UPDATES ON PEDIATRIC SLE

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“Stand for something or you will fall for anything. Today’s mighty oak is yesterday’s nut that held its ground.”

Rosa Parks
February 4, 1913 – October 24, 2005
OBJECTIVES

• RECOGNIZE THE PRESENTATION OF PEDIATRIC SLE (PSLE).

• REVIEW THE UPDATES IN SLE
OUTLINE

• OVERVIEW OF EPIDEMIOLOGY OF PSLE

• UPDATES ON PATHOPHYSIOLOGY OF SLE

• OVERVIEW OF CLINICAL MANIFESTATIONS OF SLE

• UPDATES ON DIAGNOSTICS OF SLE

• UPDATES ON MANAGEMENT OF SLE
INTRODUCTION

- THE IMMUNE SYSTEM IS A POWERFUL DEFENSE OPERATION.

- DYSFUNCTIONS OF THE IMMUNE SYSTEM LIE AT THE CENTRE OF A WIDE VARIETY OF DISEASES; AUTOIMMUNITY, ALLERGY, INFECTIONS, CANCER, AND CARDIOVASCULAR DISEASE.
INTRODUCTION

• A CENTRAL CONCEPT TO THE PATHOGENESIS OF AUTOIMMUNE DISEASES IS THAT THE “TOLERANCE TO SELF IS VIOLATED.”

DEFINITION

- SLE HAS BEEN CLASSICALLY DESCRIBED AS A PROTOTYPIC AUTOIMMUNE DISEASE

- CHARACTERIZED BY THE PRODUCTION OF AUTO-ANTIBODIES TO COMPONENTS OF THE CELL NUCLEUS.

GILBERT ET AL. PEDIATRIC RHEUMATOLOGY 2014, 12:16
NEW LUPUS CASES/DEATHS

New cases/ deaths

Case series Publications

SLE related deaths

>5 1-5 None

>50 20-50 10-20 5-10 1-5

New cases
UPDATES ON PATHOPHYSIOLOGY
PATHOPHYSIOLOGY

Viruses or bacteria → UV → Apoptotic material → Dendritic cell → Activated conventional Dendritic cell

Plasmacytoid Dendritic cell

- IFN-α

Immunocomplexes → CD4+ T cell

- IL-21

Autoantibodies

Plasma cell

- BCR

TLR9

CD40L

- CD40

- B cell
NUCLEAR EXTRACELLULAR TRAPS
CLINICAL MANIFESTATIONS
“1000 Faces”
Brain: Persistent and unusual headaches, memory loss, or confusion

Eyes: Dry or puffy eyes, and increasing sensitivity to light

Mouth and Nose: Sores inside the mouth and/or nose

Skin: A "butterfly" rash on the face usually over the cheeks and bridge of the nose or other rashes that can worsen with sun exposure

Lungs/Heart: Shortness of breath and/or pain in the chest

Fingers, toes, or the tip of the nose may turn white or blue with exposure to cold or during stressful situations

Stomach: Nausea, vomiting, recurring and persistent abdominal pain, bladder infections, and blood in urine

Fatigue and unexplained fevers

Persistent pain and swelling of the legs, joints, and/or feet
Discoid lupus: skin lesions, face

[Image of skin lesions on the face]
Systemic lupus erythematosus: malar rash, face
Systemic lupus erythematosus: alopecia, scalp
CUTANEOUS LUPUS

• THE FREQUENCY OF CUTANEOUS MANIFESTATIONS IN SLE IS AS HIGH AS 70%

• DISCOID RASH-SPECIFIC HYPMETHYLATIONS WERE FOUND IN TAP1 AND PSMB8, GENES INVOLVED IN ANTIGEN PROCESSING AND PRESENTATION.

• CURR OPIN RHEUMATOL. 2016 SEPTEMBER ; 28(5): 453--459.

