Seafood Allergy

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Disclosure

- I am not a marine biologist, neither a SEAFOOD allergist by training
- Main interest was dust mites and now is in wheat allergy
- No vested interest in this topic
Seafood as a significant part of everyday’s life in the Asia Pacific
Seafood - major economic foods for exportation for the Asia Pacific esp fishes and shrimps
Bangkok – the ‘Shrimp Heaven’
Category of Seafood

• Fishes
  • Bony fishes
  • Cartilaginous fishes

• Shellfishes – crustaceans and molluscs
  • Crustaceans – shrimps, crabs
  • Molluscs – clams, mussel, cockles, abalone, squid
Commonly consumed fishes in Thailand

- Mackerel
- Giant Mackerel
- Pomfret
- Striped snakehead fish
- Catfish
- Threadfin fish
My Favorites – the Perciformes

ปลานิล Nile Tilapia – Oreochromis niloticus

ปลากระพง Silver perch, Bass
Barramundi

ปลากระพงทอดมะนาว
Fried Perch with lemon

ปลากระพงทอดมะนาว
Steamed Tilapia with lemon

ปลากระพงทอดมะนาว
Fried Perch with lemon
Fish allergy

• Prevalence of fish allergy
  • Norway – self-reported 3% almost as common as egg allergy
  • USA – random telephone survey – 0.4% - Sicherer 2004
  • Asia - Singapore 0.26%, Thailand 0.29%, Phillipines 2.29%
    • (Connett and Shek et al., Int Arch Allergy Immunol 2012)
    • Questionnaire based – 14-16 year-old children surveyed

• Common age of presentation:
  • unknown – thought to occur in older children and adults
  • In Thailand – very young age – at the time grandma introduce fish with rice – less than 1 year of age
Symptoms of allergy to fish

- Symptoms
  - ‘Typical symptoms of fish allergy – mild GI tract, vomiting, diarrhea, abd pain’
  - Thailand – symptoms were more severe
    - angioedema and urticarial
    - anaphylaxis
  - Can occur by inhalation of fish vapors
Box 1. Key features of all fish allergy

Usually presents between 9 and 12 months of age, often associated with other food allergies

Symptoms on first ingestion, which may include contact urticaria

Usually first contact with white fish (hake, megrim) Urticaria, rash, worsening of atopic dermatitis, and delayed symptoms even with vapor

Diagnosis is via clinical history; skin prick tests and/or serum fish-IgE positivity

Food challenge is necessary if relationship with species is not well established

## Table 3. Occurrence of symptoms of convincing fish allergy

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Philippines (n = 262) (%)</th>
<th>Singapore (n = 17) (%)</th>
<th>Thailand (n = 6) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hives</td>
<td>217 (83)</td>
<td>8 (47)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Throat itchiness</td>
<td>98 (37)</td>
<td>6 (35)</td>
<td>0</td>
</tr>
<tr>
<td>Lips swelling</td>
<td>73 (28)</td>
<td>6 (35)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Coughing</td>
<td>43 (16)</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Throat tightness</td>
<td>43 (16)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>40 (15)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28 (11)</td>
<td>3 (18)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>28 (11)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22 (8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LOC</td>
<td>21 (8)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>20 (8)</td>
<td>1 (6)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Eyes swelling</td>
<td>19 (7)</td>
<td>2 (12)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>19 (7)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

LOC = Loss of consciousness.
Types of fishes causing allergy

• Depending of geographical and cultural differences
• First extensive study – Baltic cod – Gad C1 – 1st parvalbumin
• Europe and USA
  • Spain – hake, megrim
  • USA – salmon, tuna, catfish, cod
• Asia – anchovy, mackerel scad
  • Singapore – threadfin, pomfret, tengiri, indian anchovy
  • Thailand – short-bodied mackerel, pomfret, tilapia, silver perch, threadfin, ATLANTIC SALMON
• Recommended testing to cover most spectrum of parvalbumin
  • Atlantic salmon, Pacific pilchard, European hake, Atlantic cod (Lopata 2014)
Major Fish Allergen – the parvalbumin

