Environmental Factors in Scleroderma

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Environmental Factors

• Gene-Environment interaction
• Diseases that mimic scleroderma
• Diseases with features of scleroderma
• Scleroderma *per se*
Causes of Autoimmune Disease
Genes and Autoimmune Disease

• For some autoimmune diseases, disease concordance in identical twins is higher than in most other diseases studied.

• For other autoimmune diseases, the genetic component is relatively small.

Identical Twin Concordance

- rheumatoid arthritis: 0 - 15%
- multiple sclerosis: 10 - 25%
- hyperthyroidism: 15 - 20%
- type 1 diabetes: 15 - 40%
- lupus: 25 - 35%
- systemic sclerosis: 4%

• Genetic susceptibility is an important determinant of autoimmune disease - but it’s not the only determinant.
Gene-Environment Interaction
Rheumatoid Arthritis

Relative risk (RR) for development of rheumatoid arthritis (RA) in current smokers (with different numbers of copies (0–2) of the shared epitope (SE) of HLA-DR) compared with never smokers. (A) RR for seropositive RA and (B) RR for seronegative RA.

Environmental Exposures and Diseases that Mimic Scleroderma

- Vinyl Chloride Disease
- Toxic Oil Syndrome
- Eosinophilia-Myalgia Syndrome
- Nephrogenic Systemic Fibrosis
Vinyl Chloride Disease
Toxic Oil Syndrome

- Spain, 1981
- Linked to adulterated rapeseed oil sold as “olive oil”
- 20,000 affected
- 1,200 deaths
Eosinophilia-Myalgia Syndrome

- United States, 1989-1990
- L-Tryptophan supplements
- 1,500 cases
- 27 deaths
Nephrogenic Systemic Fibrosis

- Initial report in 2000
- Associated with exposure to Gadolinium as MRI contrast agent in patients with renal impairment
Environmental and Occupational Exposures and Diseases with Features of Scleroderma

- Pulmonary Fibrosis
- Pulmonary Arterial Hypertension
- Raynaud’s Phenomenon
Environmental and Occupational Exposures and Diseases with Features of Scleroderma

- Pulmonary Fibrosis
  - Silica dust, asbestos, beryllium
  - Radiation
  - Drugs - Bleomycin, Amiodarone, Nitrofurantoin, Methotrexate, etc.
  - Herbicides
Environmental and Occupational Exposures and Diseases with Features of Scleroderma

• Pulmonary Arterial Hypertension
  – Appetite suppressants
  – Cocaine
  – HIV infection
  – Jamaican bush tea
Environmental and Occupational Exposures and Diseases with Features of Scleroderma

- Raynaud’s Phenomenon
  - Hand/Vibration Syndrome
  - Drugs
    - Migraine and ADHD Rx
    - Beta blockers
  - Solvents
Conclusion. We found that exposure to solvents may be associated with the development of RP, supporting previous work indicating that solvent exposure may be an etiological factor in systemic sclerosis. J Rheumatol 2011;38:1940–6.
Environment and Autoimmune Disease

• Two examples of environmental exposures that may increase the risk for SSc
  • Silica dust
  • Solvents
Association of SSc with Silica Exposure and Silicosis

1914 Scottish stonemasons
1957 S. African gold miners
1967 American coalminers
1985 German coalminers
1995 Italian workers
FINDINGS

The Panel finds a probable connection between systemic sclerosis and occupational exposure to silica.

The Panel recommends the following rule:

ELIGIBILITY RULE:

A) Workers suffering from systemic sclerosis [scleroderma] with occupational exposure to silica for a minimum of three years are entitled to compensation

or

B) Claims from workers with less than three years exposure shall be considered on their own merits. Claims from workers who have experienced high intensity exposure to silica shall be given special consideration.
Crystalline Silica (Silicon Dioxide)

• Crystalline silica (quartz) - abundant mineral in sand, rock, clay
• Respirable silica can result in chronic, progressive lung disease (silicosis)
• Traditional “dusty trades” include mining, construction, ceramic manufacturing, pottery; grinding
• Silica serves as an “Adjuvant” - generalized stimulation of immune response
• Silica is different from silicone
Occupational Exposure to Silica Dust
IS OCCUPATIONAL ORGANIC SOLVENT EXPOSURE A RISK FACTOR FOR SCLERODERMA?

