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

Reading

- IgE, mast cells, basophils, and eosinophils

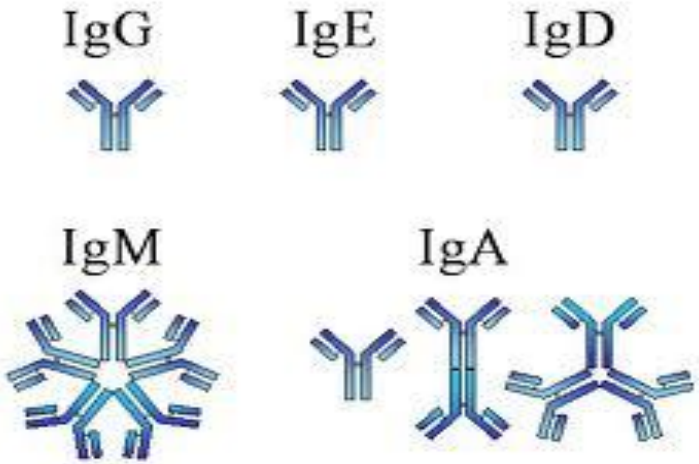
  Kelly D. Stone, MD, PhD, Calman Prussin, MD, and Dean D. Metcalfe, MD

  JACI 2010

- Regulation and biology of Ig E , chapter 4

  Pediatric Allergy

  Leung D, Sampson H First Edition

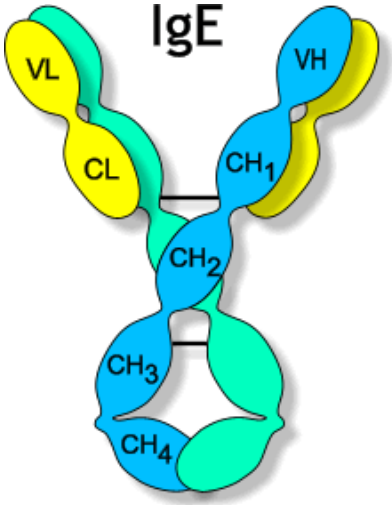


immunoglobulins

- 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

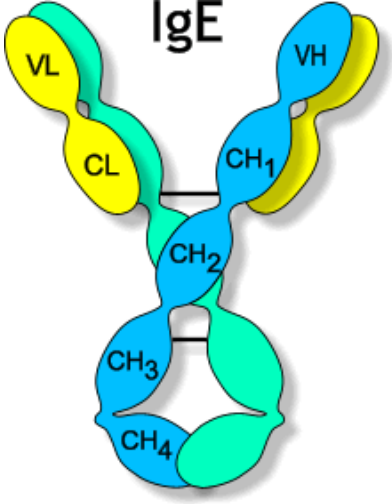
- IgE antibodies are tetramers- 2 heavy and 2 light chains
- Heavy chains : V1 C4
- Light chains : V1 C1
- Connected by interchain disulphide bonds
- C : interact with FCRI and CD23



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: presense of IgE is not automatically indicative of disease

