COMMON ALLERGY PROBLEMS IN PRIMARY CARE

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ALLERGY - AN OVERVIEW

- PATHOGENESIS
- CLINICAL ASPECTS
- RELEVANT INVESTIGATIONS
- FUTURE DIRECTIONS

ALLERGIC DISEASES - Prevalence

- Weiss et al (1992) - USA data

- Allergic rhinitis 20 million
- Asthma 9-12 million with active disease
- Dermatitis 5.8 million visits to Dr./year
- Skin reactions 12 million visits
- Anaphylaxis 1-2 million/year

- Estimated 30% of population are atopic

HYPERSENSITIVITY

- TYPES I - IV

I - IgE MEDIATED REACTION -

- Binding of antigen to IgE on the surface of mast cells causes release of inflammatory mediators
- ANAPHYLAXIS - Rapid systemic reaction

II - CYTOTOXIC REACTION -

- Binding of antibody to cell surface leads to activation of complement and damage to host cell

HYPERSENSITIVITY

III - IMMUNE COMPLEX REACTION (Arthus) -

- Formation of complexes between antigen & antibody leads to tissue damage as a result of deposition in blood vessels (vasculitis) and activation of inflammatory pathways

IV - CELL MEDIATED REACTION (DTH) -

- Activation of T cells around site of antigen leads to T cell cytotoxicity & activation of macrophages, causing tissue damage

IMMUNE RESPONSES

ALLERGENS

- Antigens that initiate an IgE-mediated response
- Main grouping into AERO & ORAL ALLERGENS

CONVENTIONAL IMMUNE RESPONSE

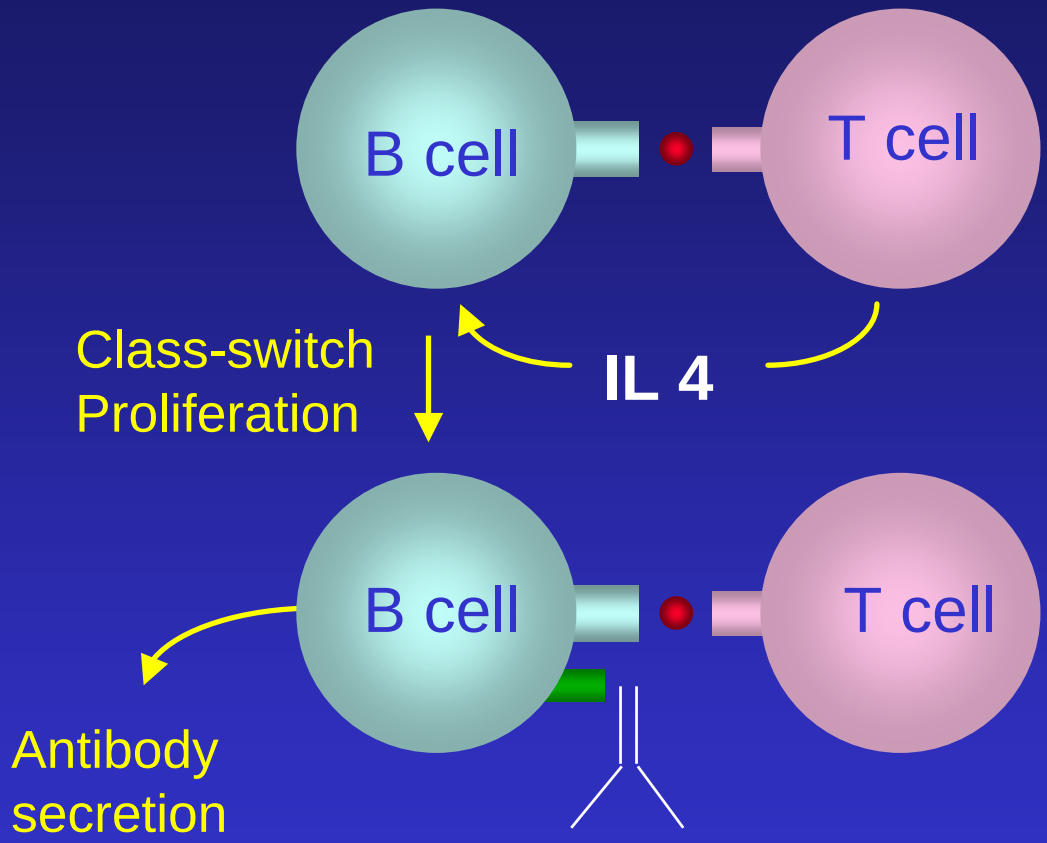
- Allergen requires processing
- Presentation to T cells results in delineation of T-helper subsets into T_H1 and T_H2 types