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Table 4. Exposure to solvents stratified by systemic sclerosis (SSc) subclassification among men only*

| Solvent, exposure type | Limited SSc | Diffuse SSc |  |
|-----------------------|-------------|-------------|  |
|                       | % exposed (n = 18) | OR (95% CI)† | % exposed (n = 19) | OR (95% CI)† |
| Any                   |             |             |  |
| Max. intensity        | 50          | 2.1 (0.7–6.6) | 63          | 3.6 (1.2–11.2)‡ |
| Cum. intensity        | 61          | 3.2 (0.9–11.3) | 58          | 2.6 (0.8–8.7) |
| Max. probability      | 28          | 1.3§         | 32          | 1.6 (0.5–5.3) |
| TCE                   |             |             |  |
| Max. intensity        | 28          | 3.0§         | 32          | 3.7 (1.0–14.2) |
| Cum. intensity        | 22          | 1.2§         | 42          | 3.2 (1.0–10.9)‡ |
| Max. probability      | 11          | 2.9§         | 21          | 7.1§‡         |
| Benzene               |             |             |  |
| Max. intensity        | 22          | 1.8§         | 32          | 3.1 (0.9–11.0) |
| Cum. intensity        | 33          | 1.5 (0.4–5.1) | 37          | 1.7 (0.5–5.4) |
| Max. probability      | 22          | 2.0§         | 26          | 2.5§         |
| CCl₄                  |             |             |  |
| Max. intensity        | 6           | 0.6§         | 5           | 0.6§         |
| Cum. intensity        | 28          | 1.3§         | 42          | 3.0 (0.9–9.8) |
| Max. probability      | 6           | 1.0§         | 16          | 3.8§         |
| TCA                   |             |             |  |
| Max. intensity        | 17          | 2.2§         | 21          | 3.2§         |
| Cum. intensity        | 22          | 1.3§         | 42          | 3.1 (1.0–10.0) |
| Max. probability      | 11          | 2.9§         | 11          | 3.9§         |
Table 5. Exposure to solvents among systemic sclerosis patients who tested positive for the anti-Scl-70 antibody, stratified by sex*

<table>
<thead>
<tr>
<th>Solvent, exposure type</th>
<th>Anti-Scl-70 positive women</th>
<th>Anti-Scl-70 positive men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% exposed (n = 19)</td>
<td>OR†</td>
</tr>
<tr>
<td><strong>Any</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max. intensity</td>
<td>5</td>
<td>0.9</td>
</tr>
<tr>
<td>Cum. intensity</td>
<td>21</td>
<td>2.4</td>
</tr>
<tr>
<td>Max. probability</td>
<td>11</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>TCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max. intensity</td>
<td>11</td>
<td>1.8</td>
</tr>
<tr>
<td>Cum. intensity</td>
<td>26</td>
<td>4.0‡</td>
</tr>
<tr>
<td>Max. probability</td>
<td>11</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Benzene</strong></td>
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<td></td>
</tr>
<tr>
<td>Max. intensity</td>
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<td>1.3</td>
</tr>
<tr>
<td>Cum. intensity</td>
<td>16</td>
<td>4.6</td>
</tr>
<tr>
<td>Max. probability</td>
<td>5</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>CCl₄</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max. intensity</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Cum. intensity</td>
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<td>0.8</td>
</tr>
<tr>
<td>Max. probability</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>TCA</strong></td>
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<td>Max. probability</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>
• In early 1980s, 2 water-supply systems found to be contaminated.
• Exposures occurred 1957 - 1985, then the wells were closed.
• Off-base dry-cleaner contaminated groundwater collected by on-base supply wells with PCE.
• Other contaminants included TCE, DCE, benzene, toluene and VC.
• TCE max level in drinking water was 1,400 ppb in May 1982. Current limit for TCE in drinking water is 5 ppb.
Contaminated Water Supplies at Camp Lejeune
Assessing Potential Health Effects

• Cancer
  – Esophageal, Lung, Breast, Bladder, Kidney
• Blood Diseases
  – Adult Leukemia, Multiple Myeloma, MDS
• Renal Toxicity
• Hepatic Steatosis
• Female Infertility, Miscarriage
• Neurobehavioral Effects
• Scleroderma

Natl Acad Sci’s National Research Council, 2009
Compensation

Exposure to Contaminated Drinking Water at Camp Lejeune

In the early 1980s at the Marine Corps Base in Lejeune, NC, it was discovered that two on-base water-supply systems were contaminated with the volatile organic compounds trichloroethylene (TCE), a metal degreaser, and perchloroethylene (PCE), a dry cleaning agent. Benzene, vinyl chloride, and other compounds were also found to be contaminating the water-supply systems. The water systems were contaminated from August 1953 through December 1987.

There is limited and suggestive evidence of an association between certain.
Obama signs law giving health care to Lejeune tainted water victims

President Barack Obama signed into law on Monday legislation to provide health care to thousands of sick Marine veterans and their families who were exposed to contaminated water at Camp Lejeune.
Genes

Nature

Environment

Nurture