WHEAT ALLERGY

A rising problem in the Asia-Pacific

Punchama Pacharn, MD
Pakit Vichyanond, MD
Department of Pediatrics,
Siriraj Hospital, Mahidol University
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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

Figure 1: The "Big Eight" Allergens: Tree Nuts, Peanuts, Soy, Egg, Milk, Fish, Wheat and Shellfish.

Causative food of immediate type food allergy

US.
1) Milk
2) Egg
3) Peanut

Liu et al. J Allergy Clin Immunol 2010;126:798-806

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

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

Immediate-type food allergy in Japan

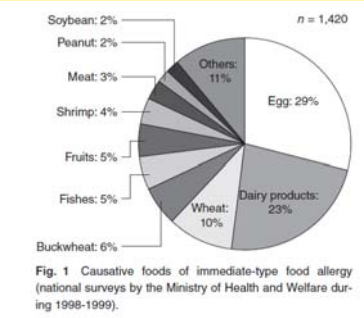


Fig. 1 Causative foods of immediate-type food allergy (national surveys by the Ministry of Health and Welfare during 1998-1999).

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

Immediate-type food allergy in Japan

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

	0 year (*n* = 416)	1 year (*n* = 237)	2-3 years (*n* = 289)	4-6 years (*n* = 140)	7-19 years (*n* = 207)	>20 years (*n* = 131)
No. 1	Egg 47.4%	Egg 30.4%	Egg 30.8%	Egg 25.0%	Buckwheat 14.0%	Seafood 16.0%
No. 2	Dairy products 30.8%	Dairy products 27.8%	Dairy products 24.2%	Dairy products 24.3%	Shrimp 13.0%	Shrimp 14.5%
No. 3	Wheat 9.6%	Wheat 8.4%	Wheat 12.1%	Wheat 8.6%	Wheat 10.6%	Buckwheat 12.2%
Total	87.8%	66.6%	67.1%	57.9%	37.6%	42.7%

Urisu et al. Allergology Iternational 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

Palosuo K. Update on wheat hypersensitivity. Curr Opin Allergy Clin Immunol 2003: 3: 205–9.

Symptoms of wheat allergy among 103 patients at Johns Hopkins

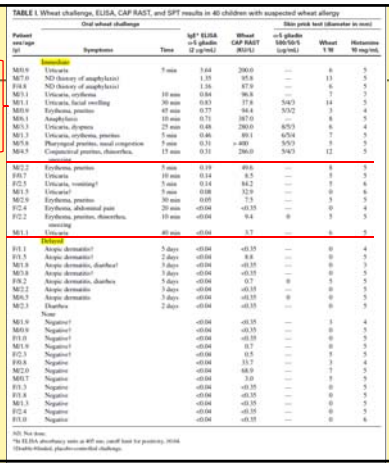
Table 2. Types of Wheat Reactions

Reaction type	No. (%) of patients
Symptoms at presentation (N = 103)	
Skin (except eczema)	31 (30)
Eczema	23 (22)
Gastrointestinal	12 (12)
Lower respiratory tract	11 (11)
Upper respiratory tract	4 (4)
Oral erythema	3 (3)
No exposure or unclear history	42 (41)
Symptoms with unintentional exposures (N = 88)	
Skin (except eczema)	51 (58)
Eczema	8 (9)
Gastrointestinal	12 (14)
Lower respiratory tract	36 (41)
Upper respiratory tract	11 (13)
Oral erythema	4 (5)
Anaphylaxis[a]	40 (45)

[a] Two or more body systems or lower respiratory tract involvement.

Keet et al. RA. Ann Allergy Asthma Immunol.2009;102(5):410–415

Anaphylaxis



Palosuo JACI 2001;108:734

Results of Food challenge in AD patients at Johns Hopkins

TABLE 2. Results of Food Challenges in 19 Patients

Food	DBPCFC		Open Challenge	
	Positive	Negative	Positive	Negative
Egg	4	3	1	4
Milk	3	7		
Soy	0	4	0	2
Wheat	3	2	0	1
Barley	2	0		
Oat			1	1
Beef	1	0	1	0
Chicken	0	3	0	1
Pork	0	2	1	0
Green beans	0	1		
Turkey	0	1		
Tangerine			1	0
Totals	13	23	5	9

Eigenmann et al Pediatrics 1998;101:1

Food Anaphylaxis

- **Australia, US, UK**
  : Peanut, Tree nuts, Seafood
  Bock SA, et al. J Allergy Clin Immunol 2001;107:191-193, Pumphrey, et al. J Allergy Clin Immunol2007;119:1018-1019
  Liew WK, et al. J Allergy Clin Immunol 2009;123:434-442
- **Japan (2008):** 319 patients
  - Milk 69.3%, Egg 45.1%, **wheat 28.8%**
  Imamura, et al. Pediatr Allergy Immunol2008;
- **Korea (2008):** 29 patients
  - **Wheat 20.7%, Buckwheat 13.8%,** Seafood 13.8%
  Yang et al. Ann Allergy Asthma Immunol2008;100:31-36
- **Thai (2007):** 24 patients
  - Seafood 45.8%, **Wheat 8.3%**
  Jirapongsananuruk et al. Ann Allergy Asthma Immunol 2007;98:157-162

