IgE Regulation and Hyper IgE Syndrome

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Immune Disorders

• Immunodeficiency – underperforms and leaves host vulnerable to infection
• Autoimmune – fails to distinguish host tissue vs pathogen, results in clinical disease
• Atopic – immune responses mounted to innocuous proteins which results in clinical disease
• IgE, mast cells, basophils, and eosinophils

*Kelly D. Stone, MD, PhD, Calman Prussin, MD, and Dean D. Metcalfe, MD*

*JACI 2010*

• Regulation and biology of Ig E, chapter 4

*Pediatric Allergy*

*Leung D, Sampson H First Edition*
immunoglobulins

- isotype specific constant chains: interact with receptors and cytokines
- During immunoglobulin synthesis – DNA transcription, excision and repair to produce the variable regions (antigen specific)
Ig E

• IgE antibodies are tetramers- 2 heavy and 2 light chains
• Heavy chains : V1  C4
• Light chains : V1 C1
• Connected by interchain disulphide bonds
• C : interact with  FCRI and CD23
Ig E

- Lowest level, shortest life span
- Production is tightly controlled
- No transplacental transfer
- Low level in cord blood, peak in adolescence, decreases thereafter
- Produced predom in B cells in mucosal related lymph tissue
- Requires the B cell to commit to irreversible genetic change (lineage/class switch)
Ig E

- Elevated in atopic individuals genetic / environmental factors
- Markedly raised: eczema, aspergillosis (trend useful as guide to response to treatment)
- NB: presence of IgE is not automatically indicative of disease
Ig E synthesis

• 2 signals required for IgE synthesis, both provided by T cells
• Allergen -> antigen presenting cell (dendritic or B cell) -> peptide/MHC II presented to T cell
• Signal 1: IL4 or IL13
  germline transcription, via STAT 6
• Signal 2: CD 154, CD 40 ligand
  activation of APC: B cells -> class switch to IgE, followed by secretion of allergen specific IgE
IgE receptor

- **High affinity** (FceRI) expressed on mast cells, basophils, APC (lower levels)
  - The α chain of FceRI binds to the Fc portion (C3 domain) of IgE
  - Exert function via cytoplasmic tyrosine kinase

- **Low affinity** (FceRII; CD23) expressed on the surface of B/T cells, macrophages, monocytes, eosinophils, Langerhans cells
  - Large transmembrane protein

- Both upregulated by IL4 and IgE
Clinical Manifestations

- Allergen-> crosslinking of receptor bound IgE
- Cascade of signaling events: immediate response
- Release of preformed mediators: histamine, proteoglycans, proteases
- Transcription of cytokines
- De novo synthesis of prostaglandins and leucotrienes
- 6-24 hours later: ongoing leucocytic influx
Clinical manifestations 2

a Internalization

IgE FcεRI

Allergen

MHC class II

APC

b Degranulation and release

IgE FcεRII

Prostaglandins

Leukotrienes

Cytokines

Histamine

Nature Reviews | Immunology

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IgE measurements

• Serum assays – allergen bound to a surface -> to which IgE binds.
• Bound IgE quantified (anti-IgE)
• Influenced by: amount, quality and stability of allergen, affinity of anti-IgE, interference by allergen specific IgG
  Also: allergen exposure, recent major reaction, immunotherapy

NB- specific affinity and activity: not reflected in assay, but affect biological activity
Clinical manifestations 2

(a) Internalization

- IgE
- FcεRI
- Allergen
- MHC class II

(b) Degranulation and release

- Allergen
- Mast cell
- Prostaglandins
- Leukotrienes
- Cytokines
- Histamine

Nature Reviews | Immunology
IgE – treatment implications

• Therapies directed at decreasing IgE effects have been developed
• Murine anti-IgE ABS binds to the C3 region of free IgE Fc fragment and decreases the free IgE available to bind to IgE receptors (2 anti-IgE per IgE molecule)
• Nb: effect on IgE assays (total Ig E raised)
• Licensed for asthma/rhinitis but used in wide variety of conditions
• Cost prohibitive
• Risk of anaphylaxis
• Fascinating molecule
• Most commonly associated with atopic disease but is also associated with one of the primary immunodeficiencies
• Hyper IgE with immunodeficiency 
  “Job’s Syndrome”
Hyper Ig E Syndrome

• Spectrum of disease
• More severe- early in life
• In others - delayed diagnosis, gen < 20
• Skin- usually severe eczema and superficial infections (bacterial and candida)
• Sinopulmonary infections (staph and haemophilus)
• NB: post –imflammatory pneumatoceles
• Facies: hypertelorism, broad mandible, bulbous nose
Hyper Ig E Syndrome