IgE

Fab recognises allergen

Fc attaches to *effector* cells
ie mast cells or basophils.
Cell binding mediated by FcεRI
and FcεRII.

IgE PRODUCTION



EARLY PHASE RESPONSE

MAST CELL

- $Fc_{\varepsilon}R1$ present at high density
- Cross-linking of $Fc_{\varepsilon}R1$ by allergen leads to activation of mast cell, resulting in :-

- *DEGRANULATION -*
  - *Release of PRE-FORMED MEDIATORS*

- *SYNTHESIS OF LIPID MEDIATORS*

PRE-FORMED MEDIATORS

HISTAMINE

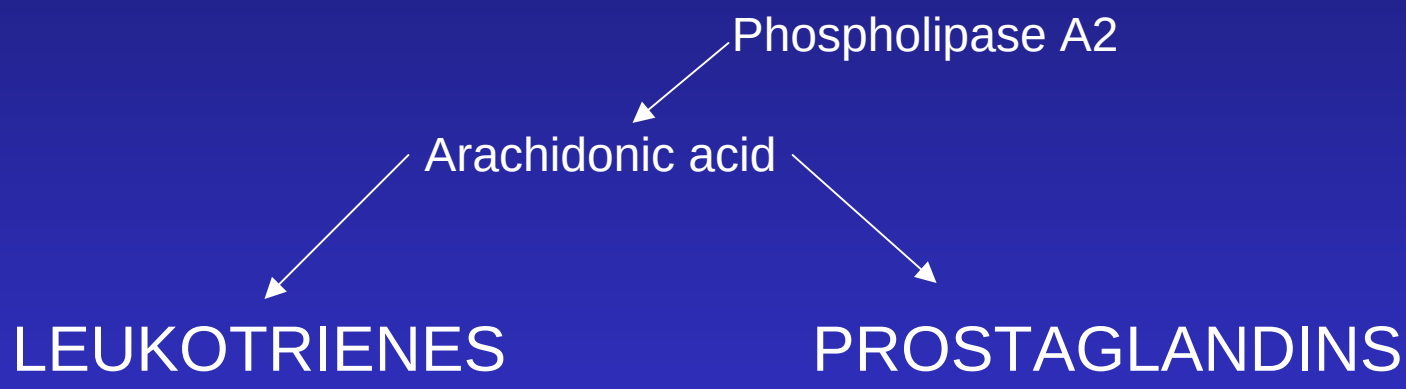
- Stimulation of *IRRITANT NERVE RECEPTORS*
- *SMOOTH MUSCLE CONTRACTION*
- *INCREASE IN VASCULAR PERMEABILITY*

KALLIKREIN

- Activates *BRADYKININ* - similar actions to histamine

LIPID MEDIATORS

- ARACHIDONIC ACID DERIVATIVES



LATE-PHASE RESPONSE - 1

BASOPHILS

- Similar properties to mast cells over longer time scale

EOSINOPHILS

- *GRANULES* contain cytotoxic proteins (e.g.ECP)
- Attracted to sites of allergic inflammation by *CHEMOKINES*
- *RELEASE CONTENTS OF GRANULES* - major source of tissue damage in allergic response

