Diagnostics in allergy

Wise choises

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content

• Definitions
• Pathogenesis allergy
• What to test in de lab
• Skinprick and provocation
• Component resolved diagnostics
• Conclusions
Why diagnostics in allergy

• Very annoying; sneezing, itching, eczema
• Severe complaints
• Analphylactic shock

• Find out what is the cause
Foodallergy

What % is allergic to some type of food?

• Less than 4%
• 4-10%
• More than 10%
Foodallergy

What % is allergic to some type of food?

- Less than 4%
- 4-10%
- More than 10% thinks so,

Hence they try a diet that might not be beneficiary
Symptoms with allergic reactions

**perception vs reality:**
- Perception of allergy: 20%
  - Children: 3-5%
  - Adults: 2-4%

**Other causes of complaints:**
- Infectious (salmonella, parasite)
- Intolerance (lactase deficiency/lactose intolerance)
- Toxic (poisoning) or pharmacologic (caffeine)
- NON-IgE mediated (celiac disease)

**Symptoms food allergy:**
- Airways: 20%
- Skin: 60-70%
- Gastrintestinal: 20%

**Symptoms inhalation allergy:**
- Nose (rhinitis), eyes (conjunctivitis)
- Airways (asthma like)
- Skin
What is an allergic reaction?

What does NOT fit the diagnosis allergy

A. Hypersensitivity to peanuts
B. Reaction to insect sting
C. Coeliaky
D. Lactose-intolerance
E. heyfever
F. Reaction to drugs
G. Rhinitis at contact with cats
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Hypersensitivity vs IgE-allergy

**Hypersensitivity**

**Immunologic hypersensitivity**
- IgE mediated
  - Insect sting
  - Drugs (ASA, penicillines)
  - parasites
  - other
- Atopic: Food, Inhaled allergens

**NON-IgE mediated**
- T-cell mediated (type IV, celiac disease)
- IgG mediated (type III, allergic alveolitis)
- oesinophil mediated (oesinophil gastroenteritis)
- other

**NON-allergic hypersensitivity**
- no immunologic mechanism
  - Examples:
    - Perfume, chloride, Na-glutamate, detergents, toxic levels of drugs due to CYP-mutations (poor metabolizer)

**Other**

- Insect sting
- Drugs (ASA, penicillines)
- parasites
- other
Hypersensitivity

Allergische reacties worden in vier typen ingedeeld:

- **Type I** → direct type (5-20 min) → IgE + mastcell / basophils
- **Type II** → cytotoxic (ADCC) (2-4 hr) → IgM / IgG + targetcell
- **Type III** → immune complex diseases (4-6 hr) → IgG + circulating antigen
- **Type IV** → Delayed Type Hypersensitivity (48-72 hr) → Cellular
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Drugs might be IgE mediated, come to that later
Case 1

• A 4-yr old boy visits your practice
• He blew up a balloon on his birthday and got swollen lips...
• It is his first contact with latex
• What will you do?
Case 1

- Nothing, it is his first contact so allergic reaction ruled out
- Total IgE
- I will ask for a RAST at the lab
**Pathogenesis**: 3 phases

**Sensibilisation:**
First recognition of allergen (exposition)

**Latent phase:**
clonal expansion of sensitised lymphocytes and production of specific antibodies (sIgE i.c.o. type I)

**Effector phase:** de immune reactivity upon contact with allergen → tissue damage
Clue with this boy

• It was his first balloon, BUT

His father is a dentist and works with latex gloves
Via contact he has inhaled latex particles earlier on
Anamnesis in allergy

- Is of extreme importance!
- First contact with allergen?
- Other contacts with allergen
- Type of reaction
- Timing of reaction

- Nothing, it is his first contact so allergic reaction ruled out
- Total IgE
- I will ask for a RAST at the lab
limited value of total IgE

- Atopic pts have high IgE
- Low/normal tIgE does not rule out
- High tIgE does not confirm
- No information on specific IgE
RAST has become sIgE

- Means Radio-Allergo-Sorbent-Test
- Name of a formerly used technique

However... the lab does not know to WHAT allergen you mean
Diagnostics in Allergy

Anamnesis

In vitro diagnostics

In vivo diagnostics

Provocation testing
All about anamnesis

- Ask about exposure
- Ask about time to complaint
- Ask about type of complaint
- Then decide about diagnostics

Lab tests
Skin prick tests
Provocation tests
Laboratory diagnosis

- Laboratory tests:
  - total IgE
  - specific IgE (formerly known as RAST: radio-allergo-sorbent-test)
  - screening panels (inhalation mix, food mix)
  - other mixes (nuts, trees, grasses, molds etc)
  - components (component resolved diagnostics)
  - ISAC (multiplex array)
Case 2

