to determine whether the pericardial effusion was infectious or inflammatory in nature.

NB Her other medications included Azathioprine. H.R was gradually transioned to adult care services in conformity with the Princess Marina Hospital policies.

Aetiology and pathogenesis

It is likely that lupus is a combination of genetic susceptibility and environmental factors, including exposure to sunlight, infections, drugs, and chemicals. Drug-induced lupus is a well-recognized form of SLE (see below). Exposure to many chemicals, including hair dye, tobacco, L-canavanine, and other environmental factors have been associated with SLE.

SLE is characterized by immune dysregulation involving both the innate and adaptive immune systems and all effector mechanisms have been shown to be defective. Much of our knowledge about immune dysregulation has been adapted from animal models because immune dysregulation in human SLE is much more difficult to study [3-7].

Lupus is thought to result from a combination of hormonal and environmental factors in a genetically pre-disposed individual. Ten percent of patients with SLE have a first-degree relative who has SLE, and affected patients are more likely to have a family member who has an autoimmune disease. HLA class II alleles DR2 and DR3 contribute to disease susceptibility in some patients, as do inherited complement deficiencies, most commonly homozygous C2 or C4 deficiency. Environmental triggers can be as varied as infection (parvovirus, Epstein-Barr virus), medication (anti-hypertensives, anticonvulsants), hormonal changes (especially sex hormones), and UV light. Disturbances in B and T cells and abnormalities in apoptosis contribute to the pathogenesis of the disease.

Reaching a diagnosis of paediatric SLE?

The diagnosis of SLE, whether affecting an adult or a child, is made based on a combination of clinical and laboratory features. The revised American College of Rheumatology (ACR) classification criteria are commonly used to diagnosis Pediatric SLE in Children, as shown in the table 1 below.

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematosus 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 sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis-convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion or pericarditis-documented by ECG or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria greater than 0.5 g/d (or > 3 + if quantitation nor performed) or cellular casts-may be red cell, hemoglobin, granular, tubular, or mixed
Neurological disorder	Seizures in the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis, or electrolyte imbalance) or psychosis in the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis, or electrolyte imbalance)
Hematological disorder	Hemolytic anemia with reticulocytosis or leukopenia less than 4000/mm^3 total on two or more occasions, or lymphopenia less than 1500/mm^3 on two or more occasions, or thrombocytopenia less than 100,000/mm^3 in the absence of offending drugs
Immunological disorder	1. a) Positive anti-DNA antibody to native DNA in abnormal titer, or 2. b) Presence of anti-Sm nuclear antigen, or 3. c) Positive finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serological test and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test.
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

Table 1: *1982 Revised Criteria for Classification of SLE.*

Another more recent diagnostic criteria used is from, the systemic lupus international collaborating clinics (2012), as shown below.

1. The patient satisfies four of the criteria, including at least one clinical criterion and one immunologic criterion or
2. The patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies.

Clinical criteria	Immunologic criteria
Acute cutaneous lupus	ANA
Chronic cutaneous lupus	Ant-dsDNA
Oral or nasal ulcers*	Anti-Smith
Non-scarring alopecia	Anti-phospholipid antibody
Arthritis	Low complement (C3, C4, CH50)
Serositis	Direct Coombs Test (Do not count in the presence of Hemolytic anemia)
Hemolytic anemia	
Leukopenia	
Thrombocytopenia (< 100,000/mm^3)	

Table 2

The ANA staining pattern is important in the evaluation of a child/adolescent suspected to have SLE:

Patterns: ANA Staining Pattern are basically of six types i.e.

i) Peripheral Pattern,

ii) Homogenous Pattern,

iii) Speckled Pattern,

iv) Nucleolar Pattern,

v) Diffuse Pattern,

vi) Centromere Pattern.

Check the ANA profile to see whether consistent with SLE versus another autoimmune disease.

Causes: Rim Pattern (Peripheral Pattern)

i) Systemic Lupus Erythematosus (Most Specific).

