Juvenile SLE

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Overview

• Epidemiology and aetiology
• Clinical features and classification criteria
• Assessment and monitoring of disease activity
• Management/treatment
• Prognosis
• Neonatal lupus
Epidemiology and aetiology
Juvenile onset SLE

- 15-20% of cases present in children ≤16 yrs
- Median age of diagnosis in children is 12.1 yrs
  - Rare under the age of 4 yrs
- Incidence around 10-20/100,000/yr
- jSLE F:M 5:1 (9:1 in adults)
- More common in non-Caucasians
- Polygenic, with environmental factors
- **Pathology: dysregulation humoral and cellular immunity**
  - Autoantibody production: HLA-DR association
  - B cell hyperactivity, auto-reactive T cells
  - Immune complex deposition
  - Driven by large apoptotic load through impaired clearance ‘**Waste disposal**’ hypothesis.
- Monogenic forms exist
Evidence for genetic influence

• Siblings of patients with SLE have 10-20 fold increased risk of developing disease.
• Monozygous twins have 24% concordance rate versus 2% dizygotic twins.
• Familial autoimmunity is a risk factor for SLE (OR 4.1 with 1 relative, 11.3 with 2 or more relatives).
• Increased susceptibility to SLE is associated with an increasing number of recognized candidate genes, including HLA haplotypes, ITGAM, IFR5, BLK, STAT4, PTPN22, and Fcy receptor polymorphisms.
Evidence for environment

- Ultra-violet (UV) light can induce flares, possibly by altering DNA methylation
- Viruses
- Hormones
- Drugs (e.g. hydralazine) have been shown to impair T cell DNA methylation leading to increased autoreactivity
Waste disposal hypothesis

Death signal

- Receptor ligation (e.g., TNF, Fas)
- Protease (caspase) cascade
  - DNA fragmentation
  - Chromatin condensation
  - Cytoplasmic blebbing
- Clearance by phagocytes
- Apoptotic bodies
- Autoreactivity
Monogenic SLE
Abnormal Cytokine signalling pathways

- TREX1
- RNASEH2A/B/C
- SAMHD1, ADAR1

intracytoplasmic DNA accumulation
trigger IFNα production

- Cytoplasmic DNA can promote IFNα production
- High level of IFNα is associated with autoimmunity

immune-complex processing

- C1q/r/s, C2, C4

Classical pathway defects induce increase of apoptotic bodies and circulating immune complexes (CIC)
Lack of regulatory functions of C1q on IFNα production

- Complement is a major regulator of apoptotic bodies and CIC clearance
- Increased level of apoptotic bodies and CIC is associated with SLE

adaptive and autoantibody production

- Fas

FasL deficiency:

Apoptosis defects induce activated T cells persistance

- Activation induced cell death defects promote autoimmunity

Activated T cells after first antigen encounter

Activated T cells persist after a second antigen encounter

Belot and Cimaz. Pediatric Rheumatology 2012, 10:21
Clinical features and classification criteria
## Updated ACR Classification criteria

(Hochberg et al, Arthritis Rheum 1997 40:1725)

<table>
<thead>
<tr>
<th>Criteria (require 4/11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
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<tr>
<td>Discoid rash</td>
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<tr>
<td>Photosensitivity</td>
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<tr>
<td>Oral or nasal ulcerations</td>
</tr>
<tr>
<td>Non erosive arthritis</td>
</tr>
<tr>
<td>Nephritis</td>
</tr>
<tr>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Pleuritis or Pericarditis</td>
</tr>
<tr>
<td>Cytopenia</td>
</tr>
<tr>
<td>Positive ANA</td>
</tr>
<tr>
<td>Positive dsDNA / Sm / aCL / LA</td>
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</tbody>
</table>
SLICC classification criteria for SLE

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

Clinical characteristics of JSLE

<table>
<thead>
<tr>
<th>Disease manifestation</th>
<th>Juvenile onset SLE</th>
<th>Adult onset SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>40-60%</td>
<td>60-80%</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>35-50%</td>
<td>35-50%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15-30%</td>
<td>20-55%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>60-70%</td>
<td>80-95%</td>
</tr>
<tr>
<td>Renal disease</td>
<td>60-80%</td>
<td>35-50%</td>
</tr>
<tr>
<td>CNS disease</td>
<td>20-45%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>15-40%</td>
<td>20-90%</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>10-15%</td>
<td>25-30%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>20-30%</td>
<td>15-25%</td>
</tr>
</tbody>
</table>

