WHEAT ALLERGY
A rising problem in the Asia-Pacific

Outline

- Wheat as a common food allergen
- Epidemiology of wheat allergy
  - Age
  - Varying manifestations
- Diagnosis of wheat hypersensitivities
- Difficulty in management
- Tolerance to wheat

Food allergy

- Food allergies affect 6% of young children
- Eight major causative foods: eggs, milk, soy, peanuts, seafood and wheat
Causative food of immediate type food allergy

US:
1) Milk
2) Egg
3) Peanut

Japan:
1) Egg
2) Diary product
3) Wheat


Immediate-type food allergy in Japan

Fig. 1 Causative foods of immediate-type food allergy (national surveys by the Ministry of Health and Welfare during 1996-1999).

Urisu et al. Allergology International 2011;60: 221-236

Immediate-type food allergy in Japan

Table 2 Causative foods of immediate-type food allergy by age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Egg</th>
<th>Shrimp</th>
<th>Peanut</th>
<th>Milk</th>
<th>Diary product</th>
<th>Fish</th>
<th>Wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>84.4%</td>
<td>21.1%</td>
<td>9.4%</td>
<td>68.0%</td>
<td>12.1%</td>
<td>9.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>2-5 years</td>
<td>84.4%</td>
<td>21.1%</td>
<td>9.4%</td>
<td>68.0%</td>
<td>12.1%</td>
<td>9.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>6-10 years</td>
<td>84.4%</td>
<td>21.1%</td>
<td>9.4%</td>
<td>68.0%</td>
<td>12.1%</td>
<td>9.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>84.4%</td>
<td>21.1%</td>
<td>9.4%</td>
<td>68.0%</td>
<td>12.1%</td>
<td>9.0%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

Urisu et al. Allergology International 2011;60: 221-236
Wheat Allergy - epidemiology

- In 2 studies from UK and 1 from Germany positive wheat challenges were seen in 0.5% of children (Zuidmeer JACI et al 2008)
- In Finland wheat allergy was physician-diagnosed in 0.9% of children aged 1-4 yrs (Pyrhonen et al PAI 2009)
- In Japan estimated prevalence of wheat allergy to school children = 0.2-0.4% (Imai 05 and Urisu 11)

Manifestations

- IgE-mediated immediate symptoms (minutes to 2 hrs after ingestion
  - Skin: urticaria, angioedema
  - Resp: wheezing
  - GI: vomiting, abdominal pain
  - systemic anaphylaxis
  - Atopic dermatitis
- Delayed reactions: include gastrointestinal symptoms and worsening of atopic dermatitis

Symptoms of wheat allergy among 103 patients at Johns Hopkins

Anaphylaxis

Results of Food challenge in AD patients at Johns Hopkins

<table>
<thead>
<tr>
<th>Food</th>
<th>DEPCIC</th>
<th>Open Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Eggs</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Peanuts</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Beef</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chicken</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pork</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Grains</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Turkey</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tangerine</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>13</td>
<td>7</td>
</tr>
</tbody>
</table>

Eigenmann et al Pediatrics 1998;101:1

Food Anaphylaxis

- **Australia, US, UK**: Peanut, Tree nuts, Seafood

- **Japan (2008)**: 319 patients
  - Milk 69.3%, Egg 45.1%, **wheat 28.8%**

- **Korea (2008)**: 29 patients
  - Wheat 20.7%, Buckwheat 13.8%, Seafood 13.8%

- **Thai (2007)**: 24 patients
  - Seafood 45.8%, **Wheat 8.3%**
Self-reported anaphylaxis in Japan


Wheat anaphylaxis in Thailand


Classification of gluten related disorder

Gluten related disorders

Pathogenesis

Autoimmune

- Celiac disease
- Gluten ataxia
- Dermatitis Herpetiformis

Allergic

- Wheat allergy
- Respiratory allergy
- Food allergy

Not autoimmune, not allergic

- Gluten sensitivity
- Wheat-dependent, exercise-induced anaphylaxis
- Contact urticaria

