Is it Lupus or Not?
A Clinical Approach to Pediatric SLE

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Mahatma Gandhi

• “....Live as if you were to die tomorrow. Learn as if you were to live forever...”
Objectives

- Recognize the presentation of Pediatric Systemic Lupus Erythematosus (pSLE).
- Develop a clinical approach to the initial work up and management of pSLE.
Introduction

- A central concept to the pathogenesis of autoimmune diseases is that “Tolerance to self is violated.”

Definition

- SLE has been classically described as a prototypic autoimmune disease with a wide array of clinical manifestations and characterized by the production of auto-antibodies to components of the cell nucleus.

Gilbert et al. Pediatric Rheumatology 2014, 12:16
Epidemiology

• pSLE makes up 20% of all cases.

• Incidence in North America is 0.3 – 2.5 cases per 100,000.

• Frequently in African-Americans, Asians and Hispanics.

• More common in adolescent age group.

• Average age at onset 12 yrs; Rare before 5 yrs.

• Female: Male = 9:1; however before puberty, it is 3:1.

Lupus in Africa - under reported?

• Incidence is unknown

• Early reports (1960s-1970s): lupus rare
  – (Uganda, Nigeria, South Africa)

• Recent (1980s-1990s): increased reports
  – (Uganda, Zimbabwe, South Africa)

• “Current” (2000’s): case series
  – 2001 (Molokhia: West Africa prevalence)
  – 2005 (Faller: South Africa pediatrics)
  – 2008 (Abdou: Senegal nephritis)
  – 2009 (Adelowo, Oguntona: Nigeria)
New lupus cases/deaths

New cases/ deaths

Case series Publications

Slide courtesy of Dr C. Hitchon
Factors

Genetic  Environmental  Immuno-regulatory  Hormonal  Epigenetic

Immune complexes  Antibodies

Cytokines  T cells

Organ damage

Kidney  Skin  Lungs  Brain  Heart

Joints
Presentation of lupus in Africa: survey

Slide courtesy of Dr. C. Hitchon

N Tiffin et al. Lupus 2014;23:102-111
SLE - Diagnostic Criteria

• Malar Rash
• Discoid Rash
• Photosensitivity
• Oral or nasal ulcers
• Nonerosive arthritis
• Pleuritis or pericarditis
• Cytopenias
• Nephritis
  – proteinuria > 0.5 g/day
  – cellular casts

• CNS involvement
  – seizures
  – psychosis
• Positive ANA
• Positive Immunoserology
  – Ab to dsDNA
  – Ab to Sm
  – Positive anti-phospholipid Ab: anti-cardiolipin Ab, lupus anti-coagulant, or false + VDRL x 6 mos

4 out of 11 criteria

# SLICC Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria) OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

## Clinical Criteria
1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm³)

## Immunologic Criteria
1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs’ test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Wangari wa Maathai

It’s the little things citizens do.....That’s what will make the difference. My little thing is planting trees.
Amelia 14 yr old teenager

History & Examination

- Ref for management of incision site abscess mid Sept 2014 foll. Appendicectomy.
- 2 months prior, hair loss, 1 month hx of appetite loss and papular skin rash.
- HR86, T40.5, RR 18, BP 109/66
- On exam malar rash, vasculitic rash, palatal ulcer, cervical lymphadenopathy and abscess at incision site.

Work up

- WBC 1.7, N 0.8, L 0.8, RBC 3.72, Hb 112 g/l, Plt 137, CRP 3.4mg/l, ESR 44mm/hr
- Peripheral blood film- 1 myelocyte
- Bone Marrow Aspirate- No malignancy
- U/A-blood, Urine prot:creat 1.85 g/g
- Renal biopsy-?
- ANA+ve (1:160), C3 0.56[N], C4 0.1
- Anti ds DNA >800, anti La +ve, anti RNP +ve
Palatal ulcer in patient with Systemic Lupus Erythematosus Courtesy of Dr R Scuccimarri
Systemic Lupus Erythematosus Malar Rash
Courtesy of Dr C. Hlela
Systemic lupus erythematosus: alopecia, scalp
pSLE – Renal disease

• Present to some degree in all children.

• More significant disease occurs in at least 75% and is often more severe in children than in adults.

• Can present with either asymptomatic proteinuria or hematuria (or both); or with hypertension; nephrotic syndrome; or renal failure.