- Major fish allergen - parvalbumin (12kDa)
  - Calcium-regulating protein in fish muscle – found more in white meat
  - Heat-stable – can be vaporized
  - α and β (1-3) isoforms
  - Monomeric vs oligomeric
  - Secondary and tertiary structures
- Cross-reactivity among fishes
  - Vast amino acid differences
  - 50% cross-reactivities
  - 1/3 to ½ of patients will be multi-fish allergy

Roman numbers – site of IgE-binding epitopes
Most important – region IV – conformational epitope

Parvalbumin – major tropical fish allergen in tropical region

• Survey of 7850 children in Singapore
• Only 10 patients allergic to fish (0.12%)
• Types of tropical fish studied
  • Threadfin
  • Pomfret
  • Indian anchovy
  • Tengiri
• SPT, SDS-Page, immunoblot (IgE), inhibition assays
• Also reagent from cod (Gad C1) was used
• 6/10 recognized parvalbumin from cod
• Suggest that IgE to cod may be used
• Avoidance to all fishes is recommended

Lim and Lee et al. Ped Allergy Immunol 2008;19:399
### Table 2. Clinical Characteristics of Singaporean fish-allergic subjects and tropical fish specific IgE levels

<table>
<thead>
<tr>
<th>Pt</th>
<th>Onset age</th>
<th>Tropical fish that elicited reaction</th>
<th>Other fish that elicited reaction</th>
<th>Fish clinically tolerated</th>
<th>Cod SPT</th>
<th>slgE</th>
<th>TF SPT</th>
<th>slgE</th>
<th>IA SPT</th>
<th>slgE</th>
<th>PO SPT</th>
<th>slgE</th>
<th>TE SPT</th>
<th>slgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 months</td>
<td>IA, PO</td>
<td>Nil</td>
<td>Not tried</td>
<td>+</td>
<td>37.7</td>
<td>+</td>
<td>45.6</td>
<td>+</td>
<td>61.4</td>
<td>+</td>
<td>42.4</td>
<td>-</td>
<td>18.0</td>
</tr>
<tr>
<td>2</td>
<td>6 months</td>
<td>TF, IA, PO</td>
<td>Cod, Snapper</td>
<td>Not tried</td>
<td>+</td>
<td>&lt;0.35</td>
<td>-</td>
<td>&lt;0.35</td>
<td>-</td>
<td>&lt;0.35</td>
<td>-</td>
<td>&lt;0.35</td>
<td>+</td>
<td>&lt;0.35</td>
</tr>
<tr>
<td>3</td>
<td>6 months</td>
<td>TF</td>
<td>Nil</td>
<td>IA, PO, TE</td>
<td>+</td>
<td>2.22</td>
<td>-</td>
<td>0.99</td>
<td>-</td>
<td>&lt;0.35</td>
<td>-</td>
<td>2.57</td>
<td>+</td>
<td>&lt;0.35</td>
</tr>
<tr>
<td>4</td>
<td>10 months</td>
<td>IA</td>
<td>Hoki</td>
<td>Not tried</td>
<td>+</td>
<td>2.36</td>
<td>+</td>
<td>2.21</td>
<td>+</td>
<td>3.09</td>
<td>+</td>
<td>2.45</td>
<td>+</td>
<td>0.80</td>
</tr>
<tr>
<td>5</td>
<td>6 months</td>
<td>IA</td>
<td>Cod, Dory</td>
<td>Not tried</td>
<td>+</td>
<td>&lt;0.35</td>
<td>-</td>
<td>&lt;0.35</td>
<td>+</td>
<td>0.50</td>
<td>+</td>
<td>0.43</td>
<td>+</td>
<td>&lt;0.35</td>
</tr>
<tr>
<td>6</td>
<td>3yr</td>
<td>TF, IA</td>
<td>Nil</td>
<td>Not tried</td>
<td>+</td>
<td>42.6</td>
<td>+</td>
<td>38.5</td>
<td>+</td>
<td>71.2</td>
<td>+</td>
<td>35.1</td>
<td>+</td>
<td>19.0</td>
</tr>
<tr>
<td>7</td>
<td>7 months</td>
<td>IA, PO, TE</td>
<td>Cod</td>
<td>TF</td>
<td>+</td>
<td>1.86</td>
<td>+</td>
<td>&lt;0.35</td>
<td>+</td>
<td>3.53</td>
<td>+</td>
<td>3.08</td>
<td>-</td>
<td>0.62</td>
</tr>
<tr>
<td>8</td>
<td>1yr</td>
<td>nil</td>
<td>Tuna, Salmon</td>
<td>PO</td>
<td>+</td>
<td>0.93</td>
<td>-</td>
<td>&lt;0.35</td>
<td>-</td>
<td>1.26</td>
<td>-</td>
<td>1.13</td>
<td>+</td>
<td>0.45</td>
</tr>
<tr>
<td>9</td>
<td>10 months</td>
<td>IA, TF</td>
<td>Flounder</td>
<td>PO</td>
<td>+</td>
<td>0.42</td>
<td>+</td>
<td>0.52</td>
<td>+</td>
<td>0.98</td>
<td>-</td>
<td>&lt;0.35</td>
<td>+</td>
<td>&lt;0.35</td>
</tr>
<tr>
<td>10</td>
<td>5 yr</td>
<td>TF, IA, PO</td>
<td>Nil</td>
<td>Not tried</td>
<td>+</td>
<td>12.3</td>
<td>+</td>
<td>31.5</td>
<td>+</td>
<td>1.69</td>
<td>-</td>
<td>8.02</td>
<td>+</td>
<td>1.13</td>
</tr>
</tbody>
</table>