Ig E synthesis

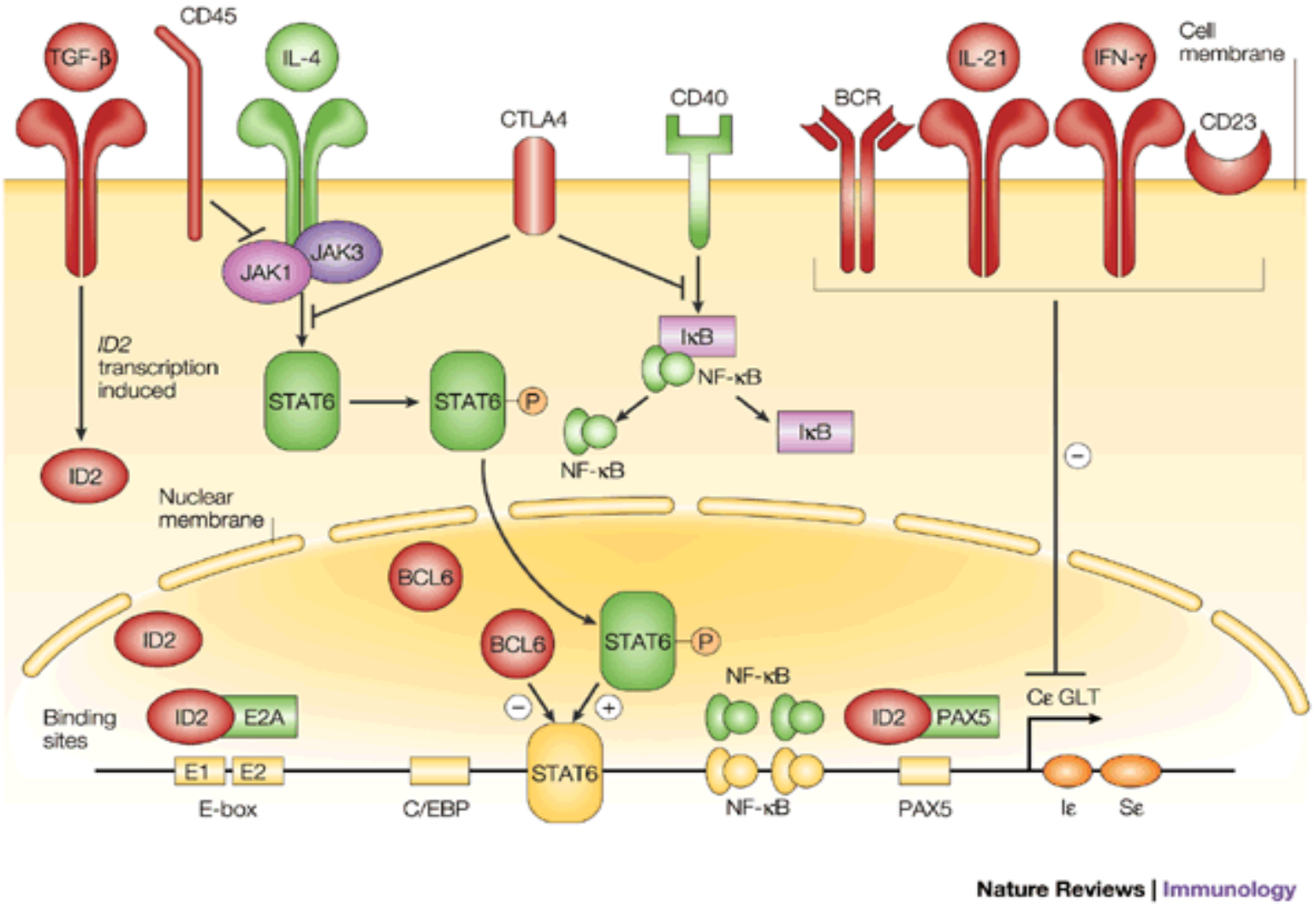
- 2 signals required for IgE synthesis , both provided by T cells
- Allergen -> antigen presenting cell (dendritic or B cell) ->peptide/MHC II presented to T cell
- Signal 1 : IL4 or IL13

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


CD45
TGF-β
IL-4
CTLA4
CD40
BCR
IL-21
IFN-γ
Cell membrane
CD23
JAK1
JAK3
ID2 transcription induced
STAT6
STAT6
P
IκB
NF-κB
IκB
NF-κB
ID2
Nuclear membrane
BCL6
ID2
BCL6
STAT6
P
NF-κB
Cε GLT
Binding sites
ID2
E2A
ID2
PAX5
E1
E2
STAT6
E-box
C/EBP
NF-κB
PAX5
Iε
Sε
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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

