A Rare Primary Immunodeficiency Disorder

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Presenting complaints

- 9yr Fch, only child to 3rd degree consanguineous parents.
- Presented with
  - Chronic mucopurulent nasal discharge
  - Recurrent purulent ear discharge
  - Recurrent pustules

  since 2yrs of age
- Dry skin for 3 yrs
- Vulval swelling for 2yrs
- H/O failure to gain weight and height

Past history

- Diarrhoea until 5 months of age
- Fracture/ Dislocation of the right elbow at 4 years of age
- No history suggestive of pneumonia

Examination

- Conscious, wt and ht < 5th centile
- Coarse facies
- Eczema
- Seborrhoeic dermatitis over scalp, face and trunk
- Healed pyoderma scars
- No BCG scar
- Goitre
- Florid dental caries

- Deciduous teeth (about 5 in number)
- Generalized lymphadenopathy
- Joint hypermobility (Beighton 9/9)
- Ear examination – left ear – suppurative otitis media with central perforation

- CVS / RS : Normal
- PA : Spleen 5cms below LCM, firm

  Liver span normal
- Genitalia : B/L enlarged and indurated vulva. No signs of inflammation
- CNS : Normal

Florid dental caries

Healed pyoderma scar

Indurated
vulval swelling

Primary immunodeficiency disorder

- ? Jobs syndrome

Investigations

- CBC – Normal
- LFT, RFT, TFT – Normal
- PS – Microcytic hypochromic RBCs with normal WBC count with predominant neutrophils

- AEC – 370 cells/ mm3
- Ig E – 4870mg/dl(1 – 22),
- Ig G – 1974 mg/dl (700 - 1600),
- Ig M – 166 mg/dl (50 - 250),
- Ig A – 250 mg/dl (45 - 250)
- NBT test – Normal
- Urine metabolic screening – Negative

- Skin biopsy – Irregular epidermal acanthosis
  Focal spongiosis
  Parakeratosis with plasma cells and neutrophils
  Mild perivascular lymphocyte infiltrates

- USG abdomen – Mild splenomegaly

- MRI pelvis – Hypertrophy of subcutaneous fat in the region of the vulva. B/L multiple enlarged inguinal lymph nodes.
- ECHO – no evidence of coronary artery aneurysm

Why is this Job's

- Recurrent bacterial infections of skin
- Failure to thrive
- Eczema, seborrheic dermatitis
- Generalised hypermobility (Beighton 9/9)
- Coarse facies
- Retained primary dentition, dental caries
- Fracture/ dislocation in childhood

- Diagnosis is more syndromic than laboratory based ,for the only constant laboratory findings are eosinophilia and elevated IgE levels.
- Diagnosis in children is difficult – symptoms evolve over a long time.

SCORING SYSTEM WITH CLINICAL AND LABORATORY TESTS

- Highest serum Ig E levels – 10 (>2000)
- Skin abcesses - 8 (4-5/yr)
- Pneumonia episodes over lifetime - 0 (none)
- Parenchymal lung anomalies - 0 (none)
- Retained primary teeth - 8 (>3)
- Scoliosis, max curvature - 2 (10-14 degrees)
- #s with minor trauma - 4 (1-2)
- Highest eosinophil count - 0 (<700)

- Characteristic face - 5 (present)
- Midline anomaly - 0 (absent)
- Newborn rash - 0 (absent)
- Eczema - 4 (severe)
- URI /yr - 4 (>6)
- Candidiasis - 0 (nil)
- Other serious infections - 0 (none)
- Fatal infections - 0 (absent)
- Hyperextensibility - 4 (8/9)
- Lymphoma - 0 (absent)
- Increased nasal width - 3(>2SD)
- High palate - 2 (present)
- Young age correction - 0 (>5yrs)

Interpretation

scores of 0 – 15 = unaffected

16 – 39 = possibly affected

40 – 59 = probably affected

60 or > = definitely affected

Index child score = 54

HYPER IG E SYNDROME

- Rare primary immunodeficiency disorder – elevated serum Ig E, dermatitis and recurrent bacterial infections of skin and lungs.
- Davis et al in 1966 – Jobs syndrome
- Buckley et al in 1972 – Hyperimmunoglobulinemia E
- Two forms – AD HIES (STAT 3 deficiency)
  - AR HIES (Genetic cause unclear)