LATE PHASE RESPONSE - 2

T CELL RESPONSES

- Th2 ACTIVITY is critical
- Involved in *EARLY AND LATE RESPONSE*
- *CYTOKINE-DRIVEN ACTIVITY* is *FUNDAMENTAL* in the *PATHOGENESIS* of allergic responses - IL3, 4, 5

Genetic influences

- Polygenic diseases
- Cytokine gene cluster IL3,5,9,13
- IL12R; IL4R
- FcεRI
- IFNγ; TNF

- NOT sufficient for disease
- ONLY susceptibility

Environmental influences

- East vs. West Germany -
  - Pollution levels
    - (Von Mutius et al BMJ (1992) 305: 1395)
- Swedish vs. Estonian children -
  - Lactobacilli vs. Clostridia in stools
    - (Sepp et al Acta Paed (1997) 86: 956)

ENVIRONMENTAL INFLUENCES

- Exposure data - HDM & asthma
    - Sensitisation to HDM most potent risk factor for childhood asthma
        - Platts-Mills et al JACI (1992) 89:1046
- Exposure -> sensitisation but NOT disease

Disease influences

- BUT…..
- African children
  - IgE response to parasitic disease normal
  - High levels of IgE & evidence of sensitisation to HDM
  - BUT
  - Those patients with schistosomiasis had decreased atopy

IMMUNOPATHOGENESIS

- NEONATAL STUDIES
  - Human cord blood - Th2 skewed response against dietary and inhalant antigens
  - By age 2 non-atopic children have switched to Th1-skewed response
  - Atopic children fail to silence Th2-skewing
  - Poor production of IFNγ by T cells

IMMUNOPATHOGENESIS

- HYGEINE HYPOTHESIS
  - Attractive idea based on Th1/Th2 paradigm
  - Increased infective burden lessens susceptibility to allergic disease
  - Rural vs. Urban children
  - Nursery vs. home care children
  - Large vs. small families

HYGIENE HYPOTHESIS

HOWEVER:

- In US, main improvements in hygiene occurred BY 1940
- Th1 related diseases e.g. IDDM have also increased
- Many chronic infections produce significant Th2-dominant responses
  - Ethiopian studies suggest rural/urban model holds for HDM sensitisation

ALLERGY - DIAGNOSIS

HISTORY

- *<50% CONFIRMED BY DOUBLE-BLIND CHALLENGE*

- Need to know:-
  - *SUBSTANCE INVOLVED (IF KNOWN)*
  - *QUANTITY INGESTED*
  - *TIME INTERVAL TO ONSET*
  - *SIMILARITY OF SYMPTOMS ON EACH OCCASION*
  - *OTHER FACTORS E.G. DRUGS*

SKIN PRICK TESTING

- Glycerinated STANDARDISED extracts (1:10 or 1:20 dilution)
- Comparative tests - positive (histamine) & negative (saline)
- Wheal & flare - WHEAL only is measured
- Positive result if at least 3mm greater than negative control

- PREDICTIVE ACCURACY
- Positive tests only 50% positive predictive value
- Negative tests >95% negative predictive value

PROBLEMS WITH SKIN PRICK TESTING

- LACK OF STANDARDISED EXTRACTS for many potential allergens
- LABILE ALLERGENS e.g. apples , potatoes , bananas

- ATOPIC individuals have HIGHER FALSE POSITIVE RATE
- Anti-histamines interfere with results

ASSAYS FOR SPECIFIC IgE

- Antigen bound to SOLID PHASE
- Patient SERUM INCUBATED with solid phase
- SPECIFIC IgE BINDS, non-specific IgE washed away
- Labelled anti-IgE added (Radiolabelled (RAST); fluorescent (FAST) or enzyme (EAST)
- Unbound anti-IgE washed away

- QUANTITATION (Scintillation; fluorometry; spectrophotometry)