Segonne et al. BMC Medicine 2012;10:13
A Thai boy, 9-year-old

CC: rash and drowsiness after exercise 5 days PTA
PI: 3 years PTA- rash and dyspnea after exercise
   1 year PTA- rash and fainting after exercise  → admitted ICU
   5 days PTA- rash, dyspnea, drowsiness  → admitted ICU

- PH: No history of atopic diseases, no history of food allergy
  Physical examination
  V/S- stable
  Other systems- Within normal limits
  Provisional diagnosis
  Exercise induced anaphylaxis

Challenge protocol

<table>
<thead>
<tr>
<th>Day</th>
<th>Type of challenge</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Exercise</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>Wheat</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>Pizza then exercise</td>
<td>Anaphylaxis</td>
</tr>
</tbody>
</table>

Skin prick test:
Histamine: 8X6 mm
Wheat: 10X6 mm
Pizza: 5X5 mm
Wheat-dependent, exercise induced anaphylaxis!

Food-dependent, exercise-induced anaphylaxis

167 Japanese FDEIA cases
Peak: 2nd and 4th decade
Men>women

Triggering factors
- Food
- Exercise
- General condition (fatigue, common cold, stress, menstruation)
- Drugs (aspirin and NSAIDs)
- Alcohol

Wheat-dependent, Exercise-induced Anaphylaxis in Thai Children

Table 1: Clinical characteristics of the patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Age at onset (years)</th>
<th>No. of allergies</th>
<th>Anaphylaxis History</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>Male</td>
<td>3</td>
<td>2</td>
<td>AD, AG</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>Male</td>
<td>14</td>
<td>4</td>
<td>No, No</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Male</td>
<td>6</td>
<td>4</td>
<td>No, No</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>Male</td>
<td>7</td>
<td>13</td>
<td>No, No</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>Female</td>
<td>16</td>
<td>1</td>
<td>No, No</td>
</tr>
</tbody>
</table>

Table 2: Excessive food, symptoms, and signs of anaphylaxis and onset of symptoms after food ingestion

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Foods</th>
<th>Skin</th>
<th>Respiratory</th>
<th>GI</th>
<th>Hypersensitive</th>
<th>Duration after food ingestion (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bread, Macaroni, Pizza</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>Pasta, Insect</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>Grater</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>10-30</td>
</tr>
<tr>
<td>4</td>
<td>Bread</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>20</td>
</tr>
</tbody>
</table>

Wheat allergen and pathogenesis

Wheat protein

- **Albumins**: water-soluble
- **Globulins**: salt-soluble
- **Gliadins**: ethanol-soluble
- **Glutenins**: alkali/acid-soluble
- **ω-5 gliadin (Tri a 19)**: major allergen in Wheat-dependent, exercise-induced anaphylaxis
Pathogenesis

Wheat-dependent, exercise-induced anaphylaxis
- IgE-mediated hypersensitivity
- Most of patients: positive result for skin prick test and RAST test for wheat.
- Exercise → enhance absorption of allergen?

Whole peptic digest of α-5 gliadin

Tissue transglutaminase (tTG)
- Enzyme in gut epithelium
- Released and activated after stress-like condition
- Forming complex with digested gliadin

SPT to peptic fraction B of α-5 gliadin

- Digested gliadin forms peptide → Cross-linked to tTG → HMW complex → Strong binding serum IgE Ab

IgE antibody level to \( \alpha-5 \) gliadin

<table>
<thead>
<tr>
<th>Immediate</th>
<th>Delayed</th>
<th>Negative</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.6</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>0.8</td>
<td>2.0</td>
<td>3.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>


### Diagnosis

### History

- Wheat is hidden in various kinds of food.
- Food labeling is neglected by sellers and customers.
- Sometimes need more than one factor to trigger symptoms.
**Diagnosis: RAST**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat CAP RAST (&gt;26 KU/L)</td>
<td>61%</td>
<td>92%</td>
<td>74%</td>
<td>87%</td>
</tr>
<tr>
<td>Wheat CAP RAST (&gt;100 KU/L)</td>
<td>13%</td>
<td>100%</td>
<td>100%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Sampson H A. J Allergy Clin Immunol 2001;107: 107-8

