Scleroderma in Children

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University of Washington School of Medicine
Disclosures

- Patent licensed to Quest Diagnostics
- Research collaboration with Seattle Genetics
- Research collaboration with Kineta, Inc. (KPI)
- Fellowship support from Pfizer, Inc.
Editorial

Juvenile-onset systemic sclerosis: children are not small adults

The majority of childhood-onset rheumatic diseases differ markedly in presentation and management from their equivalent adult conditions, and juvenile-onset systemic sclerosis (JSSc) is no exception. Chronic ill health from any cause in childhood impacts heavily, not only on physical growth and development, but also in terms of social, educational and psychological development. Even localized scleroderma, the most common spectrum in to puberty, again challenges the dogma that oestrogens are solely responsible for the increased autoimmune propensity in females, with X-inactivation chimerism cited as an alternative mechanism.

While the overall mortality of juvenile-onset disease is lower, those with a poor outcome tend to progress more rapidly than their adult counterparts. Cardio disease in adults is rarely the
American Academy of Pediatrics Admits that Children Really are Little Adults

Washington, D.C. – A year-long undercover investigation into the American Academy of Pediatrics’ claim that pediatric patient management was distinct from that of adults has revealed widespread evidence to the contrary.

Faced with a crushing epidemic of ovarian cancers, post-CABG MIs, and amyloidosis, the nation’s pediatric departments began steadily consulting their internal medicine colleagues for management tips. Medicine resident William Quiroga was one of the first to blow the whistle. “At first it was just a trickle, but then I was getting slammed every time I was on consults with 5-6 requests a day from the pediatrics department. I would see the patient and give recommendations, and note that they were followed to the letter. Sometimes the peds resident would make a big show about calculating drug dosages by weight or something just to contribute, but then when I would come back I would see my original dosage was re-ordered.”
Systemic Sclerosis (SSc) in kids—RARE but potential for serious organ involvement

Internationally % SSc that are childhood onset : 1-9%

(increase with teen age)

Age at Symptom Onset

University of Pittsburgh cohort: 111/2670 (4%)

Number of Patients
Are Children with Scleroderma Little Adults?

(1) frequency, incidence
(2) clinical classification
(3) organ system involvement
(4) serologic results
(5) natural history of disease and survival
Diagnosis

Raynaud Phenomenon is not common or normal in young kids
Systemic Sclerosis: Using High-Resolution CT to Detect Lung Disease in Children

Jean M. Seely¹,²
Luann T. Jones³
Carol Wallace³
David Sherry⁴
Eric L. Effmann⁵

**OBJECTIVE.** The purpose of this study was to determine the prevalence of interstitial lung disease and the severity of disease in children with systemic sclerosis using high-resolution CT (HRCT).

**SUBJECTS AND METHODS.** Eleven children (mean age, 11 years) with scleroderma underwent HRCT, chest radiography, and pulmonary function testing. Eight of these 11 patients also underwent follow-up HRCT. HRCT studies were assessed by two observers for ground-glass attenuation, honeycombing, and other abnormalities. Profusion scores for

Beginning of the study:
- Chest radiographs predicted interstitial lung disease in only two patients
- HRCT showed interstitial lung disease in eight patients (p = 0.05).
  - Groundglass attenuation in 8 (73%)
  - Honeycombing 5 (45%)
  - Linear opacities in 6 (55%)
  - Subpleural micronodules in seven patients (64%).

End of the study:
- 10 patients (91%) had evidence of ILD by HRCT
- HRCT revealed worsening disease in 3/8
30% of kids with Raynaud Phenomenon will develop a connective tissue disease within 6 years (mean 2 years)

Less likely if negative ANA, normal nailbed capillaries

Nigrovic J Pediatrics 2003
Can Nailbed Capillaries in Raynaud P. Predict Disease? Prospective Observation of 250 Children with Raynaud P.

- 9 (3.6%) SLE - Nonspecific capillary changes occurred in 2 of 9
- 10 (4%) RA (6 JIA) – 3 of 10
- 13 (5.2%) Scleroderma

Only 10 showed sclerodermatous disease type capillary changes  
- Predicted scleroderma

Architectural disorganization, giant capillaries, haemorrhages, loss of capillaries, angiogenesis and avascular areas
Not acrocyanosis
– Anorexia
– Methylphenidate
5 major jSSc cohort studies:


How does pediatric onset SSc compare to adult onset?

