Characteristics of allergy in autoimmune thyroid diseases

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Relationship between allergic responses and thyroid autoimmunity

IgE levels

- IgE deposits are present in Graves’ thyroid and orbital tissues

- Elevated IgE levels associated with hyperthyroid Graves’ disease
  (Akira S et al., J Clin Endocrinol Metab 1999; 84:3602-3605.; Takashi Y et al., J Clin Endocrinol Metab 2000; 85:2775-2778.)

- Evidence of immunoglobulin E autoantibodies to thyrotropin receptor (TSH rec) and thyroid peroxidase (TPO)

Th2-derived cytokine profils

- Elevated serum levels of IL-5 and IL-13 cytokines.
  (Hidaka Y et al., Thyroid 1998; 8:235-239.; Ichiro K et al., J Clin Endocrinol Metab 2001; 86:3540-3544.)

Allergic rhinitis associated frequently with Graves’ disease

(Amino N et al., Thyroid 2003; 13:811-814.; Hidaka Y et al., Thyroid 1996; 6: 349-351.)

Common key factors regulate the immune responses in both allergic and autoimmune conditions

(Rottem M et al., Dev Immunology 2002; 9: 161-167.)
Previous results

- Graves’ ophthalmopathy associated with increased total IgE serum levels.
  

- Hyperthyroid Graves’ ophthalmopathy demonstrated elevated serum IL-5 levels compared to patients who had no eye signs.
  

- Decreased serum levels of nerve growth factor (NGF) associated with hyperthyroid Graves’ ophthalmopathy compared to those who had no eye signs.
  
  Molnár I et al., Cytokine 2006; 35: 109-114.

- A difference in the balance shift of IL-12/IL-5 between Graves’ patients with and without ophthalmopathy was demonstrated.
  
Patients and methods

- 324 patients were investigated, of whom 149 suffered from Graves’ disease (57 with ophthalmopathy), 110 had Hashimoto’s thyroiditis, and 65 euthyroid goitre formed controls.

- Allergen-specific IgE detection was carried out with immunoblot method using commercial AllergyScreen™ test (MEDIWISS Analytic GmbH, Germany) and Kodak camera was used for evaluation. The levels of thyroid hormones and antibodies were measured using commercial kits in a fully automated way, except TSH receptor antibody, that was measured with radioimmunoassay (Brahms Diagnostics, Germany).

- Chi-squared with Yates correction and Mann-Whitney nonparametric comparative tests were used for statistical analysis.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Graves’ disease n=149</th>
<th>Hashimoto’s thyroiditis n=110</th>
<th>Controls n=65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 13</td>
<td>50 ± 14</td>
<td>48 ± 13</td>
</tr>
<tr>
<td>Gender (male / women)</td>
<td>28 / 121</td>
<td>6 / 104</td>
<td>4 / 61</td>
</tr>
<tr>
<td>Duration of thyroid disease (months)</td>
<td>71 ± 81</td>
<td>44 ± 57</td>
<td>38 ± 45</td>
</tr>
</tbody>
</table>
Respiratory allergens
### Prevalence of allergic symptoms in autoimmune thyroid diseases

<table>
<thead>
<tr>
<th>Allergic symptoms</th>
<th>Graves’ disease (n=149)</th>
<th>Hashimoto’s thyroiditis (n=110)</th>
<th>Controls (n=65)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>94 (63,1%)</td>
<td>63 (57,3%)</td>
<td>54 (83,1%)</td>
<td>211 (65,1%)</td>
</tr>
<tr>
<td>Rhinitis *</td>
<td>11 a (7,4%)</td>
<td>20 a (18,2%)</td>
<td>10 (15,4%)</td>
<td>41 (12,7%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>37 b (24,8 %)</td>
<td>21 c (19,1%)</td>
<td>0 b, c</td>
<td>58 (17,9%)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>7 (4,7%)</td>
<td>5 (4,5%)</td>
<td>1 (1,5%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>1 (0,9%)</td>
<td>0</td>
<td>1 (0,3%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>149</strong></td>
<td><strong>110</strong></td>
<td><strong>65</strong></td>
<td><strong>324</strong></td>
</tr>
</tbody>
</table>

