AN INTERESTING CASE OF PROGRESSIVE PNEUMONIA

PRESENTER - DR. REKHA

DEPARTMENT OF PAEDIATRICS
PAEDIATRIC INTENSIVE CARE UNIT
SRMC & RI
HISTORY

- 3 months old male child
- **Complaints:**
  - cough & cold - 4 days
  - increased work of breathing - 1 day
- No h/o fever, vomiting, loose stools, rashes
  - **Antenatal:**
    - PIH.
  - **Natal:**
    - born preterm (35 weeks) by LSCS
    - Birth Weight - 2 kgs.
  - **Postnatal:**
    - uneventful.
Past history:
- Baby was admitted earlier in SRMC at 40 days of life for umbilical sepsis
- At 47 days of life child was admitted and treated for seizures after DPT vaccine (hypocalcemia)

Family history:
- 2\textsuperscript{nd} born to 2\textsuperscript{nd} degree consanguineous parents.
Family history (contd.)

- First child
  - had lymphadenopathy following BCG vaccine was on INH prophylaxis for 6 months
  - had congenital heart disease
  - Had failure to thrive and was only about 5 kg at 1 year
  - Required ICU admission at 11 months of age for prolonged fever, jaundice, hepatosplenomegaly and respiratory distress
  - died at 1 yr of life
Developmental history:
  • social smile not attained.

Immunisation history:
  • Received BCG at birth (no complication), 1st dose of DPT

Dietary history
  • On Exclusive breast feeds.
GENERAL PHYSICAL EXAMINATION

- Child conscious, afebrile.
- Had respiratory distress.
- No pallor, icterus, cyanosis, lymphadenopathy, clubbing, pedal edema.
- No dysmorphic facies
- VITALS:
  - Temp-98.4 F, HR-153/min,
  - RR-70/min, BP-60/37mm Hg.
• ANTHROPOMETRY:

<table>
<thead>
<tr>
<th></th>
<th>Observed</th>
<th>Expected (as per WHO 2007 charts)</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>3.4 kg</td>
<td>6.5 kg</td>
<td>&lt; -3 SD</td>
</tr>
<tr>
<td>Length</td>
<td>52 cms</td>
<td>64 cms</td>
<td>&lt; -3 SD</td>
</tr>
<tr>
<td>Head circumference</td>
<td>38 cms</td>
<td>40.2 cms</td>
<td>- 2 SD</td>
</tr>
</tbody>
</table>

• RS:
  • NVBS heard / Bilateral wheeze

• Abdomen, CVS, CNS: Normal
  •
COURSE IN THE HOSPITAL

- Child was admitted with provisional diagnosis of Bronchiolitis and treated symptomatically
- Initial routine investigations were normal except for hypocalcemia (iv calcium given) and increased alkaline phosphatase
- Nasopharyngeal aspirate was positive for RSV.
- Respiratory distress progressed and Child developed fever spikes with pneumonic changes in CXR and seizures.
<table>
<thead>
<tr>
<th></th>
<th>26/9/10</th>
<th>30/9/10</th>
<th>5/10/10</th>
<th>11/10/10</th>
<th>24/10/10</th>
<th>26/10/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>9.3</td>
<td>8.5</td>
<td>7.1</td>
<td>15.9</td>
<td>11.0</td>
<td>12.9</td>
</tr>
<tr>
<td>TC</td>
<td>7450</td>
<td>3700</td>
<td>2230</td>
<td>3730</td>
<td>15460</td>
<td>9880</td>
</tr>
<tr>
<td>DLC</td>
<td>P30L53E7M10</td>
<td>P52L41E4M2</td>
<td>P55L38E5M2</td>
<td>P73L22EoM5</td>
<td>P95L6EoM0</td>
<td>P96.3L3.5E0Mo</td>
</tr>
<tr>
<td>Plt. count</td>
<td>7.47</td>
<td>4.91</td>
<td>2.88</td>
<td>1.42</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P/S</td>
<td></td>
<td>Anisopoikilocytosis, WBC &amp; Plt. normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALCIUM</td>
<td>6.8</td>
<td>10.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bld C/S</td>
<td>NG</td>
<td>NG</td>
<td>Klebsiella pneumoniae</td>
<td>NG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antibiotics were added in view of worsening respiratory distress.

Repeat Blood culture
  • grown Klebsiella species and antibiotics given based on sensitivity

CSF analysis – normal.