- **Same subtypes present with similar organ manifestations:**
  - **Diffuse cutaneous (dcSSC)**
    - widespread & rapidly progressive skin thickening
    - early lung (ILD), heart, kidney involvement
    - Associated with Topoisomerase (Scl-70) Ab
  - **Limited cutaneous (lcSSc)**
    - restricted & non-progressive skin thickening
    - late organ involvement: lung (PAH), GI malabsorption
    - Associated with centromere Ab
  - **Overlap**
    - diffuse or limited scleroderma with features of another connective tissue disease, e.g., PM/DM, SLE
    - Myositis and arthritis
    - Associated with U1-RNP and PM-Scl Ab
...*But with different frequency*

<table>
<thead>
<tr>
<th>Clinical subsets</th>
<th>Pediatric onset</th>
<th>Adult onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>dcSSc</td>
<td>30-40%</td>
<td>35-45%</td>
</tr>
<tr>
<td>lcSSc</td>
<td>30-40%</td>
<td>40-50%</td>
</tr>
<tr>
<td>Overlap</td>
<td><strong>15-25%</strong></td>
<td>9%</td>
</tr>
</tbody>
</table>
Ped SSc – organ involvement (Univ Pitt)

Figure 1. Organ system involvement during the course of SSc by age at onset group. Capital letters: Denominator is the number of patients who had objective testing performed. Significant differences between age at onset groups: *B vs C, p < 0.0002; **B vs C, p < 0.05; †B vs C, p < 0.005; ††A vs B, p < 0.0002; A vs C, p < 0.0002; ^B vs C, p < 0.002; ^^A vs C, p < 0.006; B vs C, p < 0.0002.
Juvenile Systemic Sclerosis Cohort within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry: Follow-up Characteristics

Brandi Stevens¹; Kathryn Torok¹; Suzanne Li²; Nicole Hershey¹; Megan Curran³; Gloria Higgins⁴; Katharine Moore⁵; C. Egla Rabinovich⁶; and Anne Stevens⁷; for the CARRA Registry Investigators⁸

¹Children’s Hospital of Pittsburgh of UPMC, ²Hackensack University Medical Center, ³Northwestern University Feinberg School of Medicine, ⁴Nationwide Children’s Hospital, ⁵Children’s Colorado, ⁶Duke University Medical Center, ⁷Seattle Children's Research Institute; University of Washington, ⁸Childhood Arthritis and Rheumatology Research Alliance
CARRA Registry Pediatric SSc (N=67)

Cumulative Data over 50.7 Person-years of Follow-up

• No reported deaths.

• No interval development of solid organ manifestations (cardiac, pulmonary, renal) after baseline visit.

Follow-up Data for n=25 jSSc Patients 1-2 Years after Enrollment

• Disease manifestations remained generally stable at follow-up.

• Paired analysis revealed trends of:
  
  o Decreased frequency of arthritis (n=4 to 1) and increased joint contractures (n=7 to 11)
  
  o Decreased disability (> Class I) by ACR Functional Class (44% to 25%)
  
  o Improved median Physician Global Disease Activity Score (3 to 2)
Comparison of jSSc Organ Manifestations and Disease Measures at Enrollment and Follow-up Within 1-2 Years‡

<table>
<thead>
<tr>
<th>Organs</th>
<th>Baseline n=64</th>
<th>Follow-up n=25</th>
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<tbody>
<tr>
<td>DERMATOLOGIC</td>
<td>93%</td>
<td>80%</td>
</tr>
<tr>
<td>VASCULAR</td>
<td>92%</td>
<td>72%</td>
</tr>
<tr>
<td>MUSCULOSKELETAL</td>
<td>46%</td>
<td>52%</td>
</tr>
<tr>
<td>GASTROINTESTINAL</td>
<td>42%</td>
<td>44%</td>
</tr>
<tr>
<td>PULMONARY</td>
<td>34%</td>
<td>37%</td>
</tr>
<tr>
<td>RENAL</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>CARDIAC</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Figure 1a. Comparison of grouped organ manifestations in baseline and follow-up subgroups by percentage of total affected. ‡Follow-up for n=25 with visit 1-2 yr after enrollment; Percentages are for those with no missing data for the characteristic.
**HRQoL: JSSc Similar to SLE**

- **ACR Functional Class:**
  - jSSc had significantly more disability (Class II or higher) at enrollment (36.1%) than
  - SLE (18%, \( p=0.001 \))
  - JIA (20.1%, \( p=0.004 \))
  - JDM (20.6, \( p=0.009 \))
  - LS (11.4%, \( p=0.0 \))

- **Pain (mean 2.3):**
  - similar to SLE, JIA, and JDM, statistically greater than LS (\( p=0.048 \))

LS = Localized Scleroderma
Significance underestimated?

