LRBA deficiency, getting to the gut of the problem

Melissa Norman
Immunology Fellow
Sydney Children’s Hospital
Background

- 7yo Turkish, non-consanguineous

- First presented age 3 in Turkey -
  - IPT -treated with IVIG and high dose methylpred
  - Chronic diarrhoea - ?associated salmonella
  - ALPS gene testing negative (FAS, FAS L, CASP10, CASP8, PRKCD)

- Diagnosed Evan’s Syndrome in Australia (4yo) 2013
  - Thrombocytopaenia
    - Bone Marrow- normocellular, increased megakaryocyte, consistent with peripheral destruction
    - DAT positive
    - Long term low dose steroids (<\=0.5mg/kg)
  - Anaemia
    - Life threatening haemolysis event (ICU) Nov 2014
    - 8 days post pneumovax
  - Fluctuating low grade neutropaenia
Infections and Immunity

- Recurrent Otitis Media-
  - Bilateral perforation and chronic d/c

- Immune work up-
  - Humoral
    - Low B cells
    - IgG initially normal (8), became low, IgM low (0.2), IgA very low (0.08)
    - Normal diphtheria, tetanus vaccine responses
    - Serology borderline Hib
    - Low pooled pneumococcal serology (3.3 pre pneumovax)

- Normal T-cell subsets and PHA
  - 8% DNTs (4% α/β T cells, 4% γ/δ T cells)

- NK cells numbers normal, reduced lysis, normal degranulation
Multi Organ Inflammation

- Hepatosplenomegaly

- Lymphadenopathy –
  - Reactive changes on Bx

- Pulmonary-
  - History of chronic cough
  - CT chest – Nov 2014 nodules
  - Bx - Patchy fibroblastic foci with chronic inflammatory change

- GIT-
  - Eosinophilic Oesophagitis April 2015
  - Colitis –
    - Abdominal pain and diarrhoea worsened Sept 2015
    - Weight loss and electrolyte disturbance – Supplemental feed/TPN
    - Chronic Clostridium Difficile and candida colonisation/infection
    - Scope – Eosinophil rich inflammatory infiltrate, candida species +
Genetics - no mutation CTLA4/ STAT3/ PIK3CD/ RAG1/2

- LRBA considered but not easily available – normal IgG

-Whole genome sequencing
LRBA Deficiency

- LPS Responsive Beige-like Anchor protein
- Co-localises with CTLA4 (inhibitory checkpoint protein) in endosome
- Trafficking to cell surface of activated T cells and Tregs -
  - Competitive inhibitor of CD28 for CD80/86 (high affinity)
  - Downregulation of T cell responses
- LRBA deficiency
  - Increased CTLA4 turnover, reduced expression on cell surface
  - Reduced Treg number and function

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune dysregulation</td>
<td>95%</td>
</tr>
<tr>
<td>Enteropathy</td>
<td>62%</td>
</tr>
<tr>
<td>AIHA</td>
<td>57%</td>
</tr>
<tr>
<td>ITP</td>
<td>52%</td>
</tr>
<tr>
<td>GLIDL</td>
<td>38%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24%</td>
</tr>
<tr>
<td>Chronic autoimmune hepatitis</td>
<td>14%</td>
</tr>
<tr>
<td>Eczema</td>
<td>10%</td>
</tr>
<tr>
<td>Uveitis</td>
<td>10%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5%</td>
</tr>
<tr>
<td>Organomegaly</td>
<td>86%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>64%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>33%</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>24%</td>
</tr>
<tr>
<td>Recurrent infections</td>
<td>71%</td>
</tr>
<tr>
<td>Parenchymal lung damage</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infections</td>
<td></td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td></td>
</tr>
<tr>
<td>Urinary infections</td>
<td></td>
</tr>
<tr>
<td>Hypo/Dy gammaglobulinemia</td>
<td></td>
</tr>
<tr>
<td>Low IgG</td>
<td>57%</td>
</tr>
<tr>
<td>Low IgA</td>
<td>52%</td>
</tr>
<tr>
<td>Low IgM</td>
<td>38%</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>24%</td>
</tr>
<tr>
<td>Deafness</td>
<td>5%</td>
</tr>
</tbody>
</table>

**FIG 1.** Clinical manifestations of LRBA-deficient patients grouped by organs or affected systems. Clinical manifestations are represented as percentages. Blue bars indicate immune dysregulatory diseases, red bars indicate organomegalias, green bars cluster respiratory tract infections and parenchymal lung damages, orange bars represent low levels of immunoglobulin classes, the dark blue bar indicates failure to thrive, and purple and dark green bars denote stroke and deafness, respectively.
Therapeutics

- **Abatacept**
  - CTLA4 Ig fusion drug
  - Competitive inhibitor of co-stimulatory T cell ligand (CD80/86)
  - Blocks activating interaction with CD28 on T cells and Tregs

- **Rapamycin (Sirolimus)**
  - mTOR inhibitor
  - Appropriate T cell activation mTOR dependent
    - Sensing, differentiation, trafficking
  - Induces lymphocyte apoptosis and increase Treg

- **Hydroxychloroquine**
  - Inhibits lysosomal degradation
  - Prevents CTLA4 loss
Treatment

- SCIG weekly Hizentra 2g (0.4mg/kg/month)
- Bactrim 125mg daily (5mg/kg)
- Prednisolone 5mg daily
- Abatacept SC weekly 250mg (10mg/kg)
  - Started at 10mg/kg IV monthly, increased to fortnightly IV, then weekly SC
- Sirolimus 1mg BD (2.5mg/m²)
  - Titrated to level
- Hydroxychloroquine 100mg daily (4mg/kg)
- Enteric coated budesonide 8mg daily
- Budesonide 2x 500mcg/2mL nebulies in slurry daily
- Fortisip 200mL x3 daily
- Lactobacillus
- Bovine Colostrum
- Fish Oil
- ?FMT
### HSCT for LRBA

<table>
<thead>
<tr>
<th>Age HSCT</th>
<th>Presentation</th>
<th>Transplant</th>
<th>Conditioning</th>
<th>Complications</th>
<th>Follow Up</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
</table>
Discussion Points

• Diagnosis -
  • Ascertainment bias effecting defined phenotypes

• Pathogenesis -
  • Role for dysbiosis/antigen stimulation
    • Anamemia post pneumovax
    • GIT dysbiosis ?FMT

• Treatment -
  • Personalised immunology
  • Doses of Abatacept
  • HSCT – risk v benefit and optimal timing
Thankyou!

Dr Brynn Wainstein
Dr Paul Gray