- Bony abnormality – fractures or loss of bone density
- Abnormal dentition: failure of 1 dental deciduousness -> either failure of 2 dentition or retention of both sets
- CNS – infection, vasculitis, CVA (stenosis, occlusion, aneurysm)
- Susceptibility to malignancy (AR) lymphoma, leukaemia, squamous cell Ca
# Hyper Ig E Syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eczema</td>
<td>100%</td>
</tr>
<tr>
<td>Facies</td>
<td>100%</td>
</tr>
<tr>
<td>Superficial skin infection</td>
<td>87%</td>
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<tr>
<td>Pneumonia</td>
<td>87%</td>
</tr>
<tr>
<td>Mucocutaneous candida</td>
<td>83%</td>
</tr>
<tr>
<td>Lung cysts</td>
<td>77%</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>76%</td>
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<tr>
<td>Delayed dental exfoliation</td>
<td>72%</td>
</tr>
<tr>
<td>Pathological fracture</td>
<td>57%</td>
</tr>
</tbody>
</table>
Hyper Ig E Syndrome facies
Hyper Ig E Syndrome - chest

Fig. 1.— Radiografía simple de tórax
Hyper Ig E Syndrome - skin
HyperIgE – Bone

- skin
Hyper Ig E Syndrome

• Genetics – multiple modes of inheritance, variable penetrance
  AD (4q)
  AR kindred
  sporadic
• Prevalence: uncertain, equal in both sexes
• Presentation: usually under 20,
Hyper Ig E Syndrome - workup

• IgE : > 10 standard deviations above age-appropriate norms (often > 100 times)
• FBC: absolute eosinophilia, preserved neutrophils and lymphs.
• Imaging : CXR/CT Chest
  Sinus CT
  Xray bones / Bone scan
  CT/MRI brain if CNS symptoms
Hyper IgE Workup

• Bronchoscopy: recurrent infection Staph Aureus, Haemophilus Influenza, Aspergillus, Gram – org (Pseudomonas) Opportunistic infections

• Histology: Prominent eosinophils (skin, lung, and other localized inflammatory processes)
Hyper IgE - Management

Multidisciplinary
Medical - sinopulmonary infection and seq, nutrition and development
Surgical: abscesses, fractures, bony deformities, osteomyelitis, broncho-pulm fistulae
Dermatology: eczema can be intractable
ID: recc infection: antibiotic choices, prophylaxis, resistance etc
Dentist
Genetics: counselling
Hyper IgE – Mx 2

Skin: emollients, topical corticosteroids, prompt treatment of superadded infection
Steroid sparing, Wet wraps

Infection: Clox/Fluclox
MRSA (hosp acquired)
Anti-staph measures
NB: Other bacteria, fungi, protozoa, mycobacteria
Hyper IgE – Mortality

- Adulthood (survival reported up to 60)
- Chronic pulmonary disease
- Superinfected lung abscesses
- CNS events
- Malignancy
Hyper Ig E Syndrome - differential diagnosis (conserved clinical picture and very high IGE)

• High IgE + ID: Wiskott-Aldrich syndrome, Omenn syndrome, immune dysregulation, Common Variable ID or Chronic granulomatous disease
• High IgE: parasitic infections and nonparasitic infections (e.g., EBV, cytomegalovirus, HIV, TB)
• Inflammatory diseases (Churg-Strauss vasculitis, and Kawasaki disease),
• Haematologic malignancies (Hodgkins lymphoma and IgE myeloma),
• Skin diseases (Netherton syndrome and bullous pemphigoid)
• cystic fibrosis, nephrotic syndrome
Conclusion

- Condition with multi-system involvement
- Early diagnosis – optimise infection control and preserve lung function
- Lifespan fair
- Morbidity can be significantly reduced by comprehensive and meticulous care

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Immune system Overview

- Anatomic-mucociliary
- Innate immunity:
  - cellular arm: pathogen associated molecular patterns eg lipopolysaccharides, mannans, DNA sequences (macrophages, NK cells, poly’s)
  - serum protein arm: rapid response, sequential patterns (complement, cytokines, acute phase proteins)

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Overview 2

• Adaptive immunity - antigen specific responses and immunologic memory.
• T cells: kill virus infected/ cancer cells, B cell activation, interact with innate immune system.
• B cells: immunoglobulins – neutralize toxins, opsonisation, upregulate innate immune responses
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Immunoglobulin Synthesis

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