May be under-diagnosed and under-treated

Severity of disease may not be reflected in reported symptoms

Major contributor to poor Quality of Life

Causes major morbidity and even death

Possible causal association to lung disease
SSc GI in CARRA Registry

Percent of Subjects

- GI Disease
- Dysphagia
- GERD
- Dysmotility
- Esophagitis
- Strictures
- Malabsorption
- Other

[Bar chart showing the percentage of subjects with various GI conditions in CARRA Registry.]
### jSSc Patient BMI, Z-Scores

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mean</th>
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<tbody>
<tr>
<td>JDM</td>
<td>0.60*</td>
</tr>
<tr>
<td>JIA</td>
<td>0.36</td>
</tr>
<tr>
<td>LSc</td>
<td>0.48</td>
</tr>
<tr>
<td>SLE</td>
<td>0.71*</td>
</tr>
<tr>
<td>jSSc</td>
<td>-0.13**</td>
</tr>
</tbody>
</table>

- Increased z scores for patients with JDM and SLE versus those with JIA, LSc, jSSc
  - Heavy steroid usage in these diseases
- Significantly lower z scores in those with jSSc versus all other patient groups
  - Indication of GI involvement that may not be captured physician assessments
  - GI involvement correlates with poorer patient reported outcome measures
Severe Malnutrition is Specific for SSc
CARRA Registry

BMI Adjusted

-3 to 3
-1.9 to -1
-0.9 to 0
0.1 to 1
1.1 to 2
2.1 to 3
>3

jSSc
SLE
LS
JIA
JDM
Juvenile Systemic Sclerosis: Comparison of Pulmonary Function (PFTs) and Esophageal and Pulmonary Findings on Radiographic Modalities

(Fluoroscopic Upper GI series and High Resolution CT)

Betty Zheng, MD, PhD
Lusine Ambartsumyan, MD
Pediatric Gastroenterology
U. Washington
jSSc: Comparison of PFTs and Esophageal and Pulmonary Findings on Radiographic Modalities

- Retrospective review of 21 children diagnosed with JSSc between 3/1994 – 2/2016 at Seattle Children’s Hospital:
  - PFT parameters
  - UGI
  - HRCT
# Demographics

<table>
<thead>
<tr>
<th>Clinical Parameters @ UGI</th>
<th>Total, N=21 (range or %)</th>
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<tbody>
<tr>
<td>Age, months</td>
<td>153.4 ± 6.6 (96.67 - 213.3)</td>
</tr>
<tr>
<td>BMI</td>
<td>18 ± 0.8 (14.55 - 27.6)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (66.7%)</td>
</tr>
<tr>
<td>Disease Duration, months</td>
<td>25 ± 5.6 (1-95)</td>
</tr>
<tr>
<td>On PPI</td>
<td>16 (76.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms at presentation</th>
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<tbody>
<tr>
<td>Total GI Symptoms</td>
<td>13 (61.9%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Reflux</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Total Pulmonary Symptoms</td>
<td>9 (42.9%)</td>
</tr>
<tr>
<td>SOB</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (14.2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>Pulm HTN</td>
<td>1 (4.8%)</td>
</tr>
</tbody>
</table>
Results

• No significant differences in demographics between normal UGI and abnormal UGI groups

• No significant difference in durations of symptoms to time of UGI between normal UGI and abnormal UGI groups
Results: Comparing UGI and PFTs

- Patients exhibiting **abnormal peristalsis and bolus clearance** on UGI had significantly *lower mean PFTS* (FEV1 %predicted, FVC %predicted, VC %predicted)

- Patients exhibiting **abnormal bolus clearance alone** on UGI also had significantly *lower mean PFTS* (FEV1 %predicted, FVC %predicted, VC %predicted)

- Patients exhibiting **presence of reflux** (spontaneous or provoked) on UGI showed *no significant changes* in PFT parameters
Results: Comparing UGI and HRCT

Significant increase in **esophageal diameter on HRCT** in patients with abnormal UGI (abnormal peristalsis and bolus clearance) compared to patients with normal UGI.

