Chronic Urticaria Is An Autoimmune Disorder: Con Position

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Objectives

- At the end of this lecture the participant will be able to:
  - Discuss the association of autoantibodies, autoimmune diseases and chronic urticaria
  - Understand the lack of functional significance of autoantibodies with chronic urticaria
  - Demonstrate the inability to differentiate treatment responses in CU patients with and without autoantibodies

What is it called when you say one thing and mean another? In a Pro/Con debate it depends

- Desultory, trivializing, mendacity - it's emotional
- Hypocrisy - it's the opposite of the truth
- Irrelevant - it's something which is not connected
- Indifference - it's a lack of interest
- Incompetence - it's a lack of ability
- Infeasible - it's something that cannot be done
- Inconsistent - it's a lack of coherency
- Hypocritical - it's something that is not true
- Hypocrisy - it's the opposite of the truth
- Irrelevant - it's something which is not connected
- Indifference - it's a lack of interest
- Incompetence - it's a lack of ability
- Infeasible - it's something that cannot be done
- Inconsistent - it's a lack of coherency
- Hypocritical - it's something that is not true

Definitions

- Autoimmune chronic urticaria or chronic autoimmune urticaria (386 refs; 1970-2013)
- Autoantibody associated chronic urticaria (78 refs; 1989-2013)
- Autologous serum skin test and chronic urticaria (167 refs; 1986-2013)
- Autologous plasma skin test and chronic urticaria (26 refs; 1988-2012)
- Chronic urticaria index (156 refs; 1977-2013)

Relevant Questions: Are Autoantibodies Relevant In CU?

- Relationship of autoimmune disorders to CU?
  - Correlations of CU index with thyroid autoantibodies?
  - Sensitivity and specificity of ASST and ASPT?
  - Utility of blood testing for autoantibodies and CU management?
  - Differences in therapeutic response in Ab+ vs. Ab- patients?
Autoantibodies and Chronic Urticaria

- Thyroid autoantibodies (95 references)
- Rheumatoid arthritis (48 references)
- Type 1 diabetes (3 references)
- Sjogren's syndrome (22 references)
- SLE (86 references)
- Celiac disease (17 references)

Evaluation of Autoantibodies In CIU

Sera from 25 patients with CIU were tested for autoantibodies and compared to 75 controls.
One patient had inflammatory bowel disease and one had multiple myeloma
- Antibodies to thyroid peroxidase and RF were increased in the CIU population but no other autoantibodies were found
- In general, non-specific autoimmunity was not identified in the CIU population

Limitations: Evidence is Still Circumstantial

This study is subject to the limitations inherent in any large population survey. To evaluate whether and which autoimmune diseases and serologic markers have the most important effect on relation to CU would require detailed information regarding the course of disease and follow-up, which is impossible in studies of this nature.


Abstract
- Seventeen patients, constituting 12.4% of 140 consecutively seen cases of chronic urticaria, demonstrated thyroid autoimmunity with thyroid microsomal antibodies (TMA) in serum titers greater than or equal to 11.6:00. Eight of these 17 patients had angioedema or thyroid dysfunction. In a control group of 477 consecutively seen patients, only 27 (5.6%) had similar TMA titers. Routine and special immunologic test results in this group of 17 patients did not differ from those found in other patients with chronic urticaria and angioedema (CUA), and the only notable clinical feature was that all 17 had angioedema. The age and sex distribution and thyroid features of these 17 patients were similar to those described in autoimmune thyroiditis. Patients (especially women) with CUA should be tested for the presence of TMA. In this subgroup, CUA may have an autoimmune basis.

SUMMARY STATEMENT 14: Numerous autoimmune disorders including thyroiditis, systemic lupus erythematosus (SLE), dermatomyositis, Sjogren's and Still's disease have been anecdotally associated with CU. (C)
IgE Mediated Autoallergy Against Thyroid Peroxidase?