ASSAYS FOR SPECIFIC IgE

ADVANTAGES

- COMPARABLE SENSITIVITY & SPECIFICITY WITH SKIN PRICK TESTING provided same allergen extract used
- If skin prick testing is likely to be difficult to interpret -
  - Significant dermographism
  - Severe skin disease
  - Suspected exquisite sensitivity
  - Unable to stop anti-histamines
- STANDARDISATION EASY TO ACHIEVE - day/day & lab/lab variation
- NEGATIVE PREDICTIVE VALUE IS HIGH

ASSAYS FOR SPECIFIC IgE

PROBLEMS

- REFERENCE SERA for most allergens are NOT AVAILABLE - quality assurance is difficult
- ARBITRARY UNITS - often misinterpreted by clinician
- CROSS-REACTIVITY between allergens is common
- The ‘ANTIGEN’ on the solid phase is LIMITING
- Most IgE is in tissue bound to mast cell surfaces, not in serum
- The PRESENCE OF SPECIFIC IgE DOES NOT INDICATE SIGNIFICANT CLINICAL ALLLERGY, only prior sensitisation to the allergen

THE ATOPIC TRIAD

- ASTHMA; ECZEMA; RHINOCONJUNCTIVITIS

- In children - AERO-allergic stimuli
  - HOUSE DUST MITE
  - GRASS/TREE POLLENS
  - ANIMAL DANDERS
- In adults - much more heterogeneous
  - Above allergens still often significant contribution
- Assessment
- Contribution of investigations

ASTHMA & RHINITIS – The one airway hypothesis

- Diseases of *INFLAMMATION & HYPER-REACTIVITY*
- In childhood - *AERO-ALLERGIC stimuli - HOUSE DUST MITE* key pathogenic importance
- *IMMEDIATE symptoms* are IgE-mediated
- *DAMAGE TO AIRWAYS* due to *LATE PHASE RESPONSE*
- Many patients with asthma have a degree of allergic rhinitis
  - Persistent – House Dust Mite
  - Intermittent – pollens
- Patients with rhinitis are at increased risk of asthma

ARIA 2001

ASTHMA

- Disease of *INFLAMMATION & HYPER-REACTIVITY* of small airways
- In childhood - *AERO-ALLERGIC stimuli - HOUSE DUST MITE* key pathogenic importance
- *IMMEDIATE symptoms* are IgE-mediated
- *DAMAGE TO AIRWAYS* due to *LATE PHASE RESPONSE*
- *DAMAGED AIRWAYS ARE HYPER-REACTIVE* to non-allergic stimuli e.g. fumes

ASTHMA

- *CLINICALLY - BRONCHOSPASM*
- Attacks triggered by *ALLERGEN or IRRITANT/INFECTION*
- *TREATMENT :-*
- *REDUCTION of INFLAMMATION - INHALED STEROID*
- *RELIEF OF BRONCHOSPASM - INHALED β_2 AGONISTS*
- *ALLERGEN AVOIDANCE/REDUCTION MEASURES*

RHINITIS

- ALLERGIC/NON-ALLERGIC

- *ALLERGIC - PERENNIAL or SEASONAL*
- Blocked nose, runny nose - often with eye symptoms

- *HOUSE DUST MITE, ANIMAL DANDERS, POLLENS*

- Treatment - *NASAL STEROIDS*

RHINITIS

- Allergic disease
  - Persistent - House Dust Mite reactivity
    - Intranasal steroids
    - Avoidance measures - how effective?
    - Immunotherapy in severe cases
  - Seasonal - pollens
    - Grass (timothy grass in UK)
    - Tree (birch most common)
    - Treatment as above
    - Specific immunotherapy

ATOPIC DERMATITIS

- DERMATITIS

MANY DIFFERENT TYPES

- ATOPIC
- CONTACT - ALLERGIC/NON-ALLERGIC

- CLINICALLY - Intense itching, blistering/weeping, cracking of skin
- HOUSE DUST MITE now thought to be MAJOR TRIGGER in atopic disease

- TOPICAL STEROIDS & MOISTURISERS

ADVERSE REACTIONS TO FOODS

- DEFINITIONS

  Adverse Food Reaction :-

  "Any aberrant reaction occurring after ingestion of food or food additive"