AD - HIES CLINICAL CHARACTERISTICS

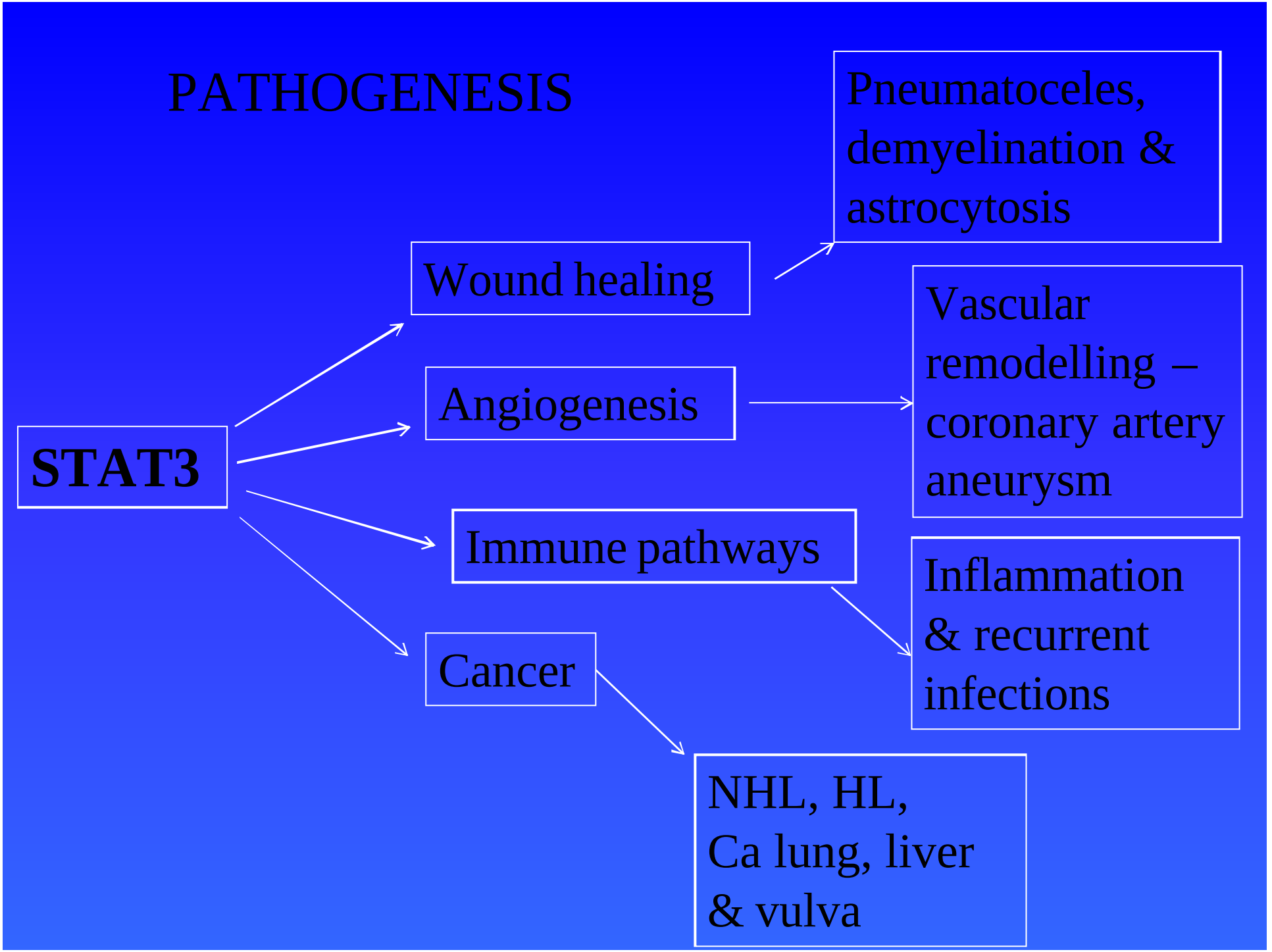
Somatic characteristics

- Characteristic face
- Hyperextensibility
- Retained primary teeth
- Minimal trauma fractures
- Scoliosis >10 degrees
- Coronary vasculature anomalies
- Arnold Chiari I malformations
- Focal hyperintensities on brain MRI

Immunologic characteristics

- Peak serum IgE >2000 IU/ml
- Recurrent pneumonias
- Parenchymal lung abnormalities
- Boils (cold abscess)
- Moderate – severe eczema
- Newborn rash
- Mucocutaneous candidiasis
- Recurrent sinusitis / otitis
- Eosinophilia
- Lymphoma

PATHOGENESIS



- Chemotactic abnormalities of neutrophils
- Normal phagocytic and bactericidal activity
- Underexpression of chemokines
- Reduced interferon gama synthesis
- Marked peripheral and local eosinophilia.