• J DERMATOL. 2011; 38(9):839--849.
UPDATES ON DIAGNOSTICS
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

<table>
<thead>
<tr>
<th>Clinical Criteria</th>
<th>Immunologic Criteria</th>
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<tbody>
<tr>
<td>1. Acute Cutaneous Lupus*</td>
<td>1. ANA</td>
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<tr>
<td>2. Chronic Cutaneous Lupus*</td>
<td>2. Anti-DNA</td>
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<tr>
<td>3. Oral or nasal ulcers</td>
<td>3. Anti-Sm</td>
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<tr>
<td>4. Non-scarring alopecia</td>
<td>4. Antiphospholipid Ab *</td>
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<tr>
<td>5. Arthritis *</td>
<td>5. Low complement (C3, C4, CH50)</td>
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<td>7. Renal</td>
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<td>8. Neurologic *</td>
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<tr>
<td>9. Hemolytic anemia</td>
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<tr>
<td>10. Leukopenia *</td>
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<tr>
<td>11. Thrombocytopenia (&lt;100,000/mm³)</td>
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†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Excessive activation of the TLR9/TGF-β1/PDGF-B pathway in the peripheral blood of patients with systemic lupus erythematosus

Yi Yuan1, Mingyue Yang1, Kuo Wang1, Jing Sun3, Lili Song1, Xue Diao1, Zhenyu Jiang7, Genhong Cheng1, and Xiaosong Wang1

Abstract

Background: Our aim is to study the existence of the TLR9/TGF-β1/PDGF-B pathway in healthy humans and patients with systemic lupus erythematosus (SLE), and to explore its possible involvement in the pathogenesis of lupus nephritis (LN).

Methods: Protein levels of the cytokines were detected by ELISA, mRNA levels of the cytokines were analyzed by real-time PCR. MTT assay was used to test the proliferation of mesangial cells under different treatments.

Results: Compared to healthy controls (Ncontrol = 56), levels of Toll-like receptor (TLR)9, transforming growth factor (TGF)-β1, and platelet-derived growth factor B (PDGF-B) were increased significantly in the peripheral blood of SLE patients (NSLE = 112). Significant correlations between the levels of TLR9, TGF-β1, and PDGF-B were observed in both healthy controls and SLE patients. The levels of TGF-β1 and PDGF-B were greatly enhanced by TLR9 activation in primary cell cultures. The proliferation of mesangial cells induced by the plasma of SLE patients was significantly higher than that induced by healthy controls; PDGF-B was involved in this process. The protein levels of PDGF-B homodimer correlated with the levels of urine protein in SLE patients with LN (NLN = 38).

Conclusions: The TLR9/TGF-β1/PDGF-B pathway exists in humans and can be excessively activated in SLE patients. High levels of PDGF-B may result in overproliferation of mesangial cells in the kidney that are involved in the development of glomerulonephritis and LN. Further studies are necessary to identify TLR9, TGF-β1, and PDGF-B as new therapeutic targets to prevent the development of glomerulonephritis and LN.

Keywords: Systemic lupus erythematosus, Toll-like receptor 9, Transforming growth factor β1, Platelet-derived growth factor B.
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
Prevalence of Normal Individuals with Positive ANA
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

Autoantigen microarrays reveal autoantibodies associated with proliferative nephritis and active disease in pediatric systemic lupus erythematosus

D. James Haddon, Vivian K. Diep, Jordan V. Price, Cindy Limb, Paul J. Utz and Imelda Balboni

Abstract

Introduction: Pediatric systemic lupus erythematosus (pSLE) patients often initially present with more active and severe disease than adults, including a higher frequency of lupus nephritis. Specific autoantibodies, including anti-C1q, anti-DNA and anti-alpha-actinin, have been associated with kidney involvement in SLE, and DNA antibodies are capable of initiating early-stage lupus nephritis in severe combined immunodeficiency (SCID) mice. Over 100 different autoantibodies have been described in SLE patients, highlighting the need for comprehensive autoantibody profiling. Knowledge of the antibodies associated with pSLE and proliferative nephritis will increase the understanding of SLE pathogenesis, and may aid in monitoring patients for renal flare.