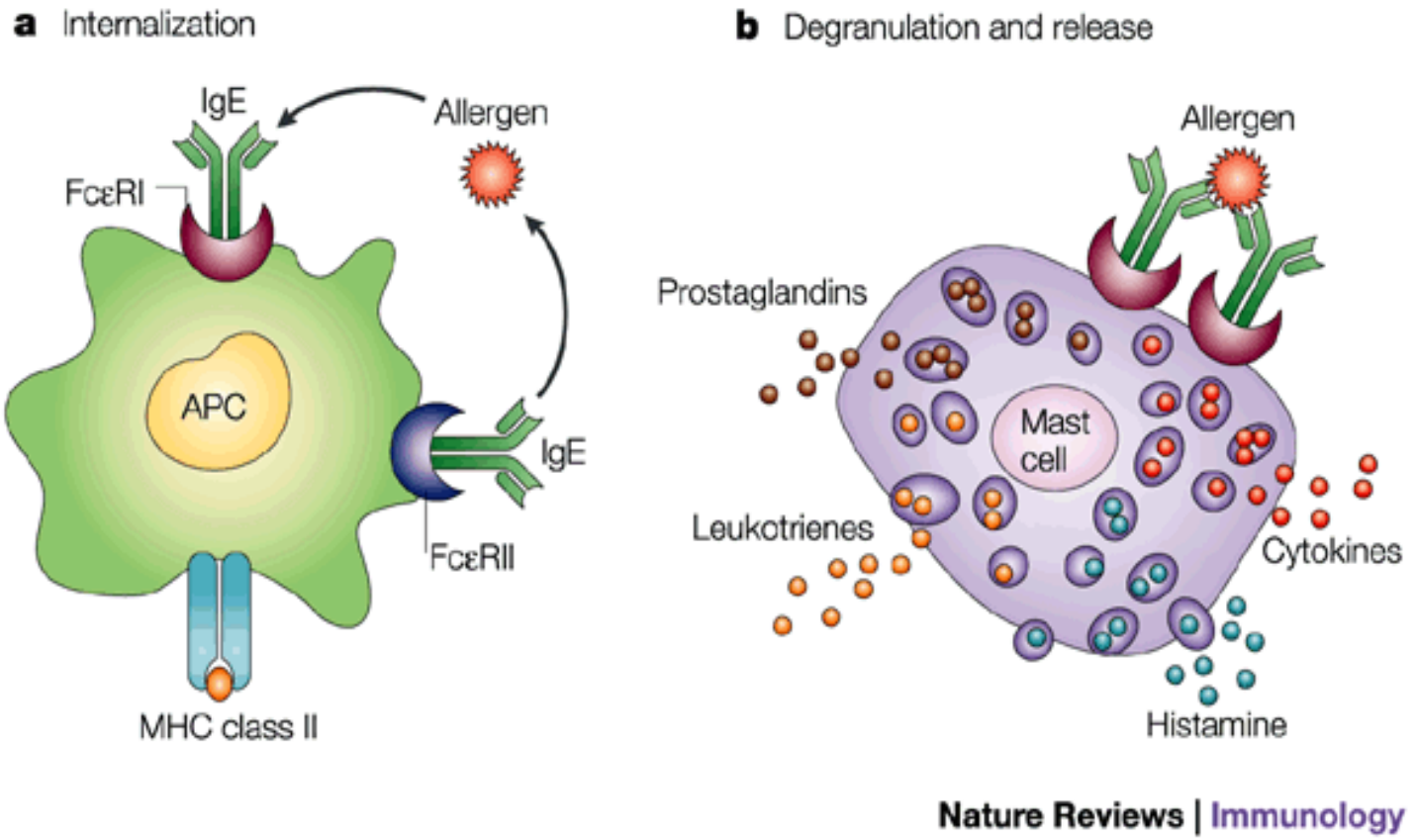
  Exert function via cytoplasmic tyrosine kinase
- Low affinity (FceRII; CD23) expressed on the surface of B / T cells, macrophages, monocytes, eosinophils ,Langerhans cells

