FACING THE WOLF – LUPUS UPDATE 2017

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I have no disclosures

https://www.youtube.com/watch?v=bueW1d9kQao
Objectives

- Review SLE and SLE types
  - SLE
  - Cutaneous LE
  - Neonatal LE/pregnancy
- Discuss differences in pediatric & adult SLE
- Review advances in management and theories of pathogenesis
Systemic Lupus Erythematosus

- Inflammatory multisystem disease
- 1.5 million cases, prevalence 1:1000
- Women>Men- 9:1 ratio (90% cases are women)
- African Americans>Whites
- Onset usually between ages 15 and 45 years (20% start in childhood)
- Highly variable course and prognosis, ranges from mild to life threatening
- Characterized by flares and remissions
- Associated with characteristic autoantibodies

CUTANEOUS LUPUS

- Variable presentation
- 20% will progress to SLE
  1. Chronic cutaneous lupus – usually discoid
  2. Subacute cutaneous LE
     SSA & SSB often present
  3. Acute cutaneous LE
     Often part of SLE, photosensitive component
### CLASSIFICATION CRITERIA

1. Malar rash
2. discoid rash
3. photosensitivity
4. oral or nasopharyngeal ulcerations

(A person shall be said to have SLE if 4 or more of the 11 criteria are present. 1997 American College of Rheumatology)
CLASSIFICATION CRITERIA

5. nonerosive arthritis
6. pleuritis or pericarditis
7. renal disorder: proteinuria >0.5g/day or cellular casts
8. encephalopathy: seizures or psychosis

CLASSIFICATION CRITERIA

9. Hematologic disorder:
   - hemolytic anemia
   - or leukopenia (<4000/mm³)
   - or lymphopenia (<1500/mm³)
   - or thrombocytopenia

10. Immunologic disorder:
    - anti-DNA antibody in abnormal titer
    - or anti-SM antibody
    - or anti-phospholipid antibody
    - or false positive test for syphilis
11. positive Antinuclear antibody (ANA)
REVISED SLICC CRITERIA

1) Fulfillment of at least four criteria, with at least one clinical criterion and one immunologic criterion
   • Broader skin, neurologic, alopecia, immunologic criteria include low complements and direct coombs

2) OR Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.

Diagnosis

Average time to diagnosis after onset of symptoms = 2.7 yr

SLE presenting symptoms
**Antinuclear Antibodies (ANA)**

- +ANA is Sensitive but not specific
  - 95–98%+ in SLE patients
- **+ANA does not equal SLE**: up to 10% of population have +ANA w/o disease
- can see +ANA with infections, medications, malignancy, autoimmune thyroiditis
- dsDNA, ENA, RNP, SSA/SSB, anti-histone

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**Serologic features in 1000 SLE patients – prevalence (%)**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibodies</td>
<td>96</td>
</tr>
<tr>
<td>Anti-dsDNA antibodies</td>
<td>78</td>
</tr>
<tr>
<td>Anti-Ro (SSA)/anti-La (SSB) antibodies</td>
<td>25/19</td>
</tr>
<tr>
<td>Anti-RNP antibodies</td>
<td>13</td>
</tr>
<tr>
<td>Anti-Sm antibodies</td>
<td>10</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>18</td>
</tr>
<tr>
<td>IgG/IgM anticardiolipin antibodies</td>
<td>24/34</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>15</td>
</tr>
</tbody>
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**MORBIDITY IN SLE**

- **RENAL**: Dialysis, transplantation
- **CNS**: Organic brain syndrome, psychosis, neuropsychiatric dysfunction
- **IMMUNE**: infections, malignancy, asplenia
- **CV**: atherosclerosis, MI, myocardiopathy, valvular disease, hypertension
- **MUSCULOSKELETAL**: osteopenia, compression fractures, osteonecrosis, stunted growth, obesity
- **OCULAR**: cataracts, glaucoma
- **ENDOCRINE**: infertility, diabetes, fetal wastage
50% of all lupus pregnancies are normal
25% will deliver premature infants
Marked improvement in pregnancy loss
(once was >40%, now almost normal risk)
All pregnancies need close management.
Maternal morbidity 20 fold higher in SLE
2% risk of neonatal LE overall, 10% risk if SSA/SSB +
PREGNANCY: MATERNAL CONCERNS