**Possible pathogenesis:** JSSc patients with esophageal involvement have ineffective esophageal bolus clearance (and peristalsis) leading to retention of esophageal lumen contents and microaspiration/silent aspiration of those contents resulting in lung injury and loss of lung function. Evaluation of esophageal motility can potentially be of prognostic value for lung disease and eventual morbidity and mortality.
Survival in jSSc Significantly Better than in Older Adult Onset

Cumulative survival rate

<table>
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<tr>
<th>Years</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
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<tbody>
<tr>
<td>jSSc</td>
<td>89%</td>
<td>80%</td>
<td>74%</td>
<td>69%</td>
</tr>
<tr>
<td>Young Adult</td>
<td>85%</td>
<td>79%</td>
<td>67%</td>
<td>52%</td>
</tr>
<tr>
<td>Older Adult</td>
<td>75%</td>
<td>55%</td>
<td>35%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Scalapino 2006
Serology in jSSc: Prognosis

• Biomarkers may help predict organ involvement, disease course, prognosis

• Most jSSc patients carry ANA, but many do not produce antibodies to topoisomerase (Scl-70) or centromere antigens (ACA), implicating other nuclear antigens.

• In adult SSc, other autoantibodies correlate with clinical phenotype.

Fritzler M, Autoimm. Rev. 2013  Kaji K et al, Arthritis Care Res 2013
Clinical-Serological Classifications of SSc

DIFFUSE

- anti-topoisomerase I (Scl-70)

LIMITED

- anti-RNA polymerase III
- anticentromere
- anti-Th/To
- anti-U3RNP
- anti-U1RNP
- anti-Pm-Scl

OVERLAP

- anti-Ku
- anti-U11/U12 RNP

Courtesy of Noreen Fertig
...But with different frequency, which associate with antibody positivity

<table>
<thead>
<tr>
<th></th>
<th>Pediatric onset</th>
<th>Adult onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>90-97%</td>
<td>90-99%</td>
</tr>
<tr>
<td>Scl-70</td>
<td>20-40%</td>
<td>20-40%</td>
</tr>
<tr>
<td>Centromere</td>
<td><strong>2-8%</strong></td>
<td>20-30%</td>
</tr>
<tr>
<td>U1RNP</td>
<td><strong>15-20%</strong></td>
<td>5%</td>
</tr>
<tr>
<td>PM-Scl</td>
<td>15 %</td>
<td>5%</td>
</tr>
<tr>
<td>RNA Pol III</td>
<td><strong>2-4%</strong></td>
<td>10-30%</td>
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</table>
Scleroderma Cases:
- 30 patients with juvenile onset systemic sclerosis
- 23 patients with localized Scleroderma

Controls:
- 35 age-matched healthy controls

Predictor Variables:
- Extended panel of SSc-specific and SSc-associated Ab
- Multi-institutional Recruitment: 5 CARRA sites and the Fred Hutchinson Cancer Research Center (Seattle, WA)
<table>
<thead>
<tr>
<th>SSc</th>
<th>Localized</th>
<th>Diffuse</th>
<th>Limited</th>
<th>75% Controls</th>
<th>95% Controls</th>
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<tr>
<td>Ro-52</td>
<td>1</td>
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<td>PDLFR</td>
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<td>Ku</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Prm Sq/75</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Prm Sq/100</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Thr/To</td>
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<td>OR890</td>
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<td>CENPB</td>
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<td>CENPA</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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</tr>
<tr>
<td>Scl 70</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>
• 35% carried ANA.
• In 62% of those with ANA, no specific antibodies to nuclear antigens were identified.
Autoantibodies to Dense Fine Speckles (DFS70) in Pediatric Diseases and Controls

Heinrike Schmeling¹,², Michael Mahler³, Deborah M. Levy⁴, Katharine Moore⁵, Anne M. Stevens⁵, James Wick⁶, Jacob D. McMillan⁶, Gerd Horneff⁷, Shervin Assassi⁸, Julio Charles⁸, Gloria Salazar⁸, Maureen D. Mayes⁸, Earl D. Silverman⁴, Marissa Klien-Gitelman⁹, Tzelan Lee¹⁰, Hermine I. Brunner¹¹, Ann M. Reed¹², Marvin J. Fritzler⁶