TF, threadfin; IA, Indian anchovy; PO, pomfret; TE, tengirri; SPT, skin prick test (a wheal of 3 mm or more above the negative control was taken as a positive result); slgE, specific immunoglobulin E as measured by UniCAP (kU/l).
Shellfish - Crustaceans

- Crustaceans
  - Shrimps and crabs
  - Phylum arthropoda, Subphylum crustacean
  - Prawn vs shrimp – perhaps the same

- Allergens may relates phylogenetically to insect (such as cockroach) and arachnids (such as dust mites)

- Wide varieties of consumable crustaceans exists
  - Sea water shrimp - Panaieds– eg Panaeus (aztecus – brown, monodon – black tiger)
  - Fresh water shrimp – Carideans – eg – Macrobrachium rosenbergii – giant fresh water shrimp

Lee and Lee et al. Asian Pac J Allergy Immunol 2012;30:3-10
Sea-water vs fresh-water shrimp

Paneus monodon กุ้งกุลา

Macrobrachium rosenbergii กุ้งแม่เน่า
Small white leg shrimp – *Litopenaeus vannamei*

Famous Thai Shrimp-fried rice

Famous Thai Shrimp-Pud Thai

Litopenaeus vannamei – white leg shrimp
Shrimp allergy

• Prevalence
  • USA – 6-7 year old children – 0.7%
  • Asia – Philippines and Singapore – teenagers – around 5% (Shek 2010)

• Age of occurrence
  • Older than fish allergy – around 6-7 years of age

• Symptoms
  • Common cause of serious anaphylaxis
  • Oral allergy syndrome can be observed

Shek et al. J Allergy Clin Immunol 2010;126:324
Sicherer et al. J Allergy Clin Immunol 2004;114:159
• Skin prick test – commercial vs fresh preparation
  • Commercial shrimp extract - Low NPV up to 30% (Jirapongsananuruk 2008)
  • Fresh extract recommended – the ‘Prick-to-prick’ test
  • Size of skin test
    • The ‘Hill’s’ standard - 8 mm
    • the Thai study 27 mm for shrimp was suggested for 90% PPV!!!
• Specific IgE – the Immunocap
  • Shrimp – f24 – mixed shrimp
  • Up to 27 fishes have been catalogued
    • Cut off – not adequately determined – particularly with tropical fishes
• Molecular diagnosis – advance made - CRD for shrimp
• Food challenge – not adequately studied
  • For definite diagnosis
  • To determine cross-reactivities
  • To determine acquisition of tolerance
60 patients with + history and + SPT to shrimp were subjected to challenges to both *Paneus* and to *Macrobrachium*:

- **Group I** – positive only to *P monodon* 12 (17.6%)
- **Group II** – positive only to *M rosenbergii* – 16 (23.5%)
- **Group III – positive to both** – 32 (47%)
- **Group IV** – negative to both – 8 (11.7%)

Species-specific allergy to shrimp can be seen.

