INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	18
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Anaphylactic Shock

Anaphylaxis : **ana** means not, **phylaxis** means protection

Dr. Richet was asked by prince Albert to study effect of Portuguese man-of-war toxin on living animals. (Early 1900s) , he did the experiment on dogs by injecting them with a protein from this animal and with the second injection they had a systemic fatal reaction rather than a protective reaction (prophylaxis)
This is similar to the immunization Dr. Edward Jenner did but it was fatal

Acute systemic anaphylaxis

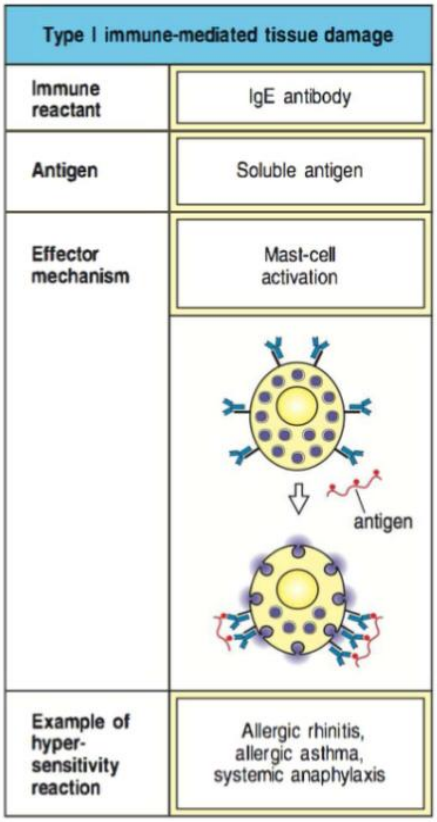
Is a medical emergency and the most urgent of clinical immunological events; it requires immediate therapy otherwise you will lose the patient.

Type 1 hypersensitivity IgE mediated that can be fatal

It results from the generation and release of a variety of potent biologically active mediators and their concerted effects on an number of target organs

Typically involves at least 2 organ systems of the body (skin, GIT,CNS,CVS)

The disseminated effects on the circulation and on the respiratory system are the most dangerous and localized swelling of the upper airways can cause suffocation



Types of Allergens

-Food such as Peanut, dairy products and shellfish

- Protein antigens found in latex (a common constituent of gloves)

-Insect venoms

-Medications such as Penicillin which contains hapte

Note: Hapten is a small incomplete non protein antigen that elicit an immune response only when attached to a large carrier such as a protein; the carrier may be one that also does not elicit an immune response by itself

IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs Serum Venoms	Intravenous (either directly or following oral absorption into the blood)	Edema Vasodilation Tracheal occlusion Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Insect bites Allergy testing	Subcutaneous	Local increase in blood flow and vascular permeability
Allergic rhinitis (hay fever)	Pollens (ragweed, timothy, birch) Dust-mite feces	Inhaled	Edema of nasal mucosa Irritation of nasal mucosa
Allergic asthma	Danders (cat) Pollens Dust-mite feces	Inhaled	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Shellfish Milk Eggs Fish Wheat	Oral	Vomiting Diarrhea Pruritus itching Urticaria (hives) Anaphylaxis (rarely)

Routes of Entry to the Body

**systemically*; IV, IM or subcutaneous .

**Ingested* (orally)

**Inhaled* (respiratory route)

Allergens introduced systematically are most likely to cause a serious clinical anaphylactic reaction through the activation of sensitized connective tissue mast cells . Ingested antigens cause a variety of symptoms through acting on mucosal mast cells.

Mechanism

Anaphylaxis requires a *latent period for sensitization* after the first introduction of antigen followed by *reexposure to the sensitizing agent* which can be any foreign protein or hapten

So acute systemic anaphylaxis occurs in two stages:

First exposure :

the allergen will enter the body,be recognized by IgM on the surface of B cells , get engulfed and processed to be presented on MHC ll molecule, then ***Th2*** cells will be activated and secrete certain cytokines such as **IL4** & **IL13** which assist in *class switching to* ***IgE*** which then will bind to mast cell receptors by their Fc portion (latent period)

Second exposure :

When exposing to the same allergen, it will bind to the *already placed IgE* on mast cells and basophils, cross linking, degranulation of the mast cells releasing the mediators of anaphylactic shock.