Causes: Homogenous Pattern (Diffuse Pattern)

1. Systemic Lupus Erythematosus (Very specific).
2. Further laboratory testing:

a. Anti-dsDNA

b. Anti-ssDNA

c. Anti-Smith.

Causes: Speckled Pattern

1. Most common, least specific.
2. Disorders
    a. Systemic Lupus Erythematosus
    b. Mixed Connective Tissue Disease
    c. Scleroderma
    d. Sjogren's Syndrome.
3. Further laboratory testing:
    a. Smith Antibody (Anti-Smith)
    b. Ribonucleoprotein Antibody (Anti-RNP)
    c. Scl-70 kD kinetochore (Anti-Topoisomerase I)
    d. Anti-La (Anti-SSB).

Causes: Nucleolar Pattern

1. Disorders
    a. Scleroderma
    b. CREST syndrome.
2. Further laboratory testing
    a. Scl-70 kD kinetochore (Anti-Topoisomerase I)
    b. PM-1.

Causes: Centromere Pattern

1. Seen in Progressive Systemic Sclerosis (PSS) with CREST syndrome (CREST syndrome, also known as limited scleroderma, is a widespread connective tissue disease characterized by changes in the skin, blood vessels, skeletal muscles, and internal organs. The symptoms involved in CREST syndrome are associated with the generalized form of the disease systemic sclerosis (scleroderma). CREST is an acronym for the clinical features that are seen in a patient with this disease.
2. (C) - Calcinosis: Calcium deposits in the connective tissues.
3. (R) - Raynaud's phenomenon: Where the hands and feet turn white and cold and then blue, in response to cold or anxiety.
4. (E) - Esophageal dysfunction resulting in swallowing difficulty.
5. (S) - Sclerodactyly: Thick and tight skin on the fingers, caused by an excess of collagen deposits within skin layers.
6. (T) - Telangiectasia: Small red spots on the hands and face that are caused by the swelling of tiny blood vessels.

Common clinical patterns in children affected with paediatric SLE

Children and adolescents with SLE frequently present with systemic, constitutional symptoms such as fever, diffuse hair loss, fatigue, weight loss, and diffuse generalized inflammation as demonstrated by lymphadenopathy and hepatosplenomegaly-in addition to specific organ involvement. This is true both at diagnosis and throughout the disease course at times of disease flare.

Muco-cutaneous, musculoskeletal and kidney disease are the most common manifestations of pSLE. Chloroquine (Hydroxychloroquine) is useful in management of all forms of Paediatric SLE.

Current classification of SLE nephritis (evolved from the previous world health organisation (WHO) classification)

Lupus nephritis is clinically evident in 50 - 60% of patients with systemic lupus erythematosus (SLE) and it is histologically evident in most SLE patients, even those without clinical manifestations of renal disease. Evaluating renal function in SLE patients is important because early detection and treatment of renal involvement can significantly improve renal outcome.

Lupus nephritis is staged according to the classification revised by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2003, as follows:

1. Class I - Minimal mesangial lupus nephritis.
2. Class II - Mesangial proliferative lupus nephritis.
3. Class III - Focal lupus nephritis (active and chronic; proliferative and sclerosing).
4. Class IV - Diffuse lupus nephritis (active and chronic; proliferative and sclerosing; segmental and global).
5. Class V - Membranous lupus nephritis.
6. Class VI - Advanced sclerosis lupus nephritis.

Therapies for lupus nephritis and SLE include the following:

- Rituximab.
- Other anti-CD20 monoclonal antibodies (e.g. ocrelizumab, ofatumumab, eprat uzumab, and TRU-015).
- Belimumab- a B-lymphocyte stimulator-specific inhibitor, was Food and Drug Administration (FDA) approved for the treatment of adult patients with active, autoantibody-positive SLE. Adult patients with SLE with active mucocutaneous symptoms have had the best response in clinical trials.
- Atacicept.
- Abetimus.
- Anti-cytokine therapies (e.g. monoclonal antibodies directed against interferon alfa, interleukin [IL]-1, IL-6, IL-10, and tumor necrosis factor alpha [TNF-α]).