Cutaneous manifestations
Lupus nephritis
Lupus nephritis

• present in 60 - 80% of JSLE cases
• influences management with immunosuppressive agents
  – earlier and more severe presentation in patients with JSLE
    (compared to adult-onset) SLE
• Presentation of renal involvement
  – proteinuria
  – microscopic (and rarely macroscopic) haematuria
  – nephrotic syndrome
  – hypertension
  – evidence of renal dysfunction
    • elevated plasma creatinine or reduced estimated glomerular filtration rate
### International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Class I** | Minimal mesangial lupus nephritis  
Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence |
| **Class II** | Mesangial proliferative lupus nephritis  
Purely mesangial hypercellularity or mesangial matrix expansion |
| **Class III** | Focal proliferative lupus nephritis  
Active or chronic focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli |
Class IV

Diffuse proliferative lupus nephritis

Active or chronic diffuse, segmental or global endo- or extracapillary glomerulonephritis involving $\geq 50\%$ of all glomeruli.
# International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Membranous lupus nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>Global or segmental subepithelial immune deposits, with or without mesangial alterations</td>
</tr>
</tbody>
</table>

Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed.

<table>
<thead>
<tr>
<th>Class</th>
<th>Advanced sclerosis lupus nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI</td>
<td>&gt;90% of glomeruli globally sclerosed without residual activity</td>
</tr>
</tbody>
</table>
Lupus nephritis

proliferative

membranous
Class 4: diffuse proliferative

Massive subendothelial deposits: “Wire loop”

Immunostaining: IgG, M, A, complement

EM: large electron dense deposits in subendothelial region
Neuropsychiatric lupus (NPS)
CNS lupus

- In 25%-90% of patients
- Headache and cognitive disturbance
- Movement disorder – chorea (APL)
- Seizures –
  - Usually focal
  - Intractable/Rasmussens
- Psychosis
- 10-20% paediatric psychosis
- Mononeuritis/transverse myelitis
- MRI can be normal
Musculo-skeletal disease

- Arthritis, arthralgia and/or tenosynovitis
- Morning stiffness common
- More than 90% with arthritis develop this within the 1st year of diagnosis
  - so always consider differential diagnosis for those with “late arthritis”
- Deforming arthritis associated with ligament and tendon laxity (Jaccoud arthritis)
- Rhupus: +RF and destructive arthritis
Haematological involvement

- Anaemia
- Coombs positivity
- Thrombocytopenia
- Leucopenia
Macrophage activation syndrome

- Uncontrolled activation of the cellular immune system
- Seen in sJIA, SLE, systemic vasculitis
- Macrophages phagocytose cells in bone marrow
- Falling: ESR, wbc, plats, & fibrinogen
- Very high ferritin
- Bone marrow aspiration may help
- Treatment-IVMP, IV ciclosporin, others
Cardiovascular Findings
In SLE

- Pericarditis
- Myocarditis
- Sterile valvular vegetations
- Arrhythmias
- Cor pulmonale
- Vasculitis (small vessels)
- Atherosclerosis/Coronary Heart disease
- Dyslipidaemia
Pulmonary Findings In SLE

• Incidence: 5-67%
• May be subclinical (abnormal PFTs)
• Pleuritis
• Pleural effusion
• Pneumonitis
• Pulmonary hemorrhage
• Bronchiectasis
• Pulmonary hypertension
• Restrictive lung disease & diffusion defects most commonly observed abnormalities on PFTs
GI INVOLVEMENT IN SLE

• Mild LFT elevation:
  – Exclude autoimmune hepatitis
• Colitis
• Mesenteric vasculitis
• Protein-losing enteropathy
• Pancreatitis
• Exudative ascites
Recommended laboratory investigations for routine (3 monthly) and annual JSLE monitoring (adapted from the UK JSLE Cohort Study)

<table>
<thead>
<tr>
<th>Routine monitoring (3 monthly)</th>
<th>Annual testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count (FBC)</td>
<td>Anti-nuclear antibodies (ANA)</td>
</tr>
<tr>
<td>Direct coombs test</td>
<td>Extra-nuclear antibodies (ENAs)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR)</td>
<td>Lupus anticoagulant</td>
</tr>
<tr>
<td>Urea and electrolytes</td>
<td>Thyroid antibodies</td>
</tr>
<tr>
<td>C reactive protein (CRP)</td>
<td>Anti-cardiolipin antibodies</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Complement 1q (C1q) antibodies</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Creatinine kinase</td>
</tr>
<tr>
<td>Complement 3 (C3) and 4 (C4)</td>
<td>Lipid profile</td>
</tr>
<tr>
<td>Anti-double stranded DNA titres</td>
<td>Thyroid function tests</td>
</tr>
<tr>
<td>Urine sediment/microscopy</td>
<td></td>
</tr>
<tr>
<td>Urine albumin:creatinine ratio</td>
<td></td>
</tr>
</tbody>
</table>