In other words Type I allergic responses are characterized by the activation of allergen- specic CD4 helper cells (Th2 cells) and the production of allergen-specic IgE antibody. The allergen is captured by B cells through their antigen- specic surface IgM and is processed so that its peptides are presented by MHC class II molecules to T-cell receptors of antigen-specic Th2 cells. The interleukins IL-4 and/or IL-13 produced by the activated Th2 cells induce a switch to the production of IgE, rather than IgG, by the B cell However, allergen-specic IgE antibodies can exist without the occurrence of anaphylaxis, suggesting that factors other than IgE may be required

.***Mediators of Anaphylaxis***

Histamine is the major mediator of the *immediate effects* of anaphylaxis causing vasodilation , bronchoconstriction & swelling, increased permeability of blood vessels causing life threatening hypotension, diarrhea and wheezing

Leukotriens cause bronchoconstriction & wheezing

Platelet activating factor (PAF) causes vasodilation and bronchoconstriction, hypotention & wheezing

Mediators of anaphylaxis

Mediator	Action	Signs/symptoms
Histamine	Vasodilation, bronchoconstriction	Pruritus, swelling, hypotension, diarrhea, wheezing
Leukotrienes	Bronchoconstriction	Wheezing
Platelet-activating factor*	Bronchoconstriction, vasodilation	Wheezing, hypotension
Tryptase	Proteolysis	Unknown

PAF isnt released from mast cells. It may be released from neutrophils, endothelial cells and platelets.

Tryptase which is proteolytic enzyme

IgE mediated reaction to extrinsic Ag à systemic anaphylaxis,acute urticaria, allergic rhinitis (affects URT), allergic asthma (affects LRT) and food allergen.

All IgE mediated response involve mast cell degranulation but the symptoms differ from person to other due to different routs of entry and different dose of allergen.

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The Case : A Life-Threatening Immune Reaction

-John Mason, 22 months old baby,

-Ate peanuts and had a swollen lips on first exposure

-The Second time of eating peanuts he started to vomit, had hoarse voice,wheezing and all the other symptoms which indicates a more severe reaction.

-IgM, IgG, IgA were all elevated

-most important symptom of these is the very low blood pressure, which makes this condition very dangerous , and it happens due to loss of fluids which produces hypovolemia

-Main treatment of this anaphylactic shock is epinephrine shot!! Which will return the blood pressure to normal immediately

-This case is similar to some extent to the case of Hereditary Angioedema

which at that time we said at the emergency room we should give epinephrine because we were not sure that the patient is having anaphylactic shock or HAE!

-We gave the baby anti-histamines, anti-inflammatory corticosteroids,

β2-agonist “by inhalation” (**albuterol**).

-Blood tests for histamine and tryptase were taken

-Discharged with Epi-Pen (epinephrin injection , usually in the thigh to spread rapidly and the dose depend on the age and weight) , with restriction of eating peanuts.

-And asked to come back after few days for immunologic test

Note: Patient should be under monitoring for 24 hours because some of them may need a backup dose of epinephrine

Diagnostic Assays

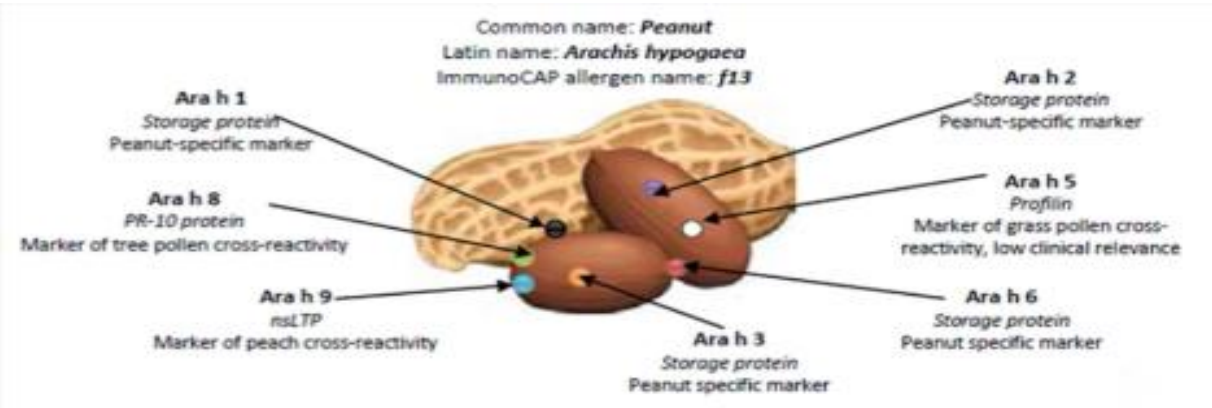
Skin break testing: on the patient's hand or back, we inject different allergens, according to the swelling are we will be able to determine the type.