• The degree of urinary abnormalities does not always predict the renal lesion thus biopsy is recommended if evidence of renal involvement.

pSLE – Renal evaluation

- Urinalysis/microscopy: proteinuria, RBCs, casts.
- Urine protein/creatinine.
- Serum creatinine, electrolytes, albumin, total protein.
- May need renal biopsy.
pSLE - Clinical Findings
Other rashes

- Photosensitivity
- Periungal erythema
- Nailfold infarcts
- Raynaud’s phenomenon
- Livedo reticularis
- Ulcerating lesions
- Erythema nodosum

- Lupus profundus (panniculitis)
- Recurrent urticaria
- Erythema multiforme
- Bullae
- Alopecia
- Hypo/hyperpigmentation
Discoid lupus: skin lesions, face
Systemic lupus erythematosus: malar rash, face
Subacute cutaneous lupus erythematosus
Livedo reticularis
Max 3½ yr old boy

History and Examination

- 2 yr history of multiple joint pain assoc with night awakening
- Early Oct 2014 3 day hx of fever ranging 38-38.5 C
- Loss of appetite and weight loss
- Known for adenotonsillar hypertrophy
- Family history of Psoriasis
- Normal systemic examination. Referral note ANA +ve, antiDNA +ve

Work up

- HR 106 RR24 T 36.7
- WBC 6, N 2.8, L 2.6, RBC 4.47, Hb 122 g/l, Plt 204
- Anti dsDNA+ve, ANA +ve 1;160, C3 1.13g/l [N], C4 0.19g/l [N]
- Urinalysis normal, Urine prot:creat normal
pSLE - Laboratory Findings

Immunoserology

• Antinuclear Antibodies (ANA)
  – always positive (>95%)
  – usually of high titre
  – **BUT** not diagnostic / not specific
  – + ANA does **NOT** confirm the dx of SLE
pSLE - Laboratory Findings

Immunoserology

• Antibodies to anti-dsDNA
  – seen in 60-70% of SLE pts
  – specific for SLE (but not sensitive)
  – seen in high titres with active nephritis

• Extractable Nuclear Antigens (ENA)
  i. Anti-sm (Smith)
    – seen in 40-50% of SLE pts
    – specific for SLE
  ii. Anti-ro; anti-la; anti-RNP can be seen; not specific

Julia 14 yr old teenager

**History and Examination**
- 1 month history of fatigue and rash on palms and soles initially diagnosed as eczema. 1 day history of fever.
- Weight loss, ongoing poor concentration since July 2015.
- 2 years prior white then red discolouration of the fingers and toes worse in the winter.
- On exam T 37.1, RR 12, HR 76, O2 99%
- No lymphadenopathy, vasculitic rash, malar erythema, polyarthritis, tender along both shins.

**Work up**
- WBC 2.63, N 1.39, L 0.9, Hb 113 g/l, Plt 130, CRP 0.7 mg/l, ESR 55 mm/hr, Uric acid 201, LDH 251 U/L
- C3 0.51[L], C4 0.1[L]
- Urinalysis-normal, prot:creat-ve
- Bone marrow-No malignancy
- Hand and feet X-rays-no bony changes or erosions, soft tissue swelling
- ANA +ve (1:160 ), anti DNA +ve (473), anti Sm+ve, anti RNP+ve
- Lupus anticoagulant+ve
Vasculitic rash in patient with Systemic Lupus Erythematosus Courtesy of Dr R.Scuccimarri
pSLE - Central Nervous System Disease

• Ranks 2nd after nephritis as a cause of morbidity and mortality in children with SLE.

• Occurs in 20-30% of patients.

• Most common presentation is headache, seizures and psychosis.

pSLE – Hematological Findings

- Anemia
  - of chronic disease.
  - 30% are coombs positive without overt hemolysis.
  - < 10% have hemolytic anemia.

pSLE – Haematological Findings

• Thrombocytopenia (< 100 000)
  – Can be due to peripheral platelet destruction or anti-platelet Ab.
  – Some children with ITP or Evan’s syndrome can progress to SLE; usually occurs within first year.
  – Splenectomy should be avoided.

• Leukopenia (< 4)
  – occurs in up to 40% of pts.
  – lymphopenia (<1.5) more common then neutropenia.

pSLE – Hematological Findings

• Coagulopathy
  – A prolonged PTT is the most common coagulation defect.
  – Due to circulating anticoagulant that blocks activation of the prothrombin activation complex in vitro.
  – The antiphospholipid Ab often cross-reacts with anticardiolipin Ab and is responsible for the false positive VDRL.
pSLE – Hematological Findings

• Coagulopathy continued
  – increased risk of thromboembolic events.
  – can have recurrent venous or arterial thromboses, emboli, stroke, chorea, livedo reticularis, hypertension, thrombocytopenia, spontaneous abortions, and fetal loss.
  – PT/PTT/INR, Lupus anticoagulant, Anti-cardiolipin Ab.
Maria 12 year old girl

**History and Examination**
- 1 month history of recurrent fever (38C-40.8C).
- Treated initially for strep throat infection.
- At presentation had a rash, and complained of muscle pain, difficulty swallowing and weight loss.
- On examination HR 100 RR24 BP 118/70 T36.7C
- Erythema nodosum on arms and shins.
- Weak neck flexors and proximal muscles. No gottron’s, heliotrope rash or cuticular hypertrophy.

