**IMMUNOLOGY 3**

# HYPERSENSITIVITY & ALLERGY

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## Learning objectives

By the end of this lecture you should be able to:

## • Outline the mechanisms by which IgE, antibodies, immune complexes and T cells can cause tissue damage and inflammation (the four types of hypersensitivity), giving examples of the clinical syndromes associated with each

## • Outline the factors underlying the development of atopic/allergic diseases

## • Describe the important clinical features of asthma, hay fever, allergic eczema and anaphylaxis

## • Briefly describe the approach to investigation and management of patients with these disorders

This lecture is intended to give you an overview of the immunopathology of hypersensitivity. The slides will be posted on the intranet.

By the end of the lecture you should understand the mechanisms leading to and the clinical manifestations of hypersensitivity reactions (4 types). These are tissue damaging immune responses to auto or alloantigens:-

* Type 1: Immediate Hypersensitivity
* Type 2: Antibody-dependent Cytotoxic Hypersensitivity

Gell & Coombs

* Type 3: Immune Complex Mediated Hypersensitivity
* Type 4: Delayed Cell Mediated Hypersensitivity

## *Allergy*

Allergy occurs when a damaging immune response develops to an otherwise innocuous foreign substance, the antigen involved is referred to as the allergen.

Most allergic disease is produced by mixed type I and type IV hypersensitivity reactions

Type I is immediate hypersensitivity/IgE- mediated

Type IV is cell mediated chronic inflammation

**Atopy** is the tendency to produce abnormally high IgE responses to otherwise harmless foreign environmental substances.

# Allergic disease is the expression of a disease caused by atopy

# general points

* common - 50% of young adult population are atopic, prevalence has increased dramatically and may still be increasing
* severity varies e.g. mild occasional symptoms, severe chronic illness to fatal anaphylactic shock
* risk factors for allergy include genetic and environmental:

## *Genetic factors*

~80% of atopics have family history of allergy (20% of general population)

Polygenic – many genes implicated:

Genes on chromosome 5 (IL-4 gene cluster) implicated in regulation of IgE

Genes on chromosome 11q (IgE receptor) linked to the atopic phenotype

## *Environmental Factors: Atopy*

age increases in children, peaks in teens, then decreases

gender commoner in boys in children, females in adults

family size less in large families

dietary factors anti-oxidants, fatty acids may protect

infections early life infections protect

animals early exposure protects

***Expression of disease*** *requires*

* sensitisation (usually in childhood), then
* exposure to the allergen

## *Immunopathogenesis:*

* Specific IgE produced on first exposure
* IgE binds to Fc receptors on mast cells
* Re-exposure to allergen cross-links IgE with mast cell activation (synthesis of prostaglandins/leukotrienes) and degranulation (histamine and other mediators) produce vasodilation, and permeability of blood vessels with fluid entering mucosal tissues with swelling (oedema), increased mucus secretion (rhinorrhoea, sputum production), neural stimulation (cough, sneezing, itch).
* Chronic inflammation with lymphocyte and eosinophil activation and infiltration

## *Clinical manifestation*

relates to the organ exposed to and responding to the allergen:

**Organ Disease Route of exposure**

nose allergic rhinitis inhaled

bronchi allergic asthma inhaled

blood circulation anaphylactic shock oral/mucosal contact/inhaled

skin allergic eczema skin contact

# Allergic rhinitis

* seasonal e.g. hayfever due to grass/tree pollen
* perennial e.g. house dust mite, animal dander
* often associated with: sinusitis, otitis media, allergic conjunctivitis, asthma

# Allergic asthma

Asthma is characterised by: Reversible generalised airway obstruction
Bronchial hyper-responsiveness
Airway inflammation

Asthma is common (4-20% UK population)

Asthma may be: Perennial (eg house dust mite, cat/dog dander)
Seasonal (eg pollens)
Occupational

Onset often in childhood, usually associated with other atopic disorders and family history of allergy

Chronic, variable disease with acute exacerbations

## *Immunopathogenesis:*

Combination of:

acute **mast cell** activation:

* mucosal oedema
* mucous secretion
* smooth muscle contraction

leading to acute, rapidly reversible narrowing of airways.

chronic **TH2 lymphocyte** and **eosinophil** activation:

* inflammatory cellular infiltration
* tissue damage
* epithelial cell shedding
* subepithelial fibrosis
* smooth muscle hypertrophy
* **Factors that may precipitate acute attack of asthma:** Viral infectionAllergen exposureCold air / Exercise

Irritants

Emotional stress

# Anaphylaxis

Uncommon but potentially fatal.