Specific IgE testing on serum (RAST) : we put the serum on different types of food, when it sticks it means that there is specific IgE,then we put secondary AB (similar to Elisa)

Oral food challenge : the gold standard, done under very careful hospital settings (for something we suspect)

Molecular allergy diagnostics (component resolved diagnostic): there are several allergens in peanut that can elicit the anaphylactic shock, one is more serious than other.It utilizes purified native or recombinant allergens to see if the patient has a reaction against it .

Each allergen in peanut has a sequential number i.e. Ara h1, Ara h2, Ara h3 which are storage proteins that are heat stable, very specific to peanut and highly responsible for severe systemic reaction. Other components are less serious i.e. there might be cross reaction between foods of the same family and also there is a cross reactivity between food and inhalants . For example the pollen of birch contains components which are highly cross reactive with other components including peanuts(Ara h8).



Not everyone who is sensitized to peanuts(have AB against it) will be allergic(have clinical symptoms).

People have cross reactivity may or may not develop clinical symptom, but if yes it will be mild.

If the patients are allergic to a storage protein they should always have an Epi-Pen

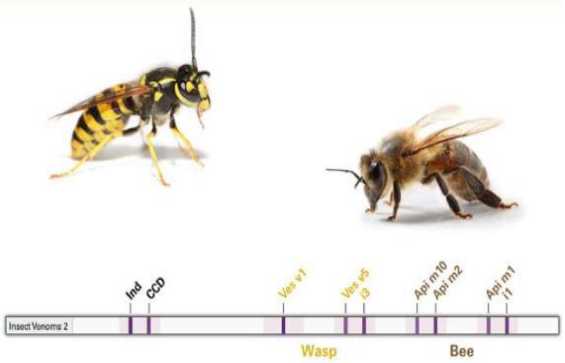
The same thing is applied on eggs and milk. Ovomucoid is the most reactive component in eggs and it is heat stable(it stays even if you boil the eggs) unlike lysozyme which is heat labile protein.

f1 (Gallus domesticus), **Egg white components**				
f1 Egg white	*Gal d1*, **Ovomucoid** *Heat stable* protein. Risk of reaction to cooked egg. Highly allergenic, associated with persisting egg allergy.	*Gal d2*, **Ovalbumin** Heat labile protein. Risk of reaction to raw/ slightly cooked egg.	*Gal d3*, **Conalbumin** Heat labile protein. Risk of reaction to raw/ slightly cooked egg.	*Gal d4*, **Lysozyme** Heat labile protein. Risk of reaction to raw/ slightly cooked egg.

f2 (Bos domesticus), **Milk- components**					
f2 Milk	**α-lactalbumin** *Bos d4* **β-lactoglobulin** *Bos d5* **Whey proteins** Heat labile protein. Risk of reactions to fresh milk, may tolerate well-cooked milk.	**Albumin** (BSA) *Bos d6* Heat labile protein. Risk for reactions to fresh milk, may tolerate well-cooked milk. Main allergen in beef/ cross-react with mammals	**Casein** *Bos d8* *Heat stable* protein. Risk of severe reactions to all forms of milk (fresh and cooked). 80% of milk proteins (cross-react between mammals).	**Lactoferrin** *Bos d lactoferrin* Heat labile protein. Risk of reactions to fresh milk, may tolerate well-cooked milk.

You have to know food families in order not to have allergy by mistake, for example coconuts and dates are from the same family, also mango and cashew nuts.

Another application is venoms. There first bite may not be very serious but on the second time it may be fatal.
It contains:
i1 (Api m1 and Api m2 which are heat stable and Api m10 which is heat labile) is a mix(boiled - Api m10 will denature)for the bee while i3 is a mix(boiled) for the wasp



Note : Immunotherapy involves changing the response from Th2 to Th1 (IgE to IgG) and allergies can be cured this way

By this test we can determine the cause and also make a decision if we want to treat with the immunological therapy as the immunological therapy to bee venoms contains Api m1 & Api m2 but not Api m10

Importance of CRD:

- To know which specific component the patient is allergic to
- To know the characteristics of the family to which the allergens belong
- To know if the allergies are specific or there is cross reactions
- To know if the allergens are heat stable or labile
- Helps in making the best management ant treatment

Quistions

1. Explain the hoarseness of voice and wheeze?

Hoarseness= Angioedema of vocal cord, may also be due to inflammation or even a tumor!