*a P < 0.014 ,  b P< 0,0001  and  c P< 0,0004 after Yates correction

*P<0,0007 after Yates correction between Graves’ patients with (n=57) and without (n=92) eye signs:32 (9,9%) vs 5 (1,5%).
The month of the onset of autoimmune thyroid diseases was similar to those characterized by the seasonal allergic attack

<table>
<thead>
<tr>
<th>Month for thyroidal onset and seasonal allergic attack is common</th>
<th>Graves’disease (n=149)</th>
<th>Hashimoto’s thyroiditis (n=110)</th>
<th>Controls (n=65)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>77 (81,9%)</td>
<td>90 (92,8%)</td>
<td>48 (78,7%)</td>
<td>215 (85,3%)</td>
</tr>
<tr>
<td>Common</td>
<td>17 (^a) (18,1%)</td>
<td>7 (^a,b) (7,2%)</td>
<td>13 (^b) (21,3%)</td>
<td>37 (14,7%)</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>97</td>
<td>61</td>
<td>252*</td>
</tr>
</tbody>
</table>

\(^a\) P < 0,04 and \(^b\) P < 0,02

* No exact data were given in 72 cases
## Prevalence of allergen-specific IgE in autoimmune thyroid diseases

<table>
<thead>
<tr>
<th>Allergen groups</th>
<th>Graves’disease (n=149)</th>
<th>Hashimoto’s thyroiditis (n=110)</th>
<th>Controls (n=65)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>D (dust mite I-II)</td>
<td>33 (22,1%)</td>
<td>25 (22,7%)</td>
<td>7 (10,8%)</td>
<td>65 (20,1%)</td>
</tr>
<tr>
<td>T (alder, birch, hazel)</td>
<td>25 \textsuperscript{a} (16,8%)</td>
<td>7 \textsuperscript{a} (6,4%)</td>
<td>6 (9,2%)</td>
<td>38 (11,7%)</td>
</tr>
<tr>
<td>W (mugwort, plantain, ragweed)</td>
<td>35 \textsuperscript{b} (23,5 %)</td>
<td>12 \textsuperscript{b} (10,9%)</td>
<td>10 (16,4%)</td>
<td>57 (17,6%)</td>
</tr>
<tr>
<td>G (grass-mixture)</td>
<td>30 (20,1%)</td>
<td>14 (12,7%)</td>
<td>7 (10,8%)</td>
<td>51 (15,7%)</td>
</tr>
<tr>
<td>E (cat, dog and others epithelia, feather-mixture)</td>
<td>40 (26,8%)</td>
<td>23 (20,9%)</td>
<td>19 (29,2%)</td>
<td>82 (25,3%)</td>
</tr>
<tr>
<td>M (molds\textsuperscript{*})</td>
<td>10 (6,7%)</td>
<td>4 (3,6%)</td>
<td>4 (6,2%)</td>
<td>18 (5,6%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>149</strong></td>
<td><strong>110</strong></td>
<td><strong>65</strong></td>
<td><strong>324</strong></td>
</tr>
</tbody>
</table>

\textsuperscript{a} P < 0,02  and \textsuperscript{b} P< 0,015  * Alternaria, Aspergillus, Cladosporium, Penicillium
Graves’ disease (n=149)
Controls (n=65)
Hashimoto’s thyroiditis (n=110)
Controls (n=65)

Dust
Alder
Birch
Hazel
Ragweed
Grass-mixture
Hamster epithelia
Dust-mite II

Prevalence of allergen-specific IgE (%)

P<0.02
P<0.05
P<0.02
P<0.04
P<0.04
P<0.01
P<0.02
P<0.02
P<0.02

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Graves’ ophthalmopathy  Hashimoto’s thyroiditis  Graves’ disease without eye signs

Allergen-specific IgE levels (IU/ml)

- **Graves’ ophthalmopathy**
- **Hashimoto’s thyroiditis**
- **Graves’ disease without eye signs**

**P < 0.04**

- (dust-mite) (alder) (birch) (hazel) (ragweed) (grass-mixture) (rye pollen) (mugwort) (hamster epithelia)
Graves' diseases without ophthalmopathy

Patient groups
- Graves' diseases without ophthalmopathy
- Graves' ophthalmopathy

Allergen-specific IgE levels (IU/ml)