Self-reported anaphylaxis in Japan

Table 2. Allergens related to self-reported anaphylaxis in Japan

Allergen	Number	Percentage of study patients (319 patients) (%)
Milk	221	69.3
Eggs	144	45.1
Wheat	92	28.8
Peanuts	27	8.5
Sesame	25	7.8
Kiwi fruit	13	4.1
Soybean	13	4.1
Buckwheat	11	3.4
Shrimps	9	2.8
Walnuts	9	2.8
Gelatine	9	2.8
Bananas	9	2.8
Salmon roe	7	2.2
red sea bream	6	1.9
Tuna	5	1.6
Others	119	37.3
Unknown	66	20.7
	785	

Imamura, et al. Pediatr Allergy Immunol 2008;18:270

Wheat anaphylaxis in Thailand

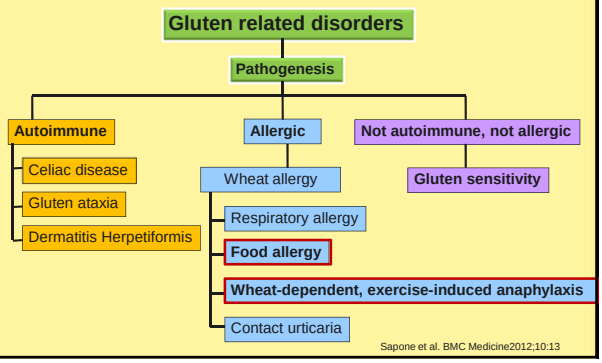
Table 1. Clinical findings in seven children with wheat-induced anaphylaxis

Patient sex/age*	Atopy	Causative food	Attacks in a year	Systemic symptoms	Treatment with epinephrine
1. M/13 (14) years	–	Bun, noodle	3	ANA, URT	+
2. F/6 months (4 years)	SPT+	Cake, macaroni	3	ANA	+
3. M/4 (8) years	–	Pizza, bun	3	ANA, URT	+
4. M/7 (20) months	–	Bread, noodle	4	ANA, URT	+
5. F/3 (14) years	SPT+	Bread	2	ANA	+
6. M/7 (24) months	AE	Bread	2	ANA, URT	+
7. M/7 (12) years	SPT+	Cracker	10	ANA, URT	+

* Onset of symptoms, in parenthesis age at diagnosis.
ANA, anaphylaxis (angioedema on the lips and face, bronchospasm and collapse); URT, generalized urticaria; AE, atopic eczema/dermatitis syndrome; SPT+, skin prick test positive (patient number 2, egg, fish, shrimp, peanut, house-dust mite; patient number 5 cockroach; patient number 7 egg).

Daengsuwan T, et al. *Allergy 2005:60;506-509*

Classification of gluten related disorder



Sapone et al. BMC Medicine2012;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

1year PTA- rash and fainting after exercise → admitted ICU

5days 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

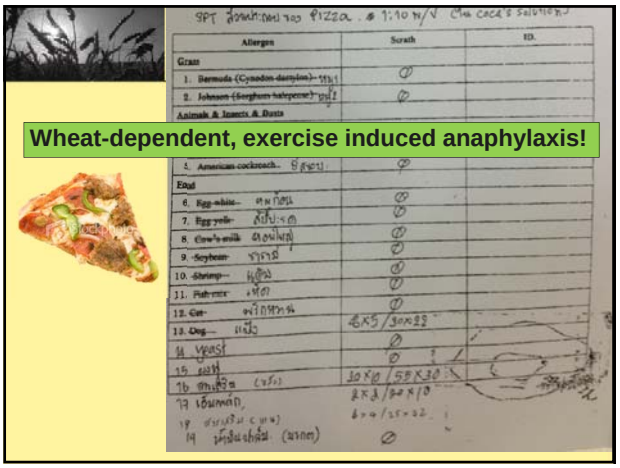
Provisional diagnosis

Exercise induced anaphylaxis

Challenge protocol

Day	Type of challenge	Result
1	Exercise	Negative
2	Wheat	Negative
3	Pizza then exercise	Anaphylaxis