- TOXIC vs. NON-TOXIC
  - TOXIC - e.g.
    - Histamine in scromboid fish poisoning
    - Bacterial toxins
  - NON-TOXIC
    - Immune (Allergy)
    - Non-immune (Intolerance)

ADVERSE REACTIONS TO FOODS

MAJOR FOOD ALLERGENS

- Water soluble glycoproteins 10 - 60 kd

- *COW'S MILK*
- *EGG*
- *LEGUMES - PEANUT; SOYBEAN; TREE NUTS*
- *FISH*
- *CRUSTACEANS / MOLLUSCS*
- *CEREAL GRAINS*

ADVERSE REACTIONS TO FOODS

CLINICAL MANIFESTATIONS

- GASTROINTESTINAL
  - ORAL ALLERGY SYNDROME
    - Contact allergy confined to oropharnyx
    - Pruritis & angioedema of lips, tongue, palate & throat
    - Ingestion of raw fruits & vegetables
    - Affected individuals commonly have allergic rhinitis caused by birch pollen

ADVERSE REACTIONS TO FOODS

- RESPIRATORY
  - Isolated symptoms are rare
  - Both upper and lower respiratory tract symptoms can occur during reactions to food
  - Sneezing , rhinorrhoea , nasal obstruction
  - Cough , wheezing , ‘chest tightness’
  - Food allergens can provoke airway hyper-reactivity

ADVERSE REACTIONS TO FOODS

- CUTANEOUS
  - Acute urticaria / angioedema said to be common
  - ‘Cause - and - effect’ usually obvious to patient
  - Eggs , milk , peanuts , other nuts in children
  - In chronic urticaria / angioedema *food hypersensitivity is rare*

ADVERSE REACTIONS TO FOODS

- CUTANEOUS
  - Atopic Dermatitis - In group of children with atopic dermatitis group on allergen-elimination diet (after appropriate identification of allergen) experienced greater improvement than controls (Sampson 1989)
  - Egg , milk , peanut , soya & wheat > 90% of reactions

ADVERSE REACTIONS TO FOODS

- FOOD INDUCED GENERALISED ANAPHYLAXIS
  - Sampson (1992) In all cases:-
    - Asthmatic
    - Unknowingly ingested allergen
    - Experienced previous allergic reactions to same food
    - Developed symptoms within minutes
  - All fatalities did NOT receive adrenaline immediately

ADVERSE REACTIONS TO FOODS

MANAGEMENT

- AVOIDANCE
- EDUCATION
- PREVENTION
- THERAPY
  - MILD / MODERATE REACTIONS
    - ANTIHISTAMINES
  - SEVERE REACTIONS
    - ADRENALINE

- RE-ASSESSMENT

FOOD ALLERGY - MANAGEMENT

- AVOIDANCE - not always easy
- Who needs an Adrenaline Epipen?
  - Difficulty in making diagnosis & predicting life-threatening events
  - Recent data, severity of initial reaction NOT a good guide to future events
- Who will grow out of their allergy?
  - Dogma - nobody
  - Recent data - low specific IgE, no reactions for two years - offer challenge test

DRUG REACTIONS

- ANTIBIOTIC ALLERGY
  - Reported commonly
  - Confirmed rarely
  - Penicillins most common
- NSAIDs
  - Disruption of arachadonic acid pathway
  - Angioedema often; urticaria less common
  - Bronchospasm - asthmatic individuals & others
- ACE inhibitors
  - Release of bradykinin
  - Angioedema - can be fatal

ANGIOEDEMA +/- URTICARIA

- > 6 weeks - CHRONIC
- CAUSES
  - Foods - additives/preservatives
  - Post infectious esp. viral
  - Drugs
  - Idiopathic/Autoimmune
  - Rarities e.g. SLE

CUA - Management

- Antihistamines are mainstay of treatment
- Combination therapy often required
- Immunomodulatory therapy in difficult cases
- Difficulties:
  - Short-term steroid use acceptable, long-term is not
  - Disease follows relapsing/remitting course - effects of treatment hard to assess
  - Does anyone need an Adrenaline Epipen?