  Large transmembrane protein
- Both upregulated by IL4 and Ig E

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 manitestions 2



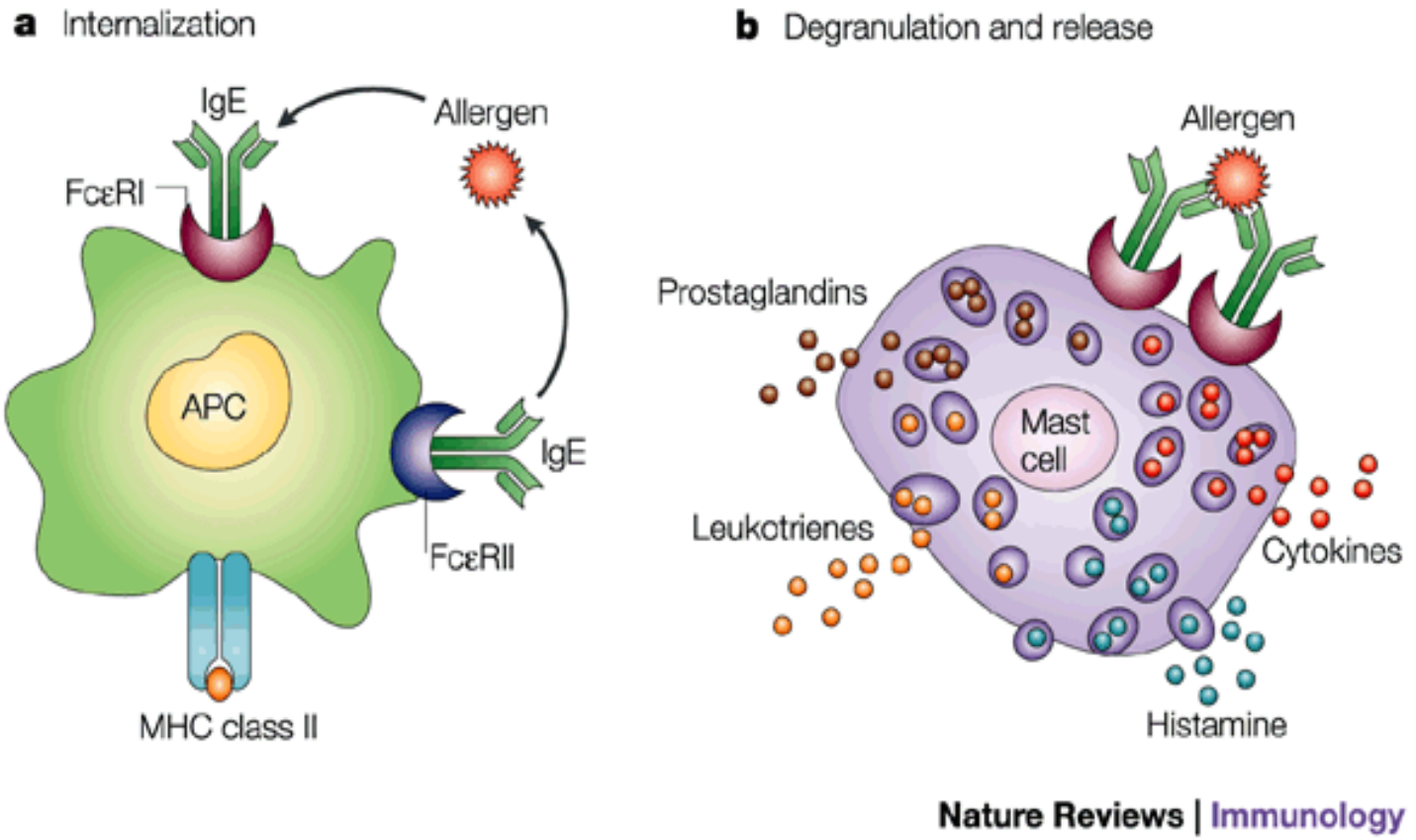
IgE measurements

- 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 manitestions 2



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)
- Licenced for asthma /rhinitis but used in wide variety of conditions
- Cost prohibitive
- Risk of anaphylaxis

IgE

- 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 superfical infections (bacterial and candida)
- Sinopulmonary infections(staph and haemophilus)
- NB: post –imflammatory pneumatocoeles
- 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 , sqamous cell Ca

Hyper Ig E Syndrome

Eczema	100%
Facies	100%
Superficial skin infection	87%
Pneumonia	87%
Mucocutaneous candida	83%
Lung cysts	77%
Scoliosis	76%
Delayed dental exfoliation	72%
Pathological fracture	57%