Wheeze= histamine and leukotrienes causing smooth muscle constriction of bronchial tubes.

2. Skin Prick and specific IgE blood tests revealed peanut allergy only, advice patient?

Avoid any foods containing peanuts, read food labels, ask in restaurants.

Avoid Peas! Wear bracelet, and Keep Epi-Pen injection at home or when traveling.

Peas should be avoided due to high incidence of cross reaction!

3. What other drug was given to John beside epinephrine?

Albuterol (β2-adrenergic agent) by inhalation à bronchodilation & vasoconstriction
In addition to treatment with Benadryl and methylprednisolone (cortisteroid) intravenously every 6 hours continued for 24 hours, by which time the facial swelling had subsided and John's blood pressure, respiratory rate, and pulse were normal
Note : If the patient was hypotensive we should give IV fluids

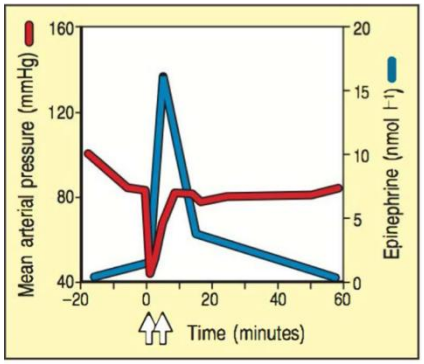
4. Why was John's blood tested for histamine and tryptase?

Released by mast cells, indication of anaphylactic shock

5. Why was Skin Prick test delayed a few days and not done on the spot in the hospital? Immediately after Anaphylactic shock, patient is unresponsive to skin prick test, why?

Tachyphylaxis (lasts 72-96 hours following anaphylaxis)

This figure was in the slides but the doctor didn't mention it:



Mean arterial pressure and epinephrine levels in a representative patient with insect-sting anaphylactic shock. Time 0 indicates the onset of the anaphylactic reaction as reported by the patient. The arrows indicate administration of antihistamines and epinephrine.

Test Yourself

1. The proper order of events which occur during allergic response is:
   I. Individuals experience symptoms
   II. Individuals are sensitized to antigen
   III. IgE attaches to mast cells
   IV. Antigen binds to IgE
      a) I,II,III,IV
      b) I,III,II,IV
      c) II,III,IV,I
      d) II,III,IV,I
      e) II,IV,III,I

2. The inflammation response triggers all of the following except:
      a) Dilation of capillaries
      b) Constriction of airways
      c) Inhibition of mucus secretion
      d) Pain
      e) Itching

3. A hypersensitivity reaction occurs:
      a) During first exposure to an antigen
      b) During second or subsequent exposure to an antigen
      c) In individuals with immunological diseases
      d) Only in children
      e) In patients of asthma

4. The primary chemical mediator in anaphylaxis is :
      a) Histamine
      b) Bradykinin
      c) IL-1
      d) Serotonin

5. A child disrupted a wasp nest is stung repeatedly and goes into shock within minutes, manifesting respiratory failure and vascular collapse. This is most likely due to:
    a) Systemic anaphylaxis
    b) Serum sickness
    c) Cytotoxic hypersensitivity
    d) HAE

6. Hypersensitivity to penicillin and poison oak are both:
    a) Mediated by IgE antibodies
    b) Initiated by haptens
    c) Mediated by IgG & IgM antibodies
    d) Initiated by Th2 Cells
    e) Complement dependent

7. A child stung by a bee experiences respiratory distress within minutes and lapses into unconsciousness. This reaction is probably mediated by:
    a) IgG antibodies
    b) IgM antibodies
    c) IgE antibodies
    d) Sensitized T cells
    e) Complement system

8. One of the following isn't a result of histamine release:
    a) Decreased vascular tone
    b) Increased vascular permeability
    c) Vasodilation
    d) Vasoconstriction
    e) Constriction of airways

9. Allergies to sea food, eggs, etc are examples of:
    a) Type I hypersensitivity
    b) Type II hypersensitivity
    c) Type III hypersensitivity
    d) Type IV hypersensitivity

10. The drug of choice for treatment of anaphylaxis:
    a) Adrenaline
    b) Hydrocortisone
    c) Promethazine
    d) Ranitidine

1	2	3	4	5	6	7	8	9	10
D	C	B	A	A	B	C	D	A	A