Scores of Activity & Damage

• BILAG 2004
• SLEDAI 2000

• SLICC/ACR damage index
Management
JSLE - treatment

- Non pharmacological
  - Limit UV exposure
  - Address vitamin D
  - OCP – avoid if aCL / LA positive
  - Issues re vaccination in immunosuppressed
  - Psychosocial issues / adherence
JSLE - treatment

- Antimalarials
- Cytotoxics
- Biologics
- Other e.g. IVIg

Corticosteroids
Corticosteroids

Required at some stage by most patients
  – E.g. 1-2 mg per kilogram/day, then tapered
  – Intravenous pulsed methylprednisolone (30 mg/kilogram X 3: “MP3”)
JSLE - treatment

- Hydroxychloroquine 5-6.5 mg/kg/day (200-400mg/day) – skin, joints, fatigue
- Cytotoxics
  - Azathioprine: 1-3 mg/kg/day (max 150 mg/day): moderate SLE
  - Methotrexate: 15 mg/m²/week (max 25 mg): Joint disease
  - Cyclophosphamide – pulsed IV 500-750 mg/m² every 3-4 weeks (max 1.2g): Severe NP-SLE; Class 4 LN?
  - Mycophenolate Mofetil: 600 mg/m² twice daily (max 1g BD) (Class 3-5 LN); Moderate-severe SLE)
Lupus nephritis
ALMS results

- Mycophenolate mofetil
- Intravenous cyclophosphamide

Patients Responding to Treatment (%)

- Overall: 56.2, 53.0
- Asian: 53.2, 63.9
- Caucasian: 56.0, 54.2
- Other: 60.4, 38.5

P-values:
- Overall: P=0.58
- Asian: P=0.24
- Caucasian: P=0.83
- Other: P=0.033
ALMS results

Black and Hispanic responded more often to MMF than other races

*Isenberg D et al Rheumatology 2010;49:128*
Rituximab

• Monoclonal antibody
  – binds to CD20 Ag
    • located on pre-B and mature B lymphocytes
    • mediates B-cell lysis
JSLE – Other treatment

- Biologics – B cell depletion therapy
  - Anti-CD20 (Ofatumumab, others..)
  - Anti-BlyS (Belimumab)

- Other
  - IVIg (thrombocytopenia, myositis, diffuse haemorrhagic alveolitis)
  - Anti-aggregation and anticoagulation for APS
  - Mepacrine – skin
  - Plasma exchange: lung haemorrhage; TTP; severe NP-SLE
  - Autologous Haematopoietic Stem Cell Transplantation
Prognosis
jSLE prognosis

- jSLE survival: 10 year survival approximately 90%
- LN: >90% renal survival
- Cardiovascular disease
  - 6-9 X increase stroke or MI
  - MI rate of 8% in 24-43 year olds who developed SLE in childhood
  - Statins did not influence subclinical measures of atherosclerosis in jSLE over 3 years (APPLE trial)
  - HCQ improves lipid profile
- Bone health: osteopenia in 40%; vertebral fractures in 6-10%
Neonatal lupus
Neonatal lupus

- Born to mothers with Ro/La antibody
  - Risk is 2% to an infant with positive mother

- Clinical features
  - **Skin**: subacute cutaneous lupus-like lesions, telangiectasia.
  - **Cardiac**: congenital heart block (2%); mortality 15-25%.
    Cardiomyopathy, prolonged QT interval, sinus bradycardia, cardiac malformations.
  - **Hepatobilary**: transaminitis, cholestasis, liver failure very rare.
  - **Haematological**: thrombocytopenia and less commonly other cytopenias.

- Recurrence in a subsequent pregnancy 15%
Neonatal lupus: Treatment/Prognosis

• Careful in utero and postnatal monitoring of at-risk pregnancies is important to ensure appropriate treatment (serial fetal echo; postnatal ECG).
• Use of maternal fluorinated corticosteroids (dexamethasone or beclamethasone) which cross the placenta may prevent progression of incomplete heart block.
• Infants with cardiac disease may need cardiac pacing.
• Skin lesions can be treated with sun avoidance, sun block and topical corticosteroids.

Prognosis
• Skin, hepatic and haematological manifestations tend to resolve spontaneously as maternal autoantibodies disappear from the infant’s circulation; complete heart block and cardiomyopathy can be life threatening.
• Affected infants may be at ↑ risk of subsequent autoimmune disease.