MEDICATIONS
- Prednisone does not cross the placenta
- Most lupus medications do not increase the risk of pregnancy loss or birth defects
- Cyclophosphamide is definitely harmful
- Should probably maintain hydroxychloroquine
- Low dose aspirin may be recommended
- Anti-coagulants, such as heparin, may be also be needed
- Breastfeeding usually fine
2% chance child will have neonatal lupus

NLE – seen mainly in mothers with SSA and SSB antibodies (1/3 of lupus patients have these antibodies)

NLE
- Heart block – usually permanent
- Skin rashes – temporary, can scar (SUN BLOCK!!!)
- Changes in blood counts – temporary, usually not a problem

Recommendations –
- Screen SLE mothers for SSA & SSB
- All infants should have an electrocardiogram and blood count
- Sunscreen, close observation
- NLE – 25% recurrence in next pregnancy
- Children of lupus mothers can have + ANA (25%) and inc risk of autoimmune diseases (JIA, thyroid, SLE)
Children get lupus too

- Accounts for ~15–20% of all lupus patients.
- More common in girls than boys.
- More common in Asian, African-American, and Hispanic than white American children.
- Rare in children under 5; more common in adolescents.
- May have more severe disease at onset & more aggressive course.

Ped SLE: worse than adult SLE!!

- Greater prevalence of rash, lymphadenopathy, cytopenias and nephritis
- Higher incidence lupus psychosis (12%)
- Similar autoantibody profiles
- Higher disease activity at presentation and during the course of the disease
Some challenges in pediatric lupus

- Family involvement
  - Medications
  - Monitoring and office visits
  - Stress, family dynamics, financial strain

- School accommodations
  - Medication
  - Academics
  - Gym class and athletics
  - Absences

SPECIAL CONSIDERATIONS IN CHILDREN AND ADOLESCENTS

- Life-long burden of renal failure and (multiple) renal transplant(s)
- Steroid toxicity
- Immunosuppressive toxicity (infertility)
- Infection risk different in children:
  - CMV, EBV
  - Bacterial infections, esp. strep
  - Fungal infections
- Developmental age and psychosocial issues
Transition to adulthood

- Often very challenging.
  - Adolescents are “invincible.”
  - Change of PCP & specialists, Change of physical location (college/job).
  - Change of insurance coverage.
  - Balancing adult responsibilities with demands of managing a chronic illness.
  - Family changes, relationships, and pregnancy.

Poor prognostic factors

- Renal disease (especially diffuse proliferative glomerulonephritis)
- Hypertension, male sex, young age
- Low socioeconomic status
- Black race, which may primarily reflect low socioeconomic status
- Antiphospholipid antibodies/APL syndrome
- High overall disease activity

STILL AWAKE?
SLE Updates

- New Treatments
- Biomarkers
  - Diagnosis
  - Pathogenesis (leads to treatment)
  - Prognosis

New Treatments for Lupus

Until 2011 it had been over 50 years since a new drug was approved for lupus! **WHY?**

- **Lupus is hard to study:**
  - Clinical expression is heterogeneous
  - Pathology is diverse
  - Disease activity is intermittent
  - Lack of agreed upon disease activity measures and endpoints
  - Small patient populations—rare disease
- **Development costs:** Estimated $1 billion to take a drug from the research stage to FDA approval
- **Lack of a clinical trial infrastructure**
The traditional treatment armamentarium

FDA approved drugs:
- Glucocorticoids
- Hydroxychloroquine
- Low dose aspirin
- Benlysta

Off-label, but standard of care:
- Azathiorprine
- cyclophoshamide

Immunosuppressives developed for other diseases:
- Mycophenolate mofetil
- Methotrexate
- Leflunomide
- Tacrolimis
- cyclosporine
- fludarabine

The benefits of hydroxychloroquine/vitamin D

- Decreased incidence and severity of flares of disease with both drugs
- Stopping hydroxychloroquine increases the risk of a lupus flare 2-3 fold.
- Low blood concentrations of plaquenil or vitamin D may predict disease flare
- Low toxicity of both – q 6-12 month eye exams but retinal toxicity is rare

Mycophenolate mofetil (CellCept®) Use for Kidney Inflammation in Lupus

- Generally well tolerated
- “Turns down” the immune system
- FDA-approved for use in patients receiving organ transplants
- May have fewer side effects than older medications
Munchies... Mood Swings... Gaining weight?
The Prednisone Makeover