<table>
<thead>
<tr>
<th>Titer of Autoantibody</th>
<th>IgE Mediated Autoallergy (n=10)</th>
<th>IgE Mediated Autoallergy (n=10)</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>8/10 (80%)</td>
<td>2/10 (20%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Negative</td>
<td>2/10 (20%)</td>
<td>8/10 (80%)</td>
<td></td>
</tr>
</tbody>
</table>


Treatment of Euthyroid Patients with CU and Thyroid Autoimmunity

- **Methods:** 15 patients with CU and thyroid autoAbs received levothyroxine + desloratidine vs desloratidine alone x 12 weeks
- **Results:** Pruritis and severity of wheals improved for both groups but no intergroup differences were observed
- **Conclusions:** Levothyroxine is not a reasonable treatment option in euthyroid patients with CU and thyroid autoimmunity


- **SUMMARY STATEMENT 16:** Thyroid autoantibodies are frequently identified in patients with CU. (C) The clinical relevance of these tests for patients with CU has not been established.

Utility of Routine Laboratory Testing In Management of Chronic Urticaria/Angioedema

- Retrospective study to investigate the proportion of abnormal test results in patients with CU leading to a change in management and in outcomes of care
- 356 CU pts seen at Cleveland Clinic


Results: 1/356 (0.28%) benefitted from testing!
• SUMMARY STATEMENT 15: Serology to diagnose underlying autoimmune diseases (e.g., connective tissue disease) is not warranted in the initial evaluation of CU. (B)

Autoantibody Associated Chronic Urticaria

Autoantibody Induced Chronic Urticaria
• 26 patients with CU were skin tested intradermally to autologous serum (0.05 ml) which elicited a wheal/flare response suggesting an autoantibody to FcεRIα subunit
• Incubation of basophils isolated from a non-atopic donor (low serum IgE) with serum from these patients demonstrated an increase in histamine release
• Passive sensitization of basophils with myeloma IgE and pretreatment with IgG fractions containing shcoklls abolished histamine release; basophils, treated with lactic acid to dissociate IgG, and then passively sensitized to serum from patients with autoantibodies to FcεRIα resulted in enhanced histamine release
• Conclusion: Proposed mechanism of autoimmune induced chronic urticaria is due to cross-linking of IgE receptors by an IgG antibody to FcεRIα resulting in release of bioactive mediators such as histamine

Autoantibody Associated Chronic Urticaria

Autoologous Serum Skin Test

ASST Shows Large Variation Of Positivity in Health Control Subjects

<table>
<thead>
<tr>
<th>Reference</th>
<th>CU</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin</td>
<td>98%</td>
<td>45%</td>
</tr>
<tr>
<td>Tedeschi et al.</td>
<td>-</td>
<td>0% (3 cases)</td>
</tr>
<tr>
<td>Sabroe et al.</td>
<td>44.51%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Akseni et al.</td>
<td>-</td>
<td>0% (20 cases)</td>
</tr>
<tr>
<td>Sabroe et al.</td>
<td>34.61%</td>
<td>2.86%</td>
</tr>
<tr>
<td>Gutman-Vassio et al.</td>
<td>53.1%</td>
<td>40.5%</td>
</tr>
<tr>
<td>Taskapan et al.</td>
<td>62.6%</td>
<td>55.55%</td>
</tr>
</tbody>
</table>


• SUMMARY STATEMENT 22: Approximately 30-50% of patients with CU produce specific IgG antibodies against FcεRIα subunit component of the high affinity IgE receptor. (C)
SUMMARY STATEMENT 23: The utility of the autologous serum skin test (ASST) and the autologous plasma skin test (APST) is unclear, as evidence has not clearly demonstrated this testing identifies a distinct subgroup of patients with CU. (C)

SUMMARY STATEMENT 32: While commercial assays are now available, the utility of testing for auto-antibodies to the high-affinity IgE receptor or auto-antibodies to IgE has not been determined. (C)
Factors That Predict The Success Of Cyclosporin Treatment For Chronic Urticaria

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>History of angioedema</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>History of atopy</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>History of childhood disease</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Use of antihistamines</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Use of systemic steroids</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Use of immunomodulators</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Use of benzodiazepines</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Use of anti-CD20 antibody</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

