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

B cell → IL 4 → T cell

Class-switch
Proliferation

B cell → Antibody secretion → T cell
EARLY PHASE RESPONSE

MAST CELL

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

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

• **SYNTHESES 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

Phospholipase A2

Arachidonic acid

LEUKOTRIENES  PROSTAGLANDINS
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
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 ALLERGY, 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 $\beta_2$ 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 oropharynx
    • 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 IFN\(_\gamma\); 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