• Rosa is coming to you with weeks of sneezing and rhinitis. Few weeks ago they got a rabbit.
• You decide to perform a lab test
• Which?
Case 2 Rosa

- Total IgE
- Inhalation screening
- sIgE against rabbit
What is in the Alatop?
What is in de Alatop

Alatop (Curaçao):

- **Allergens:**
  - Dandermix ex1: *dog, cat, cow, horse dander*
  - Weedmix wx1: *Ambrosia artemisiifolia (A. elatior), Artemisia vulgaris, Plantago lanceolata, Chenopodium album, Salsola kali*
  - Mix of grasses gx2: *Cynodon dactylon, Lolium perenne, Phleum pratense, Poa pratensis, Sorghum halepense, Paspalum notatum*
  - Mix of housedustmites and cockroache hx2:
    *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Blatella germanica*
  - Moultmix mx1: *Penicillium chrysogenum, Cladosporium herbarum, Aspergillus fumigatus, Alternaria alternate*
  - Mesquite *Prosopis juliflora* t20 pollen of the juliflora-tree

- **No rodent-dander**
Sequential analyses

**Inhalation panel (Alatop)**
(see previous slide)

- **Screening for sensitisation:**
  - Inhalationmix: IgE to most seen allergies analysed at once.
  - if positive separate allergen(mixes) are tested for

- No atopy
- Positive? > 0.35 kU/L
- Test for separate IgE
- No atopy found
Case 2 Rosa

• Anti-Rabbit sIgE <0.35 kU/L
• Inhalationmix positive
• Developed complaints in season for grasses

• Why would you perform inhalation screening?
Case 2 Rosa

Sensitisation to inhalation allergens is a risk factor for the development of asthma
Case 3 Robert

- Robert complaints of itching eczema
- His mother asks you whether it could be a food allergy
- Would you perform a food IgE?
Desired answer is “no”
Case 3 Robert

- Eczema makes the skin thin
- Losing barrier function
- Making sensitisation likely, without it being the cause
What is in the food mix?
What is in the food mix?

Food mix (non specific):

- **Allergens:**
  - Egg white
  - Cow milk
  - Cod fish
  - Barley
  - Soybean
  - Peanut
Sequential analyses

Food panel (fx5)  
(see previous slide)

No atopy

Positive?  
> 0.35 kU/L

Yes

Test for separate IgE

No

sensitisation

Yes

Positive?

No

No atopy found

• Screening for sensitisation:
  • foodmix : IgE to most seen allergies analysed at once (especially in children).
  • if positive separate allergens are tested for
When would you request food mix?

Some considerations:
- sIgE measures sensitisation not allergy
- Height of sensitisation relates to allergy but for different allergens at different levels
- When you want to exclude
- When you want to confirm
## Result classes

<table>
<thead>
<tr>
<th>Class</th>
<th>KU/l</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.35</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.7</td>
<td>Weak positive</td>
</tr>
<tr>
<td>2</td>
<td>0.7-3.5</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.5-17.5</td>
<td>Strong positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-50</td>
<td>Strong positive</td>
</tr>
<tr>
<td>5</td>
<td>50-100</td>
<td>Strong positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;100</td>
<td>Strong positive</td>
</tr>
</tbody>
</table>

More than 80% asymptomatic
Skin prick test or provocation?
POUSA / PAUZE / BREAK

Unless you want to continue?
Let’s get back to the drug related allergies
What is an allergic reaction?

What does NOT fit the diagnosis type I (sIgE) allergy

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B. Reaction to insect sting
C. Celiac disease
D. Lactose-intolerance
E. heyfever
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G. Rhinitis at contact with cats

Drugs might be IgE mediated, come to that later
Diagnostic options depend on ...

Table 1 - Hypersensitivity reactions in beta-lactam allergies

<table>
<thead>
<tr>
<th>Gel-Coombs classification</th>
<th>Mechanism</th>
<th>Examples of adverse reactions to penicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Anaphylactic (IgE-mediated)</td>
<td>Acute anaphylaxis, urticaria</td>
</tr>
<tr>
<td>II</td>
<td>Complement cytolysis (IgG/IgM)</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interstitial nephritis</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Lesion by immune-complexes</td>
<td>Serum disease</td>
</tr>
<tr>
<td></td>
<td>Drug fever</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Some rashes and vasculitis</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Late or cell-mediated hypersensitivity</td>
<td>Contact dermatitis</td>
</tr>
<tr>
<td></td>
<td>Morbilliform rashes</td>
<td></td>
</tr>
</tbody>
</table>
In analphylaxis search for cause
How to find the cause