Alder       Birch         Hazel     Ragweed   Grass-mixture
P<0.033

P<0.021

P<0.01

P<0.046

P<0.012

Gx

G12

E1

E5

M2

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<table>
<thead>
<tr>
<th>IU/ml</th>
<th>Class</th>
<th>Allergen-specific IgE content</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.35</td>
<td>0</td>
<td>none</td>
</tr>
<tr>
<td>0.35 – 0.69</td>
<td>1</td>
<td>low</td>
</tr>
<tr>
<td>0.7 – 3.4</td>
<td>2</td>
<td>increased</td>
</tr>
<tr>
<td>3.5 – 17.4</td>
<td>3</td>
<td>significantly increased</td>
</tr>
<tr>
<td>17.5 – 49.9</td>
<td>4</td>
<td>high</td>
</tr>
<tr>
<td>50 – 100</td>
<td>5</td>
<td>very high</td>
</tr>
<tr>
<td>&gt;100</td>
<td>6</td>
<td>extremely high</td>
</tr>
</tbody>
</table>
Allergen-specific IgE levels (IU/ml)

Patient groups

- Hyperthyroid
- Euthyroid
- Hypothyroid

Class 1-2 → 3-4

Allergens:
- dust-mite
- mite
- alder
- birch
- hazel
- ragweed
- grass-mixture
- rye pollen
- cat
- dog

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Graves’ disease

- **TSH receptor antibody antibody negative**
- **TSH receptor antibody antibody positive**

**Allergen-specific IgE levels (IU/ml)**

- **Graves’ disease**
  - dust-mite
  - alder
  - birch
  - hazel
  - ragweed
  - rye pollen
  - plantain
  - cat
  - dog
  - cladosporium
  - grass-mixture
  - mugwort
  - epithelia
  - aspergillus

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\[ P < 0.032 \]
Graves’ disease

- Anti-TPO negative
- Anti-TPO positive

(TPO: thyroid peroxidase)

Allergen-specific IgE levels (IU/ml)

Graves’ disease can involve an allergic response, with elevated IgE levels against various allergens. The graph shows the levels of IgE against different allergens in anti-TPO negative and anti-TPO positive individuals. The allergens include:

- Dust-mite
- Alder birch hazel
- Ragweed
- Rye pollen
- Plantain
- Cat dog
- Penicillium
- Aspergillus
- Grass-mixture
- Mugwort
- Epithelia
- Cladosporium

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Allergen-specific IgE levels (IU/ml)

Graves’ disease
- anti-Htg negative
- anti-Htg positive
(Htg: human thyroglobulin)

* P<0.046

- dust-mite I
- dust-mite II
- alder
- birch
- hazel
- ragweed
- grass-mixture
- rye pollen
- plantain
- mugwort
- cat epithelia
- dog epithelia

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Graves’ disease without ophthalmopathy

- anti-Htg negative
- anti-Htg positive

(Htg: human thyroglobulin)

Allergen-specific IgE levels (IU/ml)