246 lupus, 54 jSSc, 11 JDMS, 27 uveitis

Journal of Rheumatology, 2015
Pediatric Anti-DFS 70

Healthy Controls: 0.8% positive
Referred for ANA testing: 0.8% positive DFS

Juvenile SSc: 10.1%
Pediatric Lupus: 8%
JIA: 2.5%
Uveitis: 11.1%
Dermatomyositis: 9.1%

DFS is significantly more common in kids with systemic autoimmune disease and in uveitis:

Opposite of the pattern described in adults

DOES NOT RULE OUT AI DISEASE
SSc Genetics

Gorlova 2011 Plos Genetics
SSc Genetics

Genome-Wide Association Studies

Chromosome Number

Strength of Association

HLA

Gorlova 2011 Plos Genetics
HLA Associations in Caucasians
with Adult-Onset Systemic Sclerosis

Caucasians
DRB1 *1104, *1101
DRB1*01
DQA1*0501, DQB1*0301

Diffuse
DQB1*0301/*0304

Protective: in Caucasians
DRB1*0701-DQA1*0201-DQB1*0202
DRB1*1501
Editorial

Juvenile-onset systemic sclerosis: children are not small adults

The majority of childhood-onset rheumatic diseases differ markedly in presentation and management from their equivalent adult conditions, and juvenile-onset systemic sclerosis (JSSc) is no exception. Chronic ill health from any cause in childhood impacts heavily, not only on physical growth and development, but also in terms of social, educational and psychological development. Even localized scleroderma, the most common spectrum in to puberty, again challenges the dogma that oestrogens are solely responsible for the increased autoimmune propensity in females, with X-inactivation chimerism cited as an alternative mechanism.

While the overall mortality of juvenile-onset disease is lower, those with a poor outcome tend to progress more rapidly than their adult counterparts. Cardiac disease in adults is rarely the
BRIEF REPORT

HLA-DRB1, DQA1, and DQB1 in Juvenile-Onset Systemic Sclerosis

Anne M. Stevens,1 Sami B. Kanaan,2 Kathryn S. Torok,3 Thomas A. Medsger,4 Maureen D. Mayes,5 John D. Reveille,5 Marisa Klein-Gitelman,6 Ann M. Reed,7 Tzielan Lee,8 Suzanne C. Li,9 Gretchen Henstorf,10 Christine Luu,2 Tessa Aydelotte,2 and J. Lee Nelson11
# Juvenile SSc HLA Study

<table>
<thead>
<tr>
<th></th>
<th>Juvenile-onset SSc</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>All (n = 76)</td>
<td>Seattle (n = 36)</td>
<td>Pittsburgh (n = 20)</td>
<td>Houston (n = 20)</td>
</tr>
<tr>
<td>Sex, (%) female</td>
<td>87</td>
<td>83</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>Age, mean, years†</td>
<td>10</td>
<td>8.9</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Age, median (IQR) years</td>
<td>11.0 (6–13)</td>
<td>10.2 (5.9–11.9)</td>
<td>11.9 (9–14.1)</td>
<td>11.5 (8.5–13.6)</td>
</tr>
<tr>
<td>SSc subtype, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dcSSc</td>
<td>37</td>
<td>50</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>lcSSc</td>
<td>63</td>
<td>50</td>
<td>75</td>
<td>75</td>
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<tr>
<td>Autoantibodies (positive), %</td>
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<tr>
<td>ANA</td>
<td>90.5</td>
<td>88.9</td>
<td>100</td>
<td>84.2</td>
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<tr>
<td>Anti–topo I</td>
<td>32.4</td>
<td>36.1</td>
<td>33.3</td>
<td>25.0</td>
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<tr>
<td>ACA</td>
<td>18.3</td>
<td>6.1</td>
<td>47.4</td>
<td>10.5</td>
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Adult SSc Genes
Age Matters: AutoAbs

**ATAL**

\[ P = 0.001 \]
\[ P = 0.042 \]

**ACAL**

\[ P = 0.041 \]

<table>
<thead>
<tr>
<th>Age Group</th>
<th>ATAL+ Count</th>
<th>ACA+ Count</th>
</tr>
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<tbody>
<tr>
<td>0-6</td>
<td>n=19</td>
<td>n=18</td>
</tr>
<tr>
<td>6-11</td>
<td>n=19</td>
<td>n=18</td>
</tr>
<tr>
<td>11-16</td>
<td>n=36</td>
<td>n=35</td>
</tr>
</tbody>
</table>