**Work up**
- WBC 5.1, N 3.3, L1.3,Hb 114g/l, Platelet 200
- Urinalysis-normal, urine prot:creat 0.01g/mmol
- C3 1.19 g/l [N], C4 0.24 g/l [N]
- 12th Jan-CK 8089 U/L,17th -3421, 20th-2590,27th -3408, 2nd Feb-5247
- Anti Sm, RNP, anti DNA, ANA +ve
- Lupus anticoagulant-ve
pSLE – Musculoskeletal System

• Arthralgias and myalgias are common.
• Non-erosive arthritis
  – usually polyarticular involvement.
  – pain is often severe even with minimal findings.
• Myositis
  – proximal muscle involvement.
pSLE – Cardiac Disease

• Pericarditis / Pericardial effusion
  – Most common cardiac feature.
  – Patients may be a/symptomatic.

• Myocarditis

• Accelerated atherosclerosis

pSLE – Pleuropulmonary Disease

• Pleural effusions or pleuritis
• Pneumonitis
• Pulmonary hemorrhage
• Restrictive lung disease
• Pulmonary embolus
• Shrinking lung
  – loss of lung volume due to diaphragmatic dysfunction.
Differential Diagnosis

• **Infection**
  – Parvovirus B19 - rash, arthritis, fever, cytopenia.
  – CMV - fatigue, cytopenia, abdominal pain, LFT abnormality.
  – HIV - fever, weight loss, lymphadenopathy, oral ulcer.
  – Hepatitis B - arthritis, antibodies.
  – Post-streptococcal disease – arthritis, fever, rash.
  – Tuberculosis – fever, weight loss, lymphadenopathy, arthritis.

• **Malignancy**
  – Lymphoma; leukemia: fever, weight loss, arthralgias, cytopenia, lymphadenopathy, rash, ANA.

• **Other autoimmune disease**
  – JIA, MCTD, systemic vasculitis.

• **Drug induced lupus**
  – Minocycline, hydralazine, procainamide, isoniazid, anti-seizure.
pSLE - Treatment

Depends on extent and severity of the disease:
• Hydroxychloroquine/Chloroquine alone.
• Hydroxychloroquine + NSAID.
• Hydroxychloroquine + NSAID + Methotrexate.
• Hydroxychloroquine + low dose prednisone.
• Hydroxychloroquine + high dose prednisone.
• Hydroxychloroquine + high dose prednisone + cytotoxic agent.
• Cytotoxic agents- azathioprine, mycophenolate mofetil, cyclophosphamide.
• Treatment of specific organ system complications.
• Sun protection; Bone Health; Immunizations.
TLR-independent mechanisms of antimalarial therapy

- UV protection
  - Local anti-inflammatory effects and upregulation of the protective c-Jun-encoding gene
  - Control of photosensitivity and cutaneous lupus

- Antilipidaemic effects
  - Act at the lipid receptor level to regulate enzyme activity and possibly also through TLRs
  - Reduce LDL, VLDL and cholesterol, and increase HDL levels

- Antiangiogenic effects
  - Reduce epidermal expression of VEGF
  - *In vitro* anti-proliferative and apoptotic effects on ECs
  - Possible mode of action in discoid lupus

- Antithrombotic effects
  - Inhibit platelet aggregation
  - Block interaction between platelets and coagulation factors
  - Reduce thrombotic events in patients with SLE
  - Possible role in primary thromboprophylaxis in APS and SLE

- MMP–TIMP modulation
  - Inhibit expression of MMP-1, MMP-2, MMP-8, MMP-9
  - Regulate ECM homeostasis
  - Inhibit excess ECM breakdown

- PLA₂ inhibition
  - Cell membrane stabilization
  - Inhibit arachidonic acid pathway and downstream synthesis of inflammatory mediators

- BAFF inhibition
  - Reduce maturation and survival of B cells, including autoreactive B cells

Anti-malarials in pSLE

• Risk of retinopathy
  – Reaches 1% after 5-7 years of use or cumulative dose of >1000 gm.
  – Need baseline ocular exam and yearly exam in children.

Retinopathy: Early and Late Bull’s Eye lesion

Course and Prognosis

- Characterized by exacerbations and remissions.
- Chronic disease that varies in severity.

- Western world: 5 year survival 94-100%
  10 year survival 81-92%
- Delayed diagnosis; access to care and treatment are significant challenges in some countries.

- End stage renal disease a significant cause of morbidity.
- Morbidity is related to disease and treatment.
- Infection is the leading cause of death.
Summary

• Diagnosis requires a combination of clinical features and relevant investigations.

• Skin, MSK and renal are the most common organ involvement in children; renal and CNS are the most severe.

• Management requires tailoring treatment to lupus specific features and severity of organ involvement.
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Mwalimu Julius Nyerere

- "...Intellectuals have a special contribution to make to the development of our nation, and to Africa. And I am asking that their knowledge, and the greater understanding that they should possess, should be used for the benefit of the society of which we are all members."

Asante! Thank you! Merci!