**Predictive capacity**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-5 gliadin ELISA (&gt;0.04 AU)</td>
<td>84%</td>
<td>100%</td>
<td>100%</td>
<td>88%</td>
</tr>
<tr>
<td>Wheat CAP RAST (&gt;0.35 KU/L)</td>
<td>95%</td>
<td>67%</td>
<td>72%</td>
<td>93%</td>
</tr>
<tr>
<td>Wheat SPT wheal Diameter (3mm)</td>
<td>89%</td>
<td>71%</td>
<td>74%</td>
<td>88%</td>
</tr>
</tbody>
</table>


**ω-5 gliadin level and wheat allergy**

Management

- Wheat avoidance!!!

Management

- Wheat-dependent, exercise-induced anaphylaxis
  - Avoidance of exercise ~ 4Hrs after wheat ingestion.
  - Avoidance of wheat after intake of aspirin and COX-1 inhibitors
  - Education, e.g., Epinephrine injection, reading food labels
Natural history

- Retrospective review of 103 children with IgE-mediated wheat allergy
- Age at initial visit 11-42 months
- Male 66%
- Associated atopic hx
  - Eczema 87%, Asthma 67%, Allergic rhinitis 60%
- Family history of atopy 75%
- 63% underwent food challenge


Peak wheat IgE level VS persistence of wheat allergy


Relationship between peak wheat IgE and tolerance

Natural history

- 28 children in Finland
- Age <1 to 8 months
- 75% had IgE-mediated wheat allergy by SPT to wheat and gliadin
- 25% had non-IgE-mediated wheat allergy
- Milk allergy 60%
- Anaphylaxis to milk (2) egg (2)


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Natural history

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 years</td>
<td>59%</td>
</tr>
<tr>
<td>6 years</td>
<td>69%</td>
</tr>
<tr>
<td>10 years</td>
<td>84%</td>
</tr>
<tr>
<td>16 years</td>
<td>96%</td>
</tr>
</tbody>
</table>

Gliadin SPT ≥5mm: median age of tolerance = 4.61 years
Gliadin SPT <5mm: median age of tolerance = 3.65 years
* Gliadin SPT ≥5mm associated with slow recovery (p=0.019)


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Specific oral tolerance induction (SOTI)

- **Indication:**
  1. Severe reactions to food proven by challenge
  2. History of accidental exposures recently
  3. Unable to avoid food on daily life
  4. Age limit beyond natural acquisition of tolerance to particular food
Specific Oral Tolerance Induction (SOTI)

- Thai boy 4 year-old
- Repeated episodes of anaphylaxis from wheat since 9 months of age
- SPT for wheat weal = 6X5 mm
- sIgE for wheat >100kUA/L
- Never ate any thing out of the home-cooked food
- 3 episodes of wheeze, turning dusky, hypotension in the last year

Wheat anaphylaxis in a Thai boy

- Parents requested something to be done other than avoidance
- Specific tolerance induction – carried out
- Provocative dose = 300 mg
- Start SOTI from 150mg
- 1st admission – passed @ dose 500mg
- 2nd admission → passed @ dose 10 gm

Specific Oral Tolerance Induction (SOTI)

<table>
<thead>
<tr>
<th></th>
<th>sIgE for wheat (kAU/L)</th>
<th>ω-5 gliadin (kAU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before SOTI</td>
<td>518</td>
<td>37.8</td>
</tr>
<tr>
<td>1 month after SOTI</td>
<td>325</td>
<td>25.1</td>
</tr>
</tbody>
</table>

15 gm/piece

40 gms/pack
Cross-reactivity among cereals?

**Cereals**

- Wheat
- Rye
- Barley
- Oat

Ovaltine, Corn flakes, Honey, Barley, Wheat, Coix cooked, Coix raw, Milo
WDEIA

- γ-70 and γ-35 secalins in rye
- γ-3 hordein in barley
- Cross-react
- ω-5 gliadin in wheat

Conclusion

- IgE mediated allergy from wheat is becoming an alarming problem around the world
- Varieties of presentation with wheat allergy
- Lack of diagnostic parameter
- Avoidance can be very tough
- Development of tolerance may be the solution

Thank you