Age at disease onset (yrs)
Adult Alleles—Older Children

![Bar charts showing percentages of DRB1*01 alleles by age at disease onset (yrs) in different groups.](chart)

- **DRB1*01**
  - 0-6 yrs: n=20
  - 6-11 yrs: n=19
  - 11-16 yrs: n=37

- **P-values:**
  - P = 0.010
  - P = 0.014
  - P = 0.024

- Groups:
  - jSSc-ACA+ (n=13)
  - jSSc-ATA+ (n=24)
  - CTL (n=581)
Summary of Differences: jSSc and AoSSc

• Demographics
  – Gender differences only in patients less than 10

• Clinical Manifestations
  – GI, lung common
  – Renal rare
  – Skeletal more common
  – Subtypes:
    • jSSc: dcSSc 30-45%; lcSSc 30-50%, overlap 10-39%
    • aoSSc: dcSSc 35-45%; lcSSc 40-55%, overlap 9-18%
    • More overlap, difficult to quantify to date

• Autoantibodies: Still a lot of unidentified ANAs
• Genes: Different HLA alleles associated, age-dependent
Understanding the Immunophenotypes of Pediatric Scleroderma

Kathryn Torok, MD (U. Pittsburgh)
Suzanne Li, MD, PhD (Hackensack U.)
Anne Stevens, MD, PhD (U. Washington)

• Clinically very different phenotypes

• Histologically similar findings

• Some preliminary work supporting similar/shared T_H1 and IFN-γ profiles

• Likely subtypes within pediatric scleroderma that encompass a particular immunophenotype despite their clinical classification
T cells and B cells

**T cells**

- $T_H = T$-helper cells (CD4+)

  - In scleroderma:
    - $T_H1$ (early/inflammatory)
    - $T_H17$ (inflammatory)
    - $T_H2$ (fibrotic)

- $T_{reg} = T$ regulatory
decreased in scleroderma

**B cells**

- Autoantibody production
  - In scleroderma:
    - ANA
    - Scl-70, centromere
    - Histone, ss-DNA

- Promote T cell differentiation

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O'Shea and Paul. 2010. Science
**INF-γ signature in the skin**

**Adult SSc Skin** (Assassi, Mayes et al Univ Texas Scleroderma Center)
Microarray of SSc skin and blood
- Interferon-γ gene signature – seen in both skin and peripheral blood SSc
  - IFN-γ, IP-10, MCP-1, I-TAC, MCP-1

**Pediatric Localized Scl Skin** (Dr. Torok, Univ Pittsburgh)
RNA Sequencing of Localized Scleroderma Pediatric Skin
- Similar Interferon-γ signature
  - Upregulated I-TAC, MIG, IP-10, CXCR3 (receptor), IFN-γ

<table>
<thead>
<tr>
<th>Figure 3. T_{H1} profile demonstrated in RNAseq analysis in pediatric LS (NRCOS) compared to healthy pediatric skin (control).</th>
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</thead>
<tbody>
<tr>
<td><strong>Chemokines associated with the recruitment of T_{H1} cells: CXCL9, CXCL10, CXCL11, and their receptor, CXCR3 are upregulated. Also, there is an increase in other “Th1” profile cytokines with IFN-γ, IL-12, and associated signaling protein STAT1 and STAT4 upregulated, respectively.</strong></td>
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<tr>
<td><strong>Colloquial name</strong></td>
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<tr>
<td>I-TAC</td>
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<td>IL-12rβ</td>
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<td>TNF</td>
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<td>Chemokine (C-X-C motif) ligand 11</td>
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<td>Chemokine (C-X-C motif) ligand 9</td>
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<td>Chemokine (C-X-C motif) ligand 10</td>
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<tr>
<td>Chemokine (C-X-C motif) receptor 3</td>
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<tr>
<td>Interferon, gamma</td>
</tr>
<tr>
<td>Interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte)</td>
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<tr>
<td>Signal transducer and activator of transcription 1, 91kDa</td>
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<tr>
<td>Signal transducer and activator of transcription 4</td>
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<tr>
<td>Interleukin 12 receptor, beta 2</td>
</tr>
<tr>
<td>Tumor necrosis factor (TNF superfamily, member 2)</td>
</tr>
</tbody>
</table>
LS/morphea and "inflammatory subtype" of SSc share the same upregulation of T cell and IFN-γ genes. 

