A Rare Primary Immunodeficiency Disorder

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Presenting complaints

• 9yr Fch, only child to 3\textsuperscript{rd} degree consanguineous parents.

• Presented with
  - Chronic mucopurulent nasal discharge since 2yrs
  - Recurrent purulent ear discharge of age
  - Recurrent pustules

• 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 – 4870 mg/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)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic face</td>
<td>5 (present)</td>
</tr>
<tr>
<td>Midline anomaly</td>
<td>0 (absent)</td>
</tr>
<tr>
<td>Newborn rash</td>
<td>0 (absent)</td>
</tr>
<tr>
<td>Eczema</td>
<td>4 (severe)</td>
</tr>
<tr>
<td>URI /yr</td>
<td>4 (&gt;6)</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>0 (nil)</td>
</tr>
<tr>
<td>Other serious infections</td>
<td>0 (none)</td>
</tr>
<tr>
<td>Fatal infections</td>
<td>0 (absent)</td>
</tr>
<tr>
<td>Hyperextensibility</td>
<td>4 (8/9)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0 (absent)</td>
</tr>
<tr>
<td>Increased nasal width</td>
<td>3 ( &gt;2SD)</td>
</tr>
<tr>
<td>High palate</td>
<td>2 (present)</td>
</tr>
<tr>
<td>Young age correction</td>
<td>0 (&gt;5yrs)</td>
</tr>
</tbody>
</table>
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

STAT3

Wound healing

Angiogenesis

Immune pathways

Cancer

Pneumatoceles, demyelination & astrocytosis

Vascular remodelling – coronary artery aneurysm

Inflammation & recurrent infections

NHL, HL, Ca lung, liver & vulva
• Chemotactic abnormalities of neutrophils
• Normal phagocytic and bactericidal activity
• Underexpression of chemokines
• Reduced interferon gamma 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