Skin prick test:
Histamine: 8X6 mm
Wheat: 10X6 mm
Pizza: 5X5 mm

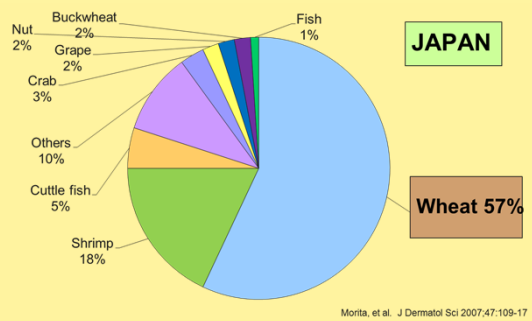


Food-dependent, exercise-induced anaphylaxis

- 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

Morita et al. Journal of Dermatological Science (2007) 47, 109—117

Food-dependent, exercise-induced anaphylaxis



Morita, et al. J Dermatol Sci 2007;47:109-17

Wheat-dependent, Exercise-induced Anaphylaxis in Thai Children

Table 1 Clinical characteristics of the patients

Patient no.	Age (years)	Sex	Age at onset (years)	No. of attack/year	Atopic history	
					Personal	Family
1	8	Male	5	2	AD, AS	AR (M*)
2	14	Male	14	4	No	No
3	10	Male	9	4	No	No
4	12	Male	7	10	No	No
5	11	Female	10	1	No	No

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

Patient no.	Foods	Symptom and sign				Duration after food ingestion (minutes)
		Skin	Respiratory	GI	Hypotension	
1	Bread, Macaroni	Y	Y	N	N	15
2	Pizza	Y	Y	Y	N	30
3	Pizza, bread	Y	Y	N	Y	30
4	Cracker	Y	Y	N	Y	10-30
5	Bread	Y	N	Y	Y	30

Y, yes; N, no.

Pacharn P, et al. APJAI (2009) 27:115-120

Wheat allergen and pathogenesis

Wheat protein

- **Albumins:** water-soluble
- **Globulins:** salt-soluble
- **Gliadins:** ethanol-soluble
- **Glutenins:** alkali/acid-soluble

Gluten

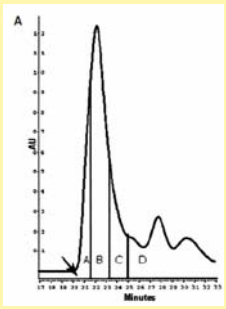
ω-5 gliadin (Tri a 19): major allergen in Wheat-dependent, exercise-induced anaphylaxis

Pathogenesis

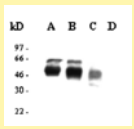
Wheat-dependent, exercise-induced anaphylaxis

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

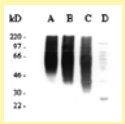
Whole peptic digest of ω-5 gliadin



Before



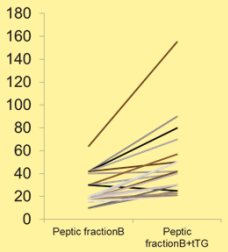
After

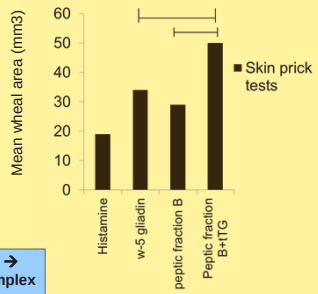


Tissue transglutaminase (tTG)
- Enzyme in gut epithelium
- Released and activated after stess-liked codition
- Forming complex with digested gliadin

Palosuo, et al. J Allergy Clin Immunol2003;111:1386-92

SPT to peptic fraction B of ω-5 gliadin

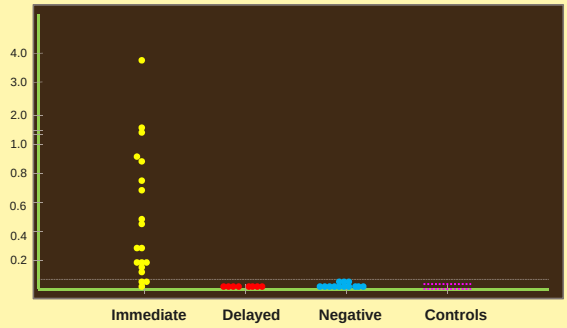




- **Digested gliadin forms peptide → Cross-linked to tTG → HMW complex → Strong binding serum IgE Ab**

Palosuo, et al. J Allergy Clin Immunol2003;111:1386-92

IgE antibody level to ω-5 gliadin



Palosuo, et al. J Allergy Clin Immunol 2001;108: 63

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

	Sensitivity	Specificity	PPV (%)	NPV (%)
Wheat CAP RAST (>26 KU/L))	61%	92%	74%	87%
Wheat CAP RAST (>100KU/L)	13%	100%	100%	76%