- P<0.044
- P<0.03

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Conclusions

- Allergic rhinitis and conjunctivitis was more frequent in autoimmune thyroid diseases.
- However, the attack of allergic rhinitis was higher in Hashimoto’s thyroiditis and allergic conjunctivitis in Graves’ disease.
- Seasonal allergic attack can play as an inducer or aggravator role in the development of Graves’ disease.
- The prevalence of allergen-specific IgE levels against trees and weeds were more frequent in Graves’ disease than in Hashimoto’s thyroiditis.
- Allergen-specific IgE levels were lower in Graves’ ophthalmopathy compared to those without eye signs, as well as lower compared to Hashimoto’s thyroiditis.
- Hyperthyroidism was associated with elevated allergen-specific IgE levels resulting in a higher class degree. (Except cat epithelia.)
- The presence of antithyroid antibodies influenced the allergen-specific IgE levels. TSH receptor antibody positive and sometimes anti-thyroid peroxidase positive patients showed higher IgE levels, but anti-thyroglobulin (Htg) positivity was associated lower IgE levels, particularly in Graves’ ophthalmopathy.
- The frequent presence of allergic conjunctivitis in Graves’ disease can lead to a difficulty in the diagnosis of ophthalmopathy.
Food allergens
<table>
<thead>
<tr>
<th>Allergen groups</th>
<th>Graves’disease (n=149)</th>
<th>Hashimoto’s thyroiditis (n=110)</th>
<th>Controls (n=65)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>F17 (hazelnut)</td>
<td>13&lt;sup&gt;a&lt;/sup&gt; (8.7%)</td>
<td>1&lt;sup&gt;a&lt;/sup&gt; (0.9%)</td>
<td>2 (3.1%)</td>
<td>16 (4.9%)</td>
</tr>
<tr>
<td>F35 (potato)</td>
<td>16&lt;sup&gt;b,c&lt;/sup&gt; (10.7%)</td>
<td>3&lt;sup&gt;b&lt;/sup&gt; (2.7%)</td>
<td>1&lt;sup&gt;c&lt;/sup&gt; (1.5%)</td>
<td>20 (6.2%)</td>
</tr>
<tr>
<td>F85 (celery)</td>
<td>24&lt;sup&gt;d&lt;/sup&gt; (16.1%)</td>
<td>5&lt;sup&gt;d&lt;/sup&gt; (4.5%)</td>
<td>4 (6.2%)</td>
<td>33 (10.2%)</td>
</tr>
<tr>
<td>F31 (carrot)</td>
<td>25&lt;sup&gt;e&lt;/sup&gt; (16.8%)</td>
<td>6&lt;sup&gt;e&lt;/sup&gt; (5.5%)</td>
<td>4 (6.2%)</td>
<td>35 (10.8%)</td>
</tr>
<tr>
<td>F25 (tomato)</td>
<td>10&lt;sup&gt;f&lt;/sup&gt; (6.7%)</td>
<td>1&lt;sup&gt;f&lt;/sup&gt; (0.9%)</td>
<td>0</td>
<td>11 (3.4%)</td>
</tr>
<tr>
<td>F33 (orange)</td>
<td>17&lt;sup&gt;g,h&lt;/sup&gt; (11.4%)</td>
<td>3&lt;sup&gt;g&lt;/sup&gt; (2.7%)</td>
<td>1&lt;sup&gt;h&lt;/sup&gt; (1.5%)</td>
<td>21 (6.5%)</td>
</tr>
<tr>
<td>F4 (wheat flour)</td>
<td>22&lt;sup&gt;i&lt;/sup&gt; (14.8%)</td>
<td>4&lt;sup&gt;i&lt;/sup&gt; (3.6%)</td>
<td>3 (4.6%)</td>
<td>29 (9%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>149</td>
<td>110</td>
<td>65</td>
<td>324</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < 0.01, <sup>b</sup> P < 0.03, <sup>c</sup> P < 0.04, <sup>d</sup> P < 0.01, <sup>e</sup> P < 0.01, <sup>f</sup> P < 0.03, <sup>g</sup> P < 0.02, <sup>h</sup> P < 0.03 and <sup>i</sup> P < 0.01 with Yates corrections.
Graves’ disease (n=149)  Controls (n=65)  
Graves’ disease without (n=92)  
Graves’ disease with ophthalmopathy (n=57)  
Hashimoto’s thyroiditis (n=110)  Controls (n=65)  

Allergen-specific IgE levels (IU/ml)  

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Graves’ disease</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F85 celery</td>
<td>P&lt;0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F31 carrot</td>
<td>P&lt;0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F35 potato</td>
<td>P&lt;0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F31 carrot</td>
<td>P&lt;0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F16 walnuts</td>
<td>P&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Allergen-specific IgE levels (IU/ml)

- **Patient groups**
  - Hyperthyroid
  - Euthyroid
  - Hypothyroid

### Results

- **F16 walnuts**
- **F35 potato**
- **F85 celery**
- **F31 carrot**
- **F33 orange**
- **F4 wheat flour**
- **F5 rye meal**
- **F14 soybeans**

* P<0.04

* ImmunSum, Baltimore, 2014
Graves’ disease

- TSH receptor antibody negative
- TSH receptor antibody positive

Allergen-specified IgE levels (IU/ml)

- hazelnuts
- paelnuts
- walnuts
- milk
- casein
- potato
- celery
- carrot
- tomato
- creb
- orange
- apple
- wheat flour
- rye meal
- Soybeans

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Graves’ ophthalmopathy

- TSH receptor antibody negative
- TSH receptor antibody antibody positive

Allergen-specific IgE levels (IU/ml)