Active Disease Phenotype

- Whitefield et al 2008
Pediatric Scleroderma Blood cells: Localized and Systemic Phenotypes

Several **shared** cytokines increased in LS and SSc compared to HC:

- IFN-γ
- IL-12p70
- TNF-α
- MCP-1
- IP-10

(considered T_H1 and IFN-γ related)

Though some significantly **different** LS vs SSc:

- MCP-1
- MIP-1α
- IL-6

were elevated in SSc compared to LS

Key:

- Pediatric Healthy (left)
- PediatricLS (middle)
- PediatricSSc (right)

Torok, et. Al (U. Pittsburgh)
Cells in the peripheral blood: Pediatric LS and SSc

**Similar** between LS, SSc
T reg cells were **lower** in LS and SSc compared to HC

**Differences:**
- SSc elevated CTL- CD8+ compared to LS and HC

Within LS:
- increased TCRαβ+, CD4+ and CD8+ cells in **active** LS

*Therefore:* different cells might be targeted for therapy in localized vs. systemic scleroderma.

Torok lab
Timeline of organ involvement in SSc

**DIFFUSE CUTANEOUS**
- interstitial lung disease
- “renal crisis”
- myocardial involvement

**LIMITED CUTANEOUS**
- Raynaud’s, digital ischemia
- tendon/bursal friction rubs; joint contractures
- Raynaud’s, digital ischemia

**OVERLAP**
- esophageal disease
- pulmonary hypertension
- malabsorption

**SKIN THICKNESS**

**TIME**

Courtesy of Dr. Medsger
Proposed conceptual model for transition from $\text{Th}1/\text{Th}17$ to $\text{Th}2$ response

- **Active Disease (Inflammation)**
  - $T_H^1/T_H^{17}$
  - Erythema
  - New/Enlarging Skin Induration

- **Disease Damage (Fibrosis/Atrophy)**
  - $T_H^2$
  - Dermal Atrophy
  - Subcutaneous Atrophy
  - Dyspigmentation
  - Skin Thickness

- Time (years)

- Severity

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- Proposed conceptual model for transition from $\text{Th}1/\text{Th}17$ to $\text{Th}2$ response
Hypothesis……

$T_H$ cells and associated cytokines in Scleroderma Phases

**Active Disease** *(Inflammation)*

- $T_H1/T_H17$
- IFN-γ, IL-12
- GM-CSF
- Activity

**Disease Damage** *(Fibrosis/Atrophy)*

- $T_H2$
- IL-4
- IL-13
- ↓IL-17A, IL-17F

**Proposed conceptual model for transition from Th1/Th17 to Th2 response**
CARRA
Consensus Treatment Plans

- Few Rx really tested in children
- Clinical trials for all Rx in children barriers
  - Disease rarity
  - Physician rarity
  - Funding scarcity
  - Not real world

- Solution – Menu of treatment plans
Scleroderma Consensus Treatment Plans

Corticosteroids

- IV 3/wk + P
- IV 3/mo + P
- IV 1/mo + P
- IV 1/wk + P
- IV 3/wk
- IV 1/mo
- IV 3/mo

- No CS / P 0.5-0.75
- P 1.0
- P 2.0

Methotrexate

- 15/m2
- 10-12.5/m2
- 20/m2
- 0.3
- 0.5
- 0.6
- 0.7-0.875

Current Practice

Consensus Treatment Plans

- No CS
- IV 3/mo OR
- IV 1/wk x 3 mo
- P 2 to 1 mg/kg/d

1.0 mg/kg SQ x 12 mo
CARRA Consensus Treatment Plans

- Collect data at each clinic visit in the CARRA Registry over time
- Compare outcomes in 3 treatments plans
- Collect samples of blood
- Compare biomarkers for prognosis
CARRA Consensus Treatment Plans
Published in Arthritis Care and Research

- SLE – induction therapy for nephritis
  – Mina 2012

- Dermatomyositis – Huber 2010, 2012

- Systemic onset JIA – DeWitt 2012

- Localized scleroderma – Li 2012
CARRA Consensus Treatment Plans
Systemic Sclerosis Next
CARRA Juvenile Systemic Sclerosis Working Group

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