Disadvantage (sIgE)

• No assay for mastcellactivation
• sIgE disappears (no exposure to drug)
• Low sensitivity (for drugs)
• Not all drugs have available “tests”
There is SPT and provoked testing

Figure 1 - Flow chart for the evaluation of type 1 hypersensitivity drug reactions.
Legend: (+) positive; (-) negative or unavailable
Open provocation for drug-related hypersensitivity

- Culprit-drug diagnosis
- Pnt is not on (culprit) drug
- Under specialised conditions due to risk for analphylaxis
Pro’s and con’s SPT

Advantages sIgE
• Only 1 venapuncture
• Independent of the medical condition (independent of drug use)
• Standaardised resultats
• No risk of analphylaxis
• Additional requests from same venapuncture
• All ages

Advantages (SPT)
• Patient directly sees result
• Representative of mastcell activation and degranulation
• Low avidity antibodies will also give positive result

Disadvantages: no standardised extracts available; no medication use allowed, rather invasive
Open and blinded provocation test

Advantages provocation over sIgE/SPT:
End-organ damage is tested
And now for something new:

• Components in type I allergy
<table>
<thead>
<tr>
<th>Indien allergisch voor:</th>
<th>Risico van allergische reactie op tenminste één van de</th>
<th>Risico in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>een peulvrucht</td>
<td>pinda, andere peulvruchten, erwten, linzen, bonen</td>
<td>5%</td>
</tr>
<tr>
<td>een noot</td>
<td>walnoot, andere noten, paranoot, cashew, hazelnoot</td>
<td>37%</td>
</tr>
<tr>
<td>een vis</td>
<td>zalm, andere vissen, zwaardvis, tong</td>
<td>50%</td>
</tr>
<tr>
<td>een schaaldier</td>
<td>garnaal, andere schaaldieren, krab, kreeft</td>
<td>75%</td>
</tr>
<tr>
<td>een graan</td>
<td>tarwe, andere granen, gerst, rogge</td>
<td>20%</td>
</tr>
<tr>
<td>Koemelk</td>
<td>rundvlees, hamburger</td>
<td>10%</td>
</tr>
<tr>
<td>Koemelk</td>
<td>geitenmelk</td>
<td>92%</td>
</tr>
<tr>
<td>Koemelk</td>
<td>paardenmelk</td>
<td>4%</td>
</tr>
<tr>
<td>Pollen</td>
<td>berk, ambrosia, fruit, groenten, appel, perzik, meloen</td>
<td>55%</td>
</tr>
<tr>
<td>Perzik</td>
<td>andere rosaceae, appel, pruim, kers, peer</td>
<td>55%</td>
</tr>
<tr>
<td>Meloen</td>
<td>ander fruit, watermeloen, banaan, avocado</td>
<td>92%</td>
</tr>
<tr>
<td>Latex</td>
<td>fruit, kiwi, banaan, avocado, latex, handschoenen</td>
<td>35%</td>
</tr>
<tr>
<td>Fruit</td>
<td>kiwi, banaan, avocado, latex, handschoenen</td>
<td>11%</td>
</tr>
</tbody>
</table>

Clinical implications of cross-reactive food allergy. Dr. S.H. Sicherer, with permission from Elsevier.
Components in allergic substances

- Allergenic component A: present in different allergenic substances
- Allergenic component B: specific for allergenic substance
- Allergenic component C: cross reactive component
Components in allergic substances

Low risk of serious reaction

High risk of serious clinical reaction

Cross reactive carbohydrate determinants (sugars)
How can we use components

- Investigate clinical relevant from irrelevant sensitisations (nuts, soybean, peanut)
Hazelnuts components

- Cor a 1: homologous to Bet v1
  - Instable (digestion and heat)

- Cor a 8: lipid transfer protein (LTP)
  - Resistent to digestion and heat
  - Sensitized patients experience serious clinical complaints
  - Mediterrenian (North of Europe often have Cora14)

- Cor a 9: 11 s globulin
  - In 86% serious clinical complaints
  - Crossreactivity with other nuts
different components in peanuts
Bee/Wasp sting

When bee (i1) and wasp (i3) are both positive

• Bee: Api m1
• Wasp: Ves v1 and Ves v5

can be tested for.

It useless to desensitize for both allergens
In conclusion

It all starts with anamnesis

- Lab tests (sIgE)
- Skin prick tests
- Provocation tests
Masha danki pa bosnan atenshon!

"Bit of a bummer really, you've got a nut allergy"