A familial connection between mast cell disorders, EDS and dysautonomia

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What is serum Tryptase?

• A mast cell content that we can measure when mast cells become activated

• When is it high typically?
  – After an allergic reaction (anaphylaxis)– only temporarily
  – Mastocytosis- having too many mast cells
  – Mast cell activation syndromes (MCAS)
AD familial tryptasemia: 30 families and counting

Familial hypertryptasemia

- **Skin**
  - Recurrent flushing, itching, swelling, hives

- **Connective Tissue**
  - Joint laxity, retained childhood teeth, scoliosis, etc.

- **Allergy**
  - Anaphylaxis, Bee sting allergy, nonallergic food, drug and smell reactions

- **Gastrointestinal**
  - Episodic pain, fecal urgency, IBS, reflux, dysmotility, gallbladder issues

- **Neuropsychiatric**
  - Dysautonomia, Anxiety/Depression, Pain, Behavior issues

Prevalence of high tryptase in the general population

$n = 420$

- Mean: 5.6 µg/L
- Geometric mean: 5.8 µg/L
- Median: 5.1 µg/L
- Range: <1-30.7 µg/L
- 2.5th percentile: 1.4 µg/L
- 97.5th percentile: 14.4 µg/L

4.3% ($n = 18$): >11.4 µg/L

Table 2  Symptoms of 100 patients with elevated basal serum tryptase (BST) and 100 controls. Patients were additionally divided into two groups (slightly elevated BST 11.4–20.0 ng/ml and BST >20 ng/ml).

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>(\chi^2)-Test patients vs. controls</th>
<th>Frequency rate&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BST ≥ 11.4 ng/ml</td>
<td>BST 11.4–20.0 ng/ml</td>
<td>BST &gt;20.0 ng/ml</td>
<td>BST ≥ 11.4 ng/ml</td>
</tr>
<tr>
<td>Number (male/female)</td>
<td>100 (32/68)</td>
<td>81 (26/55)</td>
<td>19 (6/13)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Frequency of symptoms</strong></td>
<td></td>
<td></td>
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<tr>
<td>Fatigue</td>
<td>56%</td>
<td>56%</td>
<td>58%</td>
<td>37%</td>
</tr>
<tr>
<td>Meteorism&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42%</td>
<td>41%</td>
<td>47%</td>
<td>15%</td>
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<tr>
<td>Headache</td>
<td>37%</td>
<td>37%</td>
<td>32%</td>
<td>38%</td>
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<tr>
<td>Muscle and bone ache</td>
<td>36%</td>
<td>36%</td>
<td>42%</td>
<td>16%</td>
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<tr>
<td>Swinging mood</td>
<td>36%</td>
<td>32%</td>
<td>47%</td>
<td>19%</td>
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<tr>
<td>Vertigo</td>
<td>31%</td>
<td>30%</td>
<td>37%</td>
<td>8%</td>
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<tr>
<td>Tachycardia</td>
<td>29%</td>
<td>28%</td>
<td>32%</td>
<td>10%</td>
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<tr>
<td>Flush</td>
<td>25%</td>
<td>25%</td>
<td>26%</td>
<td>7%</td>
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<tr>
<td>Acid reflux</td>
<td>24%</td>
<td>25%</td>
<td>21%</td>
<td>15%</td>
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<tr>
<td>Palpitations</td>
<td>23%</td>
<td>22%</td>
<td>26%</td>
<td>8%</td>
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<tr>
<td>Pruritus</td>
<td>22%</td>
<td>22%</td>
<td>21%</td>
<td>18%</td>
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<tr>
<td>Diarrhoea&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22%</td>
<td>20%</td>
<td>32%</td>
<td>8%</td>
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<tr>
<td>Hypotension</td>
<td>18%</td>
<td>16%</td>
<td>26%</td>
<td>7%</td>
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<tr>
<td>Abdominal pain&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18%</td>
<td>16%</td>
<td>26%</td>
<td>7%</td>
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<tr>
<td>Angio-oedema</td>
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<td>16%</td>
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<tr>
<td>Nausea</td>
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<td>14%</td>
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<td>4%</td>
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<td>Urticaria</td>
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<td>4%</td>
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<tr>
<td>Collapse</td>
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<td>9%</td>
<td>11%</td>
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<td>0%</td>
<td>0%</td>
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<tr>
<td>Rash</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>3%</td>
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<tr>
<td>Vomiting</td>
<td>4%</td>
<td>4%</td>
<td>5%</td>
<td>1%</td>
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</tbody>
</table>

<sup>a</sup> The frequency rate refers to how much more frequently a certain symptom occurs in patients compared to controls.

<sup>b</sup> Patients with fructose malabsorption and/or lactose intolerance were excluded. Fellinger et al. *Allergol Immunopathol.* 2014
How do we treat these families?

• Very similar to mast cell activation syndrome patients
  – Antihistamines (e.g. allegra), ranitidine (zantac), cromolyn sodium (gastrocrom), aspirin, omalizumab (xolair), steroids
  – Biofeedback
  – Consult with GI, genetics, cardiology (for dysautonomia)
Concluding points

- A specific syndrome of high tryptase, symptoms of mast cell activation, EDS-like symptoms and dysautonomia can run in families in a dominant fashion.
- Many of these symptoms can be seen in families who do not have elevated serum tryptase.
- Our ongoing research is to find the single genetic cause of this, in the hopes of identifying a target to treat.
- In the meantime, management is symptomatic, not magic!
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