TAKE PREDNISONE THEY SAID
YOU'LL FEEL BETTER THEY SAID

PREDNISONE / CORTICOSTEROIDS
3 RD  GRADE
4 TH  GRADE
Biological Therapies

• Proteins that affect cells or signals in the immune system

• Usually need to be injected or infused (IV)

Examples of success of Biologics: RA

• Anti-TNFs
  – Etanercept
  – Infliximab
  – Adalimumab
  – Golimumab
  – Certolizumab

• Anti-cytokine
  – Kineret (IL-1ra)
  – Tocilizumab (anti-IL-6)

• B cell depletion
  – Rituximab

• Blockade of co-stimulation
  – Abatacept
Belimumab (anti-BAFF) - Benlysta for Treatment of SLE

- Blocks a B cell survival factor, inducing B cell death
- Approved for the treatment of SLE
- **First Drug Approved for Lupus in Over 50 Yrs**
- **First Biological Approved for Lupus**
- **Not approved for children**

SLE Clinical Trials: Cytokines

Targeting cytokines of pathogenic importance

- Targeting Interferon α
  - Anti-interferon α (Genentech; phase I): enrollment complete, ROSE
- Targeting IL-6
IFN as a common denominator in trigger of flares

- Sun exposure
- Drug reactions, e.g. sulfa drugs
- Infections

Some of our current drugs are now believed to target IFN pathways: e.g. anti-malarials

Rituximab = anti-CD20 = B cell depletion

- Two large trials of anti-CD20 (rituximab) in SLE failed to meet their primary outcomes
- Advances in the field on how to successfully do lupus clinical trials
- Rituximab is still thought to be effective in lupus and indicated for a subset of refractory patients

Repurposing drugs:

- New ALR–LRI collaboration
- Finding drugs and other treatment strategies that may be ripe for repurposing in lupus
- 20 candidate drugs expected to emerge for further study in small focused science–rich clinical trials
The etiology of SLE remains unknown. Yet, SLE is clearly multifactorial:
- Genetic factors
- Immunologic factors
- Hormonal factors
- Environmental factors

EBV?

Genetic predisposition

Infection

Baseline immunological abnormalities

Abnormal control of immune responses

Hormonal factors

SLE

Current Theories Of Pathogenesis In SLE

- Etiology unknown
- Multiple genes involved
- Immune dysregulation of B and T cell responses
- Immune complex deposition
- Abnormalities of complement
- Decreased clearance of apoptotic debris
- Hormonal imbalance
- Environmental triggers including UV light, infection
- Loss of tolerance to chromatin and other autoantigens
- Cross reactivity between bacterial and mammalian DNA
- Abnormal response to DNA?

These factors, acting alone or together, may trigger onset of disease in a genetically predisposed host.
Early signs of lupus

Genetics and Lupus
- Lupus is more common in families with lupus or other immune system diseases; twin data
- Some groups, such as African Americans, Hispanics, and Asians get lupus more commonly and with more severe symptoms
- Intense efforts: SLEGEN- consortium to conduct large genome wide association studies with 2.5 million genetic markers
- ImmunoChip: technology offers the ability to study 250,000 genes and their variants in each of a large number of participants
- Over 40 SLE associated genes identified
Biomarkers: Diagnosis and Disease Subsets

**Genetics and Lupus**

- ImmunoChip technology
- Comparison of SLE vs. ANA negative individuals
- Preliminary analysis anticipates 15-20 new SLE associated genes
- Toll-like receptors are coming up as a big common pathway

Predicting flares with B cell biomarkers

![Graph showing flare prediction with B cell biomarkers.](chart.png)

- Active Disease Like Cluster
- Healthy Like Cluster
- Days from Baseline
- p=0.04
Things to Remember Tomorrow

- SLE is a heterogeneous autoimmune disease that typically affects young women in their child-bearing years
- SLE can be mild & almost always treatable
- Although lupus can affect almost any part of the body, most people experience symptoms in only a few organs.
- Consider the balance of treatment of active disease vs. complications of treatment

Concluding points - treatment

- We are learning how to “borrow” drugs used to treat other diseases
- Some drugs may provide clues about how lupus develops
- Despite barriers, novel mechanism-based therapies are in development for SLE
- Therapy will attempt to target specific pathways in the body
- Eventual treatments may involve combination therapies, i.e., “cocktails” of targeted and semi-targeted therapies