Hyper Ig E Syndrome facies

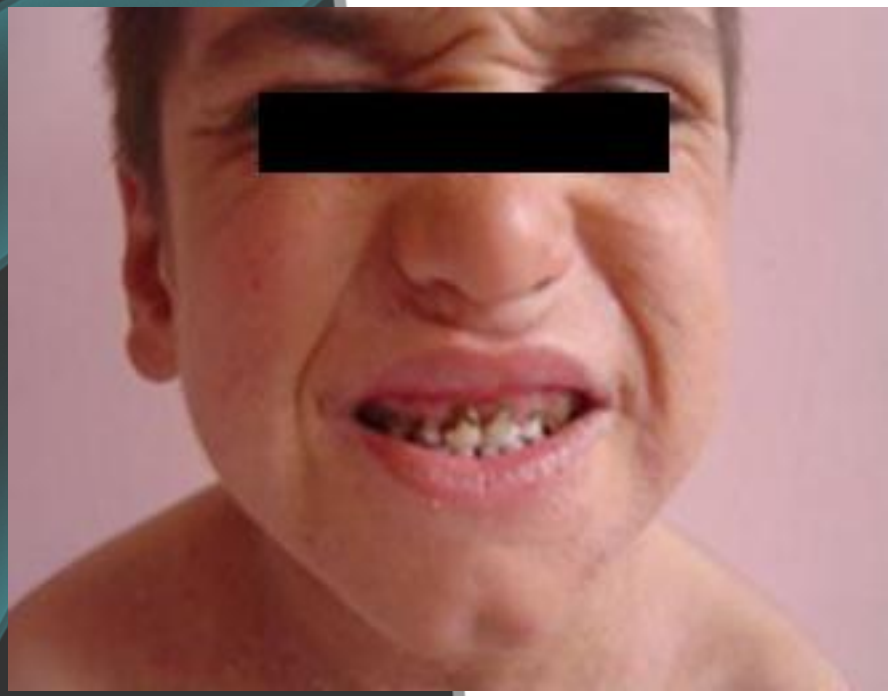


Fig. 3.– Rasgos faciales de la paciente

Hyper Ig E Syndrome- chest