Assessment of Usefulness of ASST in CU

  - **Aim:** To assess frequency of ASST and determine its correlation with disease severity.
  - **Study population:** 74 CU pts (67F; mean age 43; ASST+ 43/58%)
  - **Results:** No difference between ASST+ or ASST - patients with respect to the occurrence of angioedema, duration of CU, severity score, effectiveness of AH or use of CS, cyclosporin (CsA)

Low Dose Cyclosporin A (CsA) in Treatment of Severe CU

- **Toubi E, et al. Allergy 1997;52:312-6**
  - **Aim:** To determine the safety of CsA treatment in CU patients and whether treatment is affected by an ASST.
  - **Study population:** 35 patients with severe CU
  - **Methods:** 19 treated with CsA for 3 months and observed for 3 months
  - **Results:** 13/19 went into complete remission; ASST didn't correlate with disease severity or response to treatment

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Is Omalizumab Effective For Treatment of Urticaria/Angioedema Based On Presence or Absence of Autoantibodies?

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age (yr)</th>
<th>Sex (M/F)</th>
<th>Number of cycles</th>
<th>Total score at week 8</th>
<th>Patient antibody</th>
<th>Baseline IGE (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>M</td>
<td>7</td>
<td>96</td>
<td>IgG</td>
<td>124</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>F</td>
<td>10</td>
<td>98</td>
<td>IgG</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>M</td>
<td>14</td>
<td>95</td>
<td>IgG</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>F</td>
<td>10</td>
<td>96</td>
<td>IgG</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>M</td>
<td>14</td>
<td>95</td>
<td>IgG</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>F</td>
<td>10</td>
<td>96</td>
<td>IgG</td>
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<td>96</td>
<td>IgG</td>
<td>98</td>
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**Table A:** Patient characteristics

- **SUMMARY STATEMENT 25:** There are no definitive studies which demonstrate that patients with refractory chronic urticaria and a positive ASST respond differently to certain medication regimens compared to those CU patients with a negative ASST; however, studies targeting B-cell clones producing these antibodies have not been performed. (C)
Witebsky's Postulates

- Three types of evidence is required to determine that a human disease is autoimmune in origin:
  - Direct proof (i.e., reproduction of disease by direct transfer of the antibody)
  - Indirect evidence (i.e., pathogenic T cells can be demonstrated by transfer)
  - Circumstantial evidence (i.e., family history of same disease, lymphocytic infiltrates in target organ, favorable response to immunosuppression)

Rose NR, Bona C. Immunology Today 14; 426-430.

Direct Evidence: In Vitro studies

- IgG and/or IgM against IgE – Gruber et al. 1988 (passive transfer of serum from patient with cold urticaria released histamine from healthy non-atopic donor basophils)
  - Cross species passive transfer of serum from CU patients with positive ASST to monkeys or guinea pigs not demonstrated
- IgE histamine releasing autoAbs caused histamine release from health donor basophils and mast cells which correlated with ASST – Gravett et al. 1991
  - Functional autoAbs with specificity against FcERI were identified by neutralization of histamine release activity of IgE prepared from CU sera with soluble alpha chain of FcERI – Gravett et al. 1993; Fahlberg et al. 1996.


SUMMARY STATEMENT 26: The pathogenesis of autoantibody associated urticaria remains elusive but in vitro/ex vivo studies demonstrate a role for T cells, sCD154 (sCD40 ligand) and basophil histamine responsiveness. (LB)

Indirect Evidence

- No animal models for CU
  - Rats immunized with myeloma IgE produced anti-IgE which elicited a positive intracutaneous skin test

Circumstantial Evidence

- CU association with other autoimmune diseases (thyroid, diabetes, RA...)
- Lymphocytic infiltration of target organs
  - T cells are found in the upper and mid-dermis with perivascular distribution in spontaneous CU weals and in the ASST
  - Statistical association with a specific MHC haplotype
  - Favorable response to immunosuppression but not due to the presence of absence of anti-FcER1a subunit Abs

Conclusions

• Clinical utility of the ASST or CU index as a diagnostic marker for differentiating subgroups of CU patients is weak
• Little to no evidence exists that autoantibodies will effect response to treatment
• Although of academic interest, these tests in general provide no added benefits to the management of CU patients