ANAPHYLAXIS

DEFINITION

Reaction to allergen sufficient to result in major systemic dysfunction

HYPOTENSION; SEVERE BRONCHOSPASM

CARDIAC ARREST

Risk Factors

Previous exposure to allergen

Parenteral exposure to allergen

Beta blockade

Atopy

AETIOLOGY OF ANAPHYLAXIS

I. IgE-MEDIATED

DRUGS - Penicillins, muscle relaxants

FOOD

INSECT STINGS

LATEX - NB bananas, avocados, kiwi, pear

?EXERCISE-INDUCED

AETIOLOGY OF ANAPHYLAXIS

II. ANAPHYLACTOID

- Direct mast cell stimulation
  - Drugs, exercise, physical
- Interference in arachadonic acid pathway
  - Aspirin, NSAIDs
- Immune aggregates
  - Dextran

NON - ANAPHYLACTOID REACTIONS

- VASODEPRESSOR REACTIONS
- RESTAURANT SYNDROMES
- FLUSH SYNDROMES
- ENDOGENOUS HISTAMINE production
- NON-ORGANIC DISEASE

ANAPYHLAXIS - MANAGEMENT

- ACUTE SETTING

- ADRENALINE
  - IM ROUTE OF CHOICE
  - SC NOT EFFECTIVE
  - 0.3 - 0.5ml of 1 in 1000
  - Repeat after 10 - 15 minutes if required

ANAPHYLAXIS - MANAGEMENT

- CORTICOSTEROIDS
  - Hydrocortisone -
  - IV 0.1 - 1g (Adult); 10 - 100mg (child)

- BETA 2 AGONISTS
  - NEBULISED preferable

ANAPHYLAXIS - MANAGEMENT

- GENERAL
  - Avoidance
  - MedicAlert bracelet
  - Stop all potentially problematic drugs
    - Beta blockers, ACE I, MAOIs, tricyclics
  - Adrenaline Epipen
    - WITH PROPER TRAINING!!

ANAPHYLAXIS - MANAGEMENT

- SPECIFIC
  - Desensitisation
    - Venom
    - Others e.g. foods not justifiable
  - Pre-treatment if further exposure vital

THEORETICAL BASIS FOR IMMUNOMODULATION

- Rationale to alter balance between Th1/Th2
- Allergen extracts

- Escalating dose regimen
- Loss of skin reactivity
- Protection/alleviation of disease

DOES IT WORK?

- Wasp venom immunotherapy
  - Long standing history
  - Whole body extracts ineffective
  - Venom therapy highly effective

  - Evidence that ANERGY of Th2 cells occurs during treatment

DOES IT WORK?

- Grass pollen immunotherapy
  - Careful studies - Durham et al
  - Protection during treatment & for up to 4 years after
  - Immunohistochemical evidence that "switch" from Th2 to Th1 occurs in nasal mucosa - mRNA for cytokines
    - Increased IFNγ; decreased IL-4

SUB-LINGUAL IMMUNOTHERAPY

- Grass pollen
  - Grazax now licensed
  - Tablet therapy - daily dose
  - Data indicates good efficacy
- Issues:
  - Compliance
  - Severely affected patients
- Other products enter market in late 2007

ANTI-IgE ANTIBODIES

- Allergic asthma
  - Effective after 12 weeks
    - (Milgrom et al NEJM 1999 341:1966)
  - Effective in steroid-dependent disease
    - (Busse et al JACI 2001 108:184)
- Allergic rhinitis (HDM)
  - Good efficacy
    - (Chervinsky et al Annals Asthma, Allergy 2003 91:160)

Extremely expensive

ISSUES FOR DISCUSSION

- WHO SHOULD GET AN EPIPEN?
- HOW FAR TO TAKE INVESTIGATION INTO CAUSE?
- WHEN TO REFER?
- OTHERS