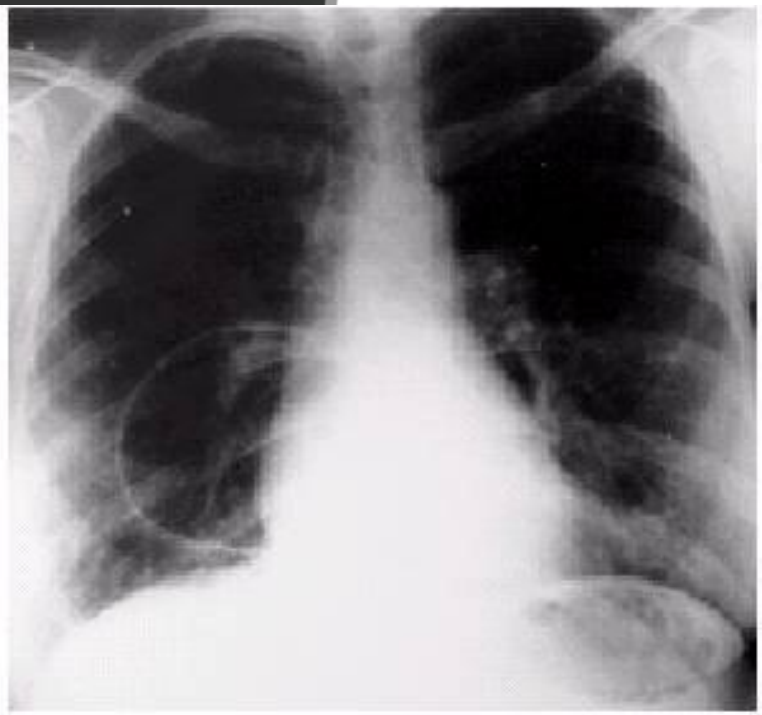
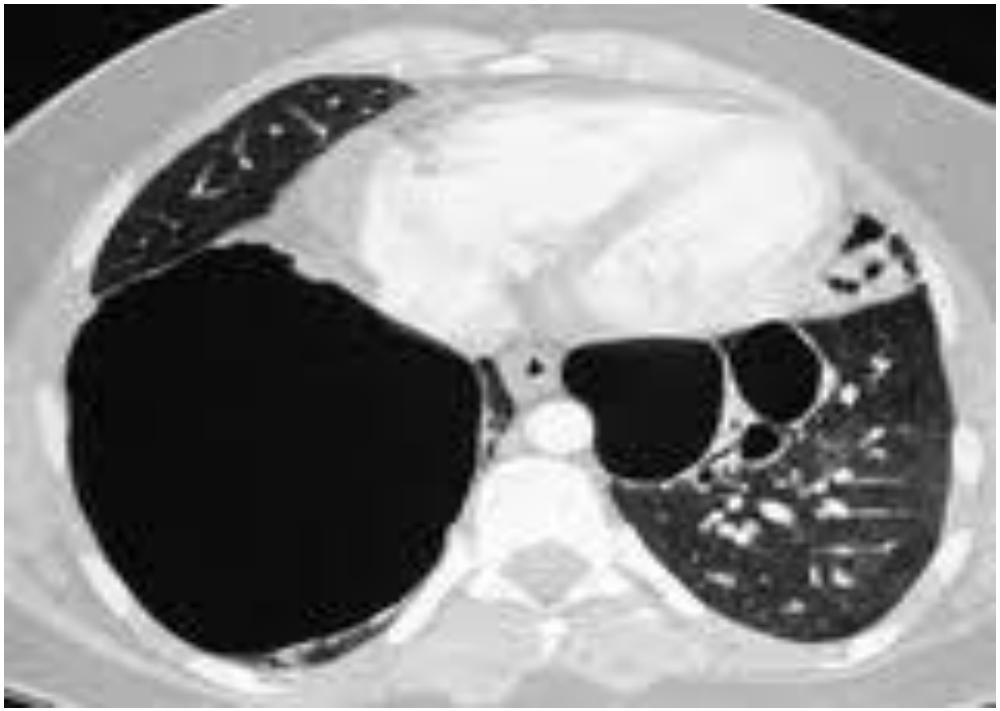
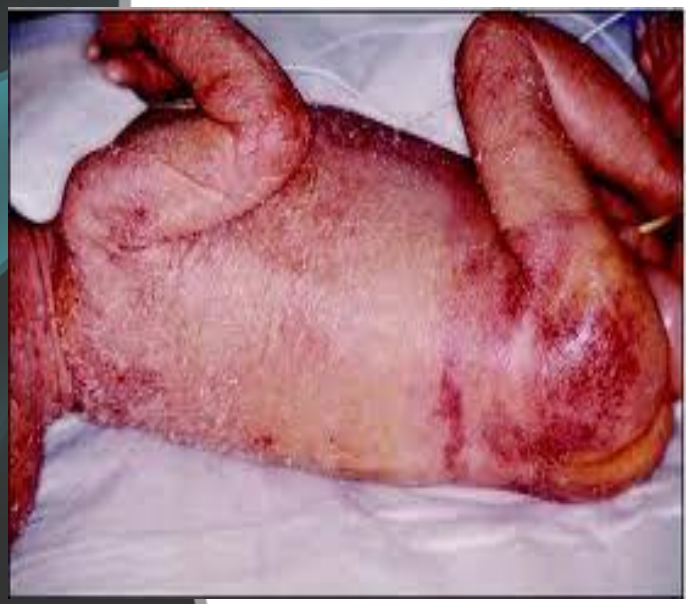
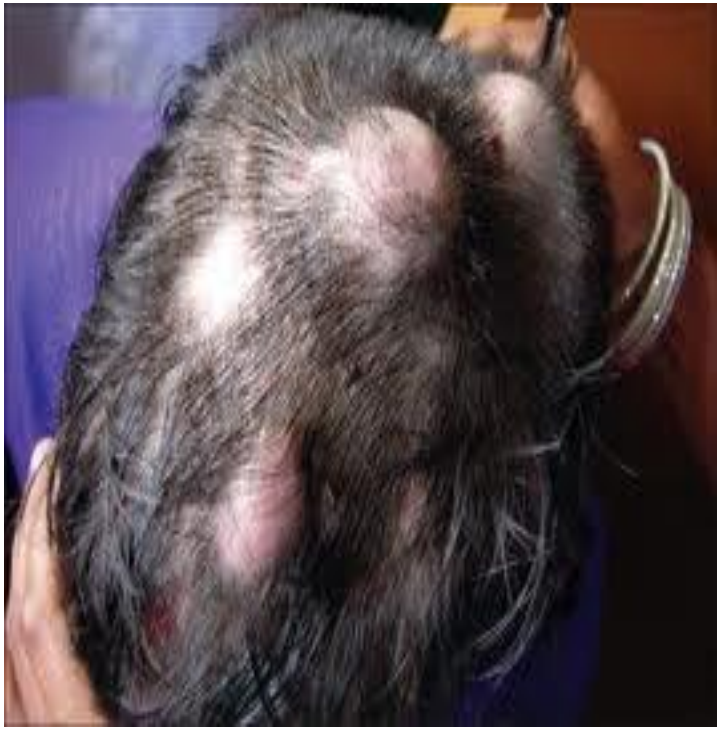