- hazelnuts
- milk
- potato
- celery
- carrot
- tomato
- orange
- apple
- wheat flour

Soybeans

* P<0.045

ImmunSum, Baltimore, 2014
Graves’ disease

- anti-TPO negative
- anti-TPO positive

(TPO: thyroid peroxidase)

<table>
<thead>
<tr>
<th>Allergen</th>
<th>ImmunoSum, Baltimore, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>hazelnuts</td>
<td></td>
</tr>
<tr>
<td>paelnuts</td>
<td></td>
</tr>
<tr>
<td>walnuts</td>
<td></td>
</tr>
<tr>
<td>milk</td>
<td></td>
</tr>
<tr>
<td>casein</td>
<td></td>
</tr>
<tr>
<td>potato</td>
<td></td>
</tr>
<tr>
<td>celery</td>
<td></td>
</tr>
<tr>
<td>carrot</td>
<td></td>
</tr>
<tr>
<td>tomato</td>
<td></td>
</tr>
<tr>
<td>orange</td>
<td></td>
</tr>
<tr>
<td>apple</td>
<td></td>
</tr>
<tr>
<td>wheat flour</td>
<td></td>
</tr>
<tr>
<td>rye meal</td>
<td></td>
</tr>
<tr>
<td>Soybeans</td>
<td></td>
</tr>
</tbody>
</table>

Allergen-specific IgE levels (IU/ml)
Graves’ disease

- **anti-Htg negative**
- **anti-Htg positive**

(Htg: human thyroglobulin)

<table>
<thead>
<tr>
<th>Allergen</th>
<th>anti-Htg negative</th>
<th>anti-Htg positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>hazelnuts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>milk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>potato</td>
<td></td>
<td></td>
</tr>
<tr>
<td>celery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>carrot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tomato</td>
<td></td>
<td></td>
</tr>
<tr>
<td>orange</td>
<td></td>
<td></td>
</tr>
<tr>
<td>apple</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wheat flour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rye meal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soybeans</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ImmunSum, Baltimore, 2014
<table>
<thead>
<tr>
<th>TSH levels (µU/ml)</th>
<th>FT4 levels (ng/dl)</th>
<th>FT3 levels (pg/ml)</th>
<th>TSH receptor antibody levels (IU/l)</th>
<th>Anti-TPO antibody levels (IU/l)</th>
<th>Anti-Htg antibody levels (IU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F78</td>
<td>0</td>
<td>5</td>
<td>P&lt;0.024</td>
<td>P&lt;0.001</td>
<td>P&lt;0.007</td>
</tr>
<tr>
<td>M1</td>
<td>0</td>
<td>5</td>
<td>P&lt;0.013</td>
<td>P&lt;0.003</td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td>0</td>
<td>5</td>
<td>P&lt;0.03</td>
<td>P&lt;0.013</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>0</td>
<td>5</td>
<td>P&lt;0.01</td>
<td>P&lt;0.013</td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td>0</td>
<td>5</td>
<td>P&lt;0.03</td>
<td>P&lt;0.013</td>
<td></td>
</tr>
<tr>
<td>M6</td>
<td>8</td>
<td>9</td>
<td>P&lt;0.042</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>W6</td>
<td>6</td>
<td>7</td>
<td>P&lt;0.021</td>
<td>P&lt;0.004</td>
<td></td>
</tr>
<tr>
<td>F14</td>
<td>3</td>
<td>4</td>
<td>P&lt;0.03</td>
<td>P&lt;0.007</td>
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</tr>
<tr>
<td>F16</td>
<td>2</td>
<td>3</td>
<td>P&lt;0.01</td>
<td>P&lt;0.004</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- Food allergen-sensitization was more frequent in Graves’ disease compared to that in Hashimoto’s thyroiditis, and it can affect our daily meals.

- Allergen-specific IgE levels were higher in Graves’ disease, but lower in Hashimoto’s thyroiditis than controls.

- Hyperthyroidism was associated with elevated allergen-specific IgE levels.

- Anti-thyroid antibodies influenced the degree of IgE levels:
  1. TSH receptor and anti-TPO antibody levels were associated with higher IgE levels. (Except milk and casein allergens).
  2. Anti-Htg antibody levels were connected to lower IgE levels.
Thank you for your attention!

This study contains works of
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