Methods: We used autoantigen microarrays composed of 140 recombinant or purified antigens to compare the serum autoantibody profiles of new-onset pSLE patients (n = 45) to healthy controls (n = 17). We also compared pSLE patients with biopsy-confirmed class III or IV proliferative nephritis (n = 23) and without significant renal involvement (n = 18). We performed ELISA with selected autoantigens to validate the microarray findings. We created a multiple logistic regression model, based on the ELISA and clinical information, to predict whether a patient had proliferative nephritis, and used a validation cohort (n = 23) and longitudinal samples (88 patient visits) to test its accuracy.

Results: Fifty autoantibodies were at significantly higher levels in the sera of pSLE patients compared to healthy controls, including anti-B cell-activating factor (BAFF). High levels of anti-BAFF were associated with active disease. Thirteen serum autoantibodies were present at significantly higher levels in pSLE patients with proliferative nephritis than those without, and we confirmed five autoantigens (dsDNA, C1q, collagens IV and X and aggrecan) by ELISA. Our model, based on ELISA measurements and clinical variables, correctly identified patients with proliferative nephritis with 91% accuracy.

Conclusions: Autoantigen microarrays are an ideal platform for identifying autoantibodies associated with both pSLE and specific clinical manifestations of pSLE. Using multiple regression analysis to integrate autoantibody and clinical data permits accurate prediction of clinical manifestations with complex etiologies in pSLE.
UPDATES ON MANAGEMENT
PSLE - TREATMENT

DEPENDS ON EXTENT AND SEVERITY OF THE DISEASE:

• HYDROXYCHLOROQUINE/CHLOROQUINE ALONE.
• HYDROXYCHLOROQUINE + NSAID.
• HYDROXYCHLOROQUINE + STEROID
• HYDROXYCHLOROQUINE + CYTOTOXIC AGENT
• HYDROXYCHLOROQUINE + HIGH DOSE PREDNISONE + CYTOTOXIC AGENT.
• 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
BIOLOGICS
THE WAY FORWARD

• DO EXTRACELLULAR TRAPS ORIGINATING FROM IMMUNE CELL POPULATIONS OTHER THAN NEUTROPHILS PLAY A ROLE IN HUMAN DISEASE?

• DOES PROTEIN CONTENT WITHIN NETS DIFFER ACROSS AUTOIMMUNE DISEASES IN ASSOCIATION WITH DISTINCT AUTOANTIBODY PROFILES?
THE WAY FORWARD

• ARE AMPLIFICATION OF TIIFN RESPONSES BY NETS UNIQUE TO SLE OR SIMILARLY FOUND IN OTHER RELATED AUTOIMMUNE DISEASES?

• CAN A STANDARDIZED BIOMARKER FOR IN VIVO NET FORMATION BE DEVELOPED AND USED TO PREDICT CARDIOVASCULAR EVENTS IN AUTOIMMUNE AND VASCULOPATHIC DISEASES AND TARGET PREVENTATIVE APPROACHES TO MINIMIZE FUTURE CARDIOVASCULAR EVENTS?
THE WAY FORWARD

• WOULD INHIBITION OF SPECIFIC CRITICAL SUBCELLULAR EVENTS BE EFFICACIOUS TO TREAT SLE OR OTHER RELATED AUTOIMMUNE DISEASES, AND WHAT WOULD BE THE POTENTIAL INFECTIOUS AND OTHER RISKS OF SUCH APPROACHES?
SUMMARY

Irreversible tissue damage → Adaptive immune system activation → Immune complexes → Environmental triggers → Innate immune system activation → Genetic predisposition → Aberrant amplification pathways → Increased resistance to therapy → Clinical disease onset → Cycle repeats
"...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."

JULIUS KAMBARAGE NYERERE, FROM HIS BOOK UHURU NA MAENDELEO (FREEDOM AND DEVELOPMENT), 1973.
ASANTE! THANK YOU! MERCI!

NAIROBI CITY