Shrimp allergens – Group I to IV

- **Group I** – Tropomyosin – MW 35-45 KDa – wide homology between shrimp and also to insects and arachnids (Der p 10 and Per a 7)
- **Group II** – Arginine kinase - 40 kDa
- **Group III** – Myosin light chain (MLC) – 20 kDa from Litopaneus vannamei
- **Group IV** – Sarcoplasmic calcium-binding protein (SCP)
Shellfish tropomyosins

• 36 kDa actin filament binding proteins with 332 aa
• Function in contractile activity of muscle cells
• Originally described as Pen i-l
• Several tropomyosin from other shrimp species were described
  • Pen a l
  • Met e l
  • Also major allergens from P monodon and M rosenbergii
• Tropomyosin inhibits 85% of IgE reactivity in most patients – major allergen

Fig. 3 Molecular model of the shrimp tropomyosin [119]. Structure of M. ensis tropomysin predicted by homology modeling. Two alpha-helical chains run in a parallel orientation to form a two-stranded coiled

Molecular diagnosis of shrimp allergy

**FIGURE 1.** Frequency of IgE recognition of recombinant allergens per group. Histogram showing the frequency of IgE recognition per protein and per group, expressed as percentages (%). *SCP*: Sarcoplasmic calcium-binding protein, α and L-beta; *TM*: tropomyosin; *Hemo*: hemocyanin; *FABP*: fatty-acid-binding protein; *MLC*: myosin light chain; *AK*: arginine kinase; *TpC*: troponin C (-GC, -L1, -L2).
Decision-making scheme for shrimp allergy

FIGURE 2. Flow diagram for shrimp allergy diagnosis. Suggested protocol using allergenic components for examining patients who are initially found sensitized to shrimp by a skin prick test regardless of whether they report allergic symptoms or not. For each test outcome the absolute number of real shrimp allergic (Shr A, subjects diagnosed by positive challenge or recent anaphylactic reaction; n = 58) and shrimp tolerant (Shr T, subjects with negative challenge; n = 28) subjects is provided.
Multiple epitopes of tropomyosin recognized by shrimp allergic patients

Ayuso et al. J Allergy Clin Immunol 2010;125"1286
Hemocyanin as a novel allergen from Macrobrachium rosenbergii

Immunoblot of Mr-sensitive patients to Mr-purified Hcs

Piboonpocanun et al. Mol Nutr Food Res 2011;55:1492

Figure 3. (A) SDS-PAGE analysis of Hc in hemolymph of three crustacean species: shrimp *Pm: P. monodon*, shrimp *Mr: M. rosenbergii* and mud crab *Ss: S. serrata*, after dialysis (D) in
Shellfish - Molluscs

- **Asian green mussel**
- **Oyster – Thai style**
- **Blood cockle - Tegillarca granosa**
- **Oyster – New Orleans style**
- **Surf clam**
- **Scallop**
Allergy to molluscs

- Molluscs
  - Bivalvia (scallop, clam, mussel, cockles, oysters)
  - Gastropoda (limpet, abalone)
  - Cephalopoda (squid, octopus, cuttlefish)

- Less studied than the crustaceanas

- Symptoms – similar to crustacean allergy

- Major allergens
  - Tropomyosin – cross reacting with crustacean – major allergens
  - Paramyosin (100 KdA) – myofibrillar protein
  - 40 kDa protein identified from Korea

Challenges for Seafood Allergy

- Improvement of diagnosis
  - Better diagnostic reagents for SPT and in vivo testing (SpIgE and CRD)
  - Better algorithm for diagnosis
  - Establish protocol for food challenge

- Strategy for avoidance
  - All vs species-specific
  - Cross-reactive species

- Research on natural history seafood allergy – on-going

- Food Labeling
  - Problem = method of measuring sea food allergens in various foods

- Oral immunotherapy
  - Indication for OIT - 2 considerations
    - Mitigate reaction from accidental exposure – desensitization – low dose OIT
    - Sustained unresponsiveness – ad lib consumption
  - Efficacy and safety of the protocol
  - Production of hypoallergenic allergens
  - Use of biologics in aiding OIT
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APAAACI
APAPARI
12-15 November
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