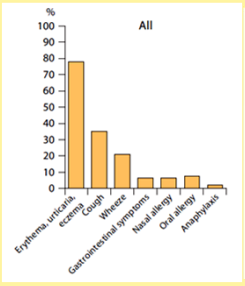
Sampson HA. J Allergy Clin Immunol 2001;107: 891-6

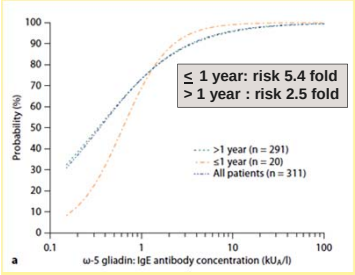
Predictive capacity

	Sensitivity	Specificity	PPV (%)	NPV (%)
ω-5 gliadin ELISA (>0.04 AU)	84%	100%	100%	88%
Wheat CAP RAST (>0.35 KU/L)	95%	67%	72%	93%
Wheat SPT wheal Diameter (3mm)	89%	71%	74%	88%

Palosuo, et al. J Allergy Clin Immunol 2001;108: 634-8

ω-5 gliadin level and wheat allergy





Ebisawa, et al. Int Arch Allergy Immunol2012;158:71-76

Management

Management

- Wheat avoidance!!!

Management

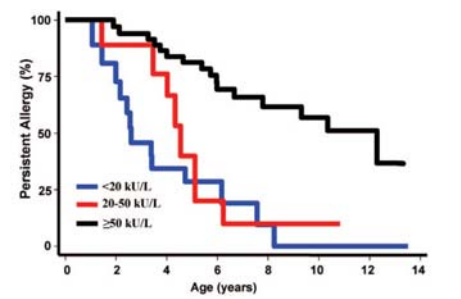
- **Wheat-dependent, exercise-induced anaphylaxis**
  - Avoidance of exercise ~ 4Hrs after wheat ingestion.
  - Avoidance of wheat after intake of aspirin and COX-1 inhibitors
- Education, e.g.,Epinephrine injection, reading food labels

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

Keet et al. Ann Allergy Asthma Immunol2009;102:410-415

Peak wheat IgE level VS persistence of wheat allergy



Keet et al. Ann Allergy Asthma Immunol2009;102:410-415

Relationship between peak wheat IgE and tolerance

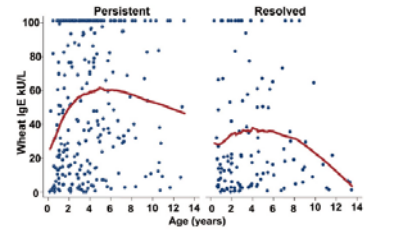


Figure 2. The relationship of wheat IgE level to age. The blue dots show the scatterplot of all wheat IgE levels recorded to the age of 14 years for those patients with (A) persistent wheat allergy (266 values) and (B) resolved wheat allergy (124 values). The red lines depict the locally weighted running means (Lowess curves) of wheat IgE level by age (bandwidth, 0.8).

Keet et al. Ann Allergy Asthma Immunol2009;102:410-415

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 nonIgE-mediated wheat allergy
- Milk allergy 60%
- Anaphylaxis to milk (2) egg (2)

Kotaniemi-Syrjanen, et al. Pediatr Allergy Immunol 2010;21:e421-e428

Natural history

Age (years)	Tolerance
4 years	59%
6 years	69%
10 years	84%
16 years	96%

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)**

Kotaniemi-Syrjanen, et al. Pediatr Allergy Immunol 2010;21:e421-e428

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)

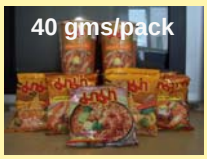
- Thai boy 4 year-old
- Repeated episodes of anaphylaxis from wheat since 9 months of age
- SPT for wheat wheal = 6X5 mm
- sIgE for wheat >100kUA/L
- Never ate any thing out of the home-cooked food
- 3 episodes of wheeze, turning dusky, hypotension in the last year

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)

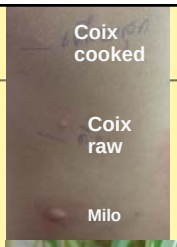
	sIgE for wheat (kAU/L)	ω-5 gliadin (kAU/L)
Before SOTI	518	37.8
1 month after SOTI	325	25.1



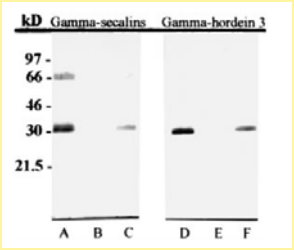
Cross-reactivity among cereals??

Cereals

- Wheat
- Rye
- Barley
- Oat



WDEIA



RYE BARLEY

- γ-70 and γ-35 secalins in rye
- γ-3 hordein in barley

↓ Cross-react

ω-5 gliadin in wheat

Palosuo et al. Clin Exp Allergy 2001;31:466-73

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