Fig. 1.– Radiografía simple de tórax



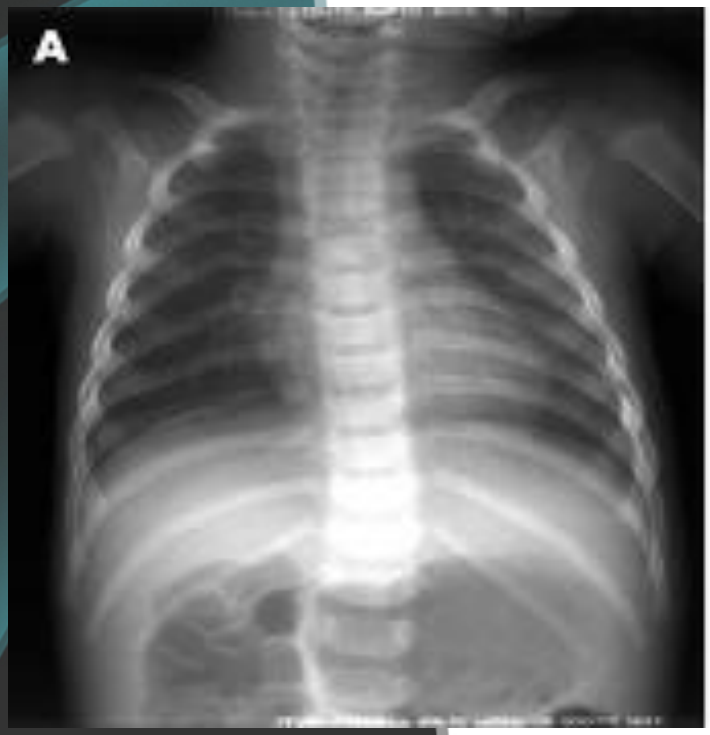
Hyper Ig E Syndrome- skin

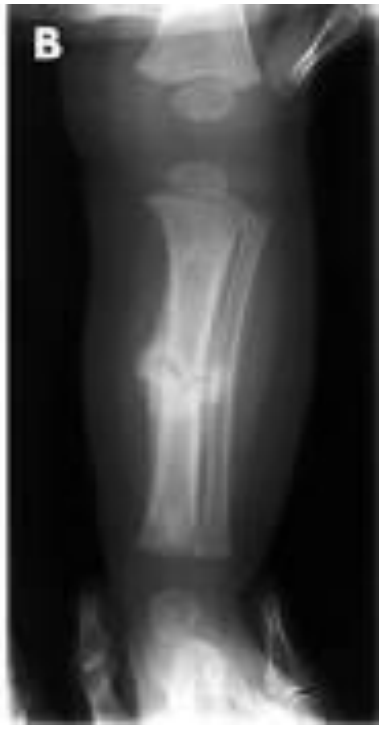




HyperIgE –Bone

- 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 : emolients , topical corticosteroids , prompt treament 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)