Most severe and dramatic form of allergy.

Generalised degranulation of IgE-sensitised mast cells and basophils.

## *Clinical features of anaphylaxis*

**Organ Feature**

Cardiovascular system Cardiovascular collapse

Respiratory system Bronchospasm, laryngeal oedema

Skin Erythema, urticaria, angioedema

Gastrointestinal system Vomiting, diarrhoea

## *Common causes of anaphylaxis*

Bee and wasp stings ie venom allergy

Food e.g. peanut allergy, shellfish, fruits & veg

Drug allergy e.g. penicillin

Where allergen is introduced directly into the blood e.g. bee sting, the reaction can be almost instantaneous with cardiovascular collapse the predominant feature.

Where the allergen is absorbed through skin or mucosa e.g. peanut allergy, the reaction may develop more slowly, but is still very rapid.

Milder forms of urticaria/angioedema much more common that full anaphylaxis.

Anaphylactoid/anaphylaxis-like reactions are clinically identical to anaphylaxis but the mast cell activation is not due to IgE-mediated allergy. No prior exposure is required. A number of other mast cell triggers may operate instead e.g. complement activation by radiocontrast media, direct stimulation of mast cells by opiates, alcoholic drink constituents or food colours e.g. tartrazine.

The treatment of the acute episode is the same.

# Food allergy

Less common than is thought, but increasing in prevalence

Common clinical features of food allergy:

* Gut: nausea/vomiting/pain/diarrhoea
* Skin: urticaria (itchy ‘wheal and flare’ type rash)
* Angioedema (soft tissue swelling)

Common allergens implicated include peanuts. Cow’s milk, egg (in young children), nuts, fruit & veg, shellfish

# Atopic/allergic eczema

* Chronic itchy skin rash in atopic persons
* Common - in 10% under 2 years of age and 2% of adults
* In infants affects face first then flexures of arms and legs
* 50% clears by 7 years, 90% by late teens
* Complicated by bacterial infection, severe herpes simplex
* 90% have high serum IgE
* House dust mite allergy may be important, food allergy is controversial

# Investigation and diagnosis of allergy

* Careful history is essential
* Immediate hypersensitivity (type I) skin prick tests very useful to confirm presence of atopy and identify possible causative allergens
* Specific IgE measurement (RAST) only necessary if:
* On antihistamines
* Extensive skin disease
* Presence of dermatographism
* Very young baby
* Previous anaphylaxis
* Skin test solution not available
* Challenge with allergen e.g. for food allergy, occupational allergy
* Other tests e.g. total IgE, lung function tests for asthma

# Approach to management of allergy

Allergen avoidance (difficult even with peanuts!)

**Topical treatment:**

* Nasal sprays for allergic rhinitis: corticosteroids, cromoglycate
* Inhalers for asthma: 2-adrenoceptor agonists (reliever), corticosteroids (preventer)
* Corticosteroid cream/ointments for atopic eczema

**Oral medication:**

* Antihistamines e.g. for allergic rhinitis, urticaria
* Corticosteroids: only for severe disease, avoid long-term use

Medic alert bracelet

Allergen immunotherapy/desensitisation e.g. for bee or wasp allergy

**Anaphylaxis:**

Adrenaline (epinephrine) IMI 500mcg (0.5mL of 1:1000), repeated at 5 min intervals as necessary. IVI 500mcg (5mL of 1:10,000), by slow injection.

Antihistamines (chlorpheniramine 10-20mg IM or slow IV)

Corticosteroids (hydrocortisone 100-300mg IM/IV)

Anaphylaxis kit (Epipen, 300mcg prefilled adrenaline)