Patients with end-stage renal disease require dialysis and are good candidates for kidney transplantation. Hemodialysis is preferred to peritoneal dialysis.

Methotrexate also can be used to treat arthritis. It is a disease-modifying agent commonly prescribed for juvenile idiopathic arthritis and works well as a steroid-sparing agent in patients with pSLE who have arthritis.

Most pediatric rheumatologists and nephrologists would treat pSLE patients with class III and IV disease aggressively. This treatment includes high-dose oral corticosteroids (2 mg/kg) or intravenous pulse methylprednisolone (30 mg/kg, max of 1g) plus potent immunosuppressive agents.

Corticosteroids are used in all patients with clinically significant renal disease. Immunosuppressive agents, particularly cyclophosphamide, azathioprine, and mycophenolate mofetil, are used in patients with aggressive renal lesions because they improve the renal outcome. They may also be used in patients with inadequate response or excessive toxicity to corticosteroids. Cyclosporine has been used in some cases. Hypertension, if present, must be treated aggressively and maintenance of a normal blood pressure should be the goal.

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 [9].

Renal biopsy should be considered in any patient with SLE who has clinical or laboratory evidence of active nephritis, especially upon the first episode of nephritis [10]. Lupus nephritis is staged according to the classification revised by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2003. This classification is based on light microscopy, immunofluorescence, and electron microscopy findings from renal biopsy specimens.

Cardiac involvement

Patients with lupus are at risk for pericarditis, pericardial effusion, myocarditis, Libman-Sacks endocarditis, bacterial endocarditis, and premature atherosclerosis. The risk of myocardial infarction is low in pSLE, although an infarct must always be considered in the differential diagnosis of chest pain. Pericarditis with pericardial effusion is the most common cardiac complication in pSLE and often is a cause of recurrent chest pain. Pericarditis presents as anterior chest pain and dyspnea that is exacerbated by lying flat. Lupus pericarditis can be treated with non-steroidal anti-inflammatory drugs(NSAIDs) alone for mild cases and with the addition of corticosteroids for large effusions or severe pain.

Other changes

Nail fold capillary changes reflect the vasculopathy that may occur in SLE. Periungal erythema is caused by dilatation of these capillaries. Livedo reticularis occurs in < 10% of patients with pSLE. This eruption presents as a reddish-purplish lacy rash, usually on the extremities or torso and often is associated with the presence of anti-phospholipid antibodies.

SLE disease activity monitoring tools

Various measures of global disease activity have been developed for SLE in adults and subsequent validation confirmed these indices have concurrent validity for measuring disease activity with pediatric SLE [11,12]. These include SLE Disease Activity Index (SLEDAI), the Systemic Lupus Activity Measure (SLAM), the European Consensus Lupus Activity Measurement (ECLAM) and the British Isles Lupus Activity Group Index (BILAG).

Patient education

The patient and his or her family must have a thorough understanding of systemic lupus erythematosus (SLE), its potential severity, and the complications of the disease and its therapy.

Treatment is difficult, especially for adolescent patients. The physician and parents should expect issues, including depression and noncompliance, to arise. The best method for deterrence is to thoroughly educate the patient and family through discussion, support groups, and literature.

Educate all patients with SLE with regard to the serious complications possible from unplanned pregnancy, poor compliance, recreational drug use, and infection, including with sexually transmitted diseases (STDs). Poor compliance, in particular, is a significant prognostic factor.

Summary and Conclusions

The successful long-term management of Pediatric SLE depends on accurate characterization of the extent and severity of organ involvement, and then tailoring of therapy based on the Child/adolescent's needs. Based on strong research evidence and consensus, the most common disease manifestations at diagnosis of pSLE are constitutional symptoms, arthritis, and malar rash. SLE is a lifelong disease, characterized by periods of flare and remission. Because the typical pSLE patient is an adolescent female, addressing the usual challenges of adolescence becomes crucial to ensuring that the adolescents are making informed choices and correct choices.

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