Treatment

- Bleach bath
- Life long antimicrobial prophylaxis to prevent skin and lung infections.
- IVIg – fulminant infections
- Periodic follow up – malignancies
- Routine dental care

Take home message

- Primary immunodeficiency is rare.
- Screen all children with eczema, recurrent URTI and pyoderma for HIES.
- HIES – heterogenous presentation hence diagnosis is difficult.
- Scoring system helpful.
- Though lung infection is the rule, may present without pulmonary involvement.
- Predisposition to malignancies.
- Significant hypermobility – comorbidities.

References :

- Nelson Textbook of Pediatrics 19th ed
- The hyperimmunoglobulin E syndrome – clinical manifestation diversity in primary immune deficiency, Szczawinska-Poplonyk et al, Orphanet J of rare diseases 2011,6:76
- STAT3 mutations in Hyper Ig E syndrome, NEJM, Oct 18 2007, 357:16
- The Hyper Ig E syndromes, Immunol Allergy Clin North Am. 2008 May;28(2):277

Thank you

Job's

- Classic triad of eczema, recurrent skin infections, lung infections and elevated IgE levels
- Expanded to include skeletal, connective tissue, cardiac and brain abnormalities

Skin involvement

- Pustular and eczematoid rashes; seen earliest in the newborn period
- Boils – degree of inflammation signs may be variable; aspirates from these “cold” abscesses grow Staphylococcus aureus

Pulmonary involvement

- Recurrent pyogenic pneumonias are the rule
- Organisms – Staphylococcus aureus, streptococcus pneumoniae, Hemophilus influenzae
- Symptoms may be less prominent
- Response to antibiotics is prompt but healing may be aberrant leading to pneumatocoeles and bronchiectasis

Other infections

- Mucocutaneous candidiasis is common – oral thrush, vaginal candidiasis and onychomycosis

Musculoskeletal features

- Scoliosis, osteopenia
- Fractures with minimal trauma
- Hyper extensibility
- Degenerative joint disease

Dental abnormalities

- Retained primary dentition – due to failure of exfoliation of primary teeth
- Permanent teeth when they erupt are normal

Arterial abnormalities

- Arterial aneurysms especially of the internal carotids and coronary arteries
- May be linked to the connective tissue abnormalities i.e. hyper mobility

Facial features

- Asymmetry
- Broad nose
- Deep set eyes
- Prominent forehead
- Rough facial skin, exaggerated pore size

Neurological abnormalities

- Craniosynostosis
- Chiari 1 malformations

Malignancies

- Hodgkins and non Hodgkins lymphoma
- Leukaemias
- Cancers of the vulva, liver and lung

- H/o seizures at 3yrs – treated with AED for 6 months

- Slightly delayed development in all domains.

Currently is normal with below average scholastic performance.

AR – HIES VS AD – HIES

- Much higher incidence of cutaneous viral infections – Molluscum contagiosum, herpes simplex and varicella zoster in AR – HIES.
- Sinopulmonary infections are common in AR – HIES
- Lung infections heal without pneumatoceles in AR – HIES

- AR – HIES patients have more symptomatic neurologic disease than those with AD – HIES
- AR – HIES lacks connective tissue and skeletal abnormalities, have normal primary tooth exfoliation, no fractures and have normal facies.

Immunomodulators

- IVIg may be useful during infections
- Omalizumab – monoclonal antibody against IgE is yet to be studied
- Levamisole, interferon gamma – not found to be of use.
- Bone marrow transplant – not useful

Why are we presenting this case

- Primary immunodeficiency disorders are rare
- Diagnosis is often difficult especially in Hyper IgE which has a very heterogenous presentation
- It may present without pulmonary involvement

- Scoring system may help in the diagnosis if the IgE levels are borderline
- Strong predisposition to vulval carcinoma which is otherwise very rare in children
- Significant generalised hypermobility should be picked up in children for it is associated with significant co morbidities

Take home message

- Screen all children with eczema, recurrent otitis media and pyoderma for Hyper IgE syndrome
- Job's syndrome can be seen without significant pulmonary involvement
- Close follow up - lymphoma (non Hodgkins, Hodgkins, vulval carcinoma)
- Significant generalised hypermobility – co morbidities