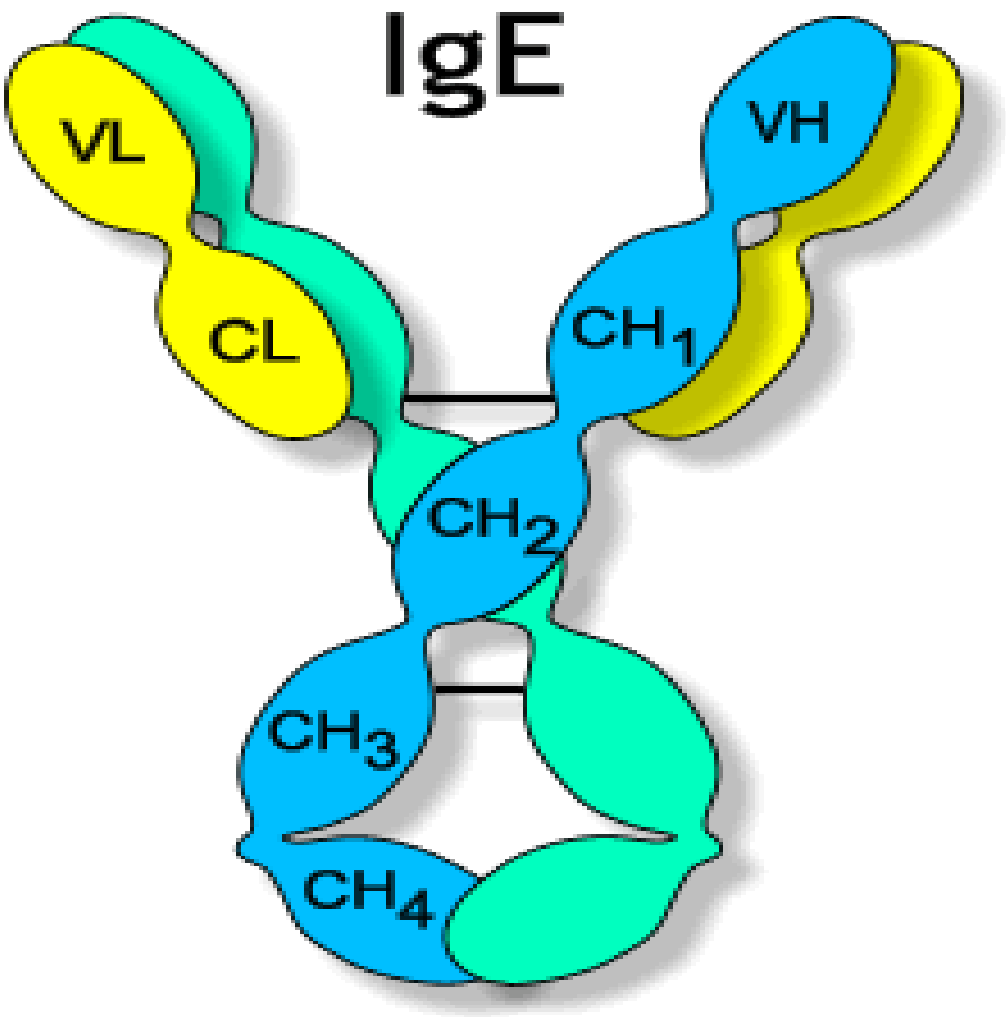
- High IgE + ID : Wiskott-Aldrich syndrome, Omenn syndrome, immune dysregulation , Common Variable ID or Chronic granulomatous disease

DD 2

- High IgE : parasitic infections and nonparasitic infections (eg, 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


IgE
VL
CL
VH
CH1
CH2
CH3
CH4

Immune system Overview

- Anatomic-mucociliary
- Innate immunity :

  cellular arm : pathogen associated molecular patterns eg lipopolysacchrides , mannans, dNA sequences(macrophages , NK cells , poly's)

  serum protein arm: rapid response , sequential patterns(complement, cytokines, acute phase proteins)

Overview 2

- Adaptive immunity- antigen specific responses and immunulogic memory.
- T cells : kill virus infected/ cancer cells , B cell activtaion , 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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