BAL analysis done in view of worsening respiratory distress
  • C/S - negative
  • PCR was positive for CMV.
  • Inj.Ganciclovir & immunoglobulin was added.
Bilateral lower lobe consolidation with multiple segmental consolidation in right middle lobe and left lingular area. Air bronchograms seen.

- Xray and CT were suggestive of thymic hypoplasia
- ECHO was normal
In view of

- similar history of recurrent infection in the first sibling child having umbilical sepsis,
- RSV Bronchiolitis,
- CMV Pneumonia and
- Klebsiella sepsis
- CT with thymic hypoplasia,
- Lymphopenia,
- Hypocalcemia
- Immunodeficiency disorder was suspected. Di George
Mother’s HIV serology - negative.

Immunoglobulin assay

<table>
<thead>
<tr>
<th>Immunoglobulins</th>
<th>Value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td>&lt; 0.45 g/l</td>
<td>0.7 – 4 g/l</td>
</tr>
<tr>
<td>IgM</td>
<td>21.88 mg/dl</td>
<td>40 – 230 mg/dl</td>
</tr>
<tr>
<td>IgG</td>
<td>&lt; 230 mg/dl</td>
<td>700 – 1600 mg/dl</td>
</tr>
<tr>
<td>IgE</td>
<td>0.30 IU/ml</td>
<td>0</td>
</tr>
</tbody>
</table>

FISH for Di George syndrome - negative.
<table>
<thead>
<tr>
<th>Investigations</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD₃⁺ (T Cells)</td>
<td>79 %</td>
<td>67 – 81</td>
</tr>
<tr>
<td>CD₃⁺ (Absolute Count)</td>
<td>20 Cells / µL</td>
<td>877 – 1875</td>
</tr>
<tr>
<td>CD₃⁺ CD₄⁺ (Helper Cells)</td>
<td>2.21 %</td>
<td>30 – 77</td>
</tr>
<tr>
<td>CD₃⁺ CD₄⁺ (Absolute Count)</td>
<td>5 Cells / µL</td>
<td>328 – 2130</td>
</tr>
<tr>
<td>CD₃⁺ CD₈⁺ (Cytoxic Cells)</td>
<td>0.31 %</td>
<td>19-33</td>
</tr>
<tr>
<td>CD₃⁺ CD₈⁺ (Absolute Count)</td>
<td>1 Cells / µL</td>
<td>200 - 616</td>
</tr>
<tr>
<td>CD&lt;sub&gt;3&lt;/sub&gt; - / CD19 + (B Cells)</td>
<td>61.9 %</td>
<td>8 – 18</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>CD&lt;sub&gt;3&lt;/sub&gt; - / CD19 + (Absolute Count)</td>
<td>157 Cells / µL</td>
<td>116 – 396</td>
</tr>
<tr>
<td>CD&lt;sub&gt;3&lt;/sub&gt; - / CD56 + (NK Cells)</td>
<td>1.0 %</td>
<td>5 – 14</td>
</tr>
<tr>
<td>CD&lt;sub&gt;3&lt;/sub&gt; - / CD56 + (NK Cells Absolute Count)</td>
<td>3 Cells / µL</td>
<td>74 - 254</td>
</tr>
<tr>
<td>T4 / T8 Ratio</td>
<td>5</td>
<td>&gt; 1.0</td>
</tr>
</tbody>
</table>

Suggestive of Severe Combined Immunodeficiency
Despite all management, child’s distress worsened, developed pneumothorax & required ventilatory support and died despite intensive care
SEVERE COMBINE IMMUNODEFICIENCY

- Absence of all adaptive immune function
- 12 mutated genes found.
- Overall incidence -3 -4/million live births. In USA, incidence is 1/50-75000 live births.
- Most severe immunodeficiency.

PATHOGENESIS:
- very small thymuses (<1 g)
  - Usually fail to descend from the neck
  - contain no thymocytes, and lack corticomedullary distinction or Hassall corpuscles.
- Both the follicular and paracortical areas of the spleen are depleted of lymphocytes.
- Lymph nodes, tonsils, adenoids, and Peyer patches are absent or extremely underdeveloped.
SEVERE COMBINED IMMUNODEFICIENCY

**CLINICAL MANIFESTATIONS:**

- 1st few months of life
- Recurrent or persistent diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections.
- Candida, varicella, measles virus, parainfluenza, CMV, EBV, adenovirus, and BCG infections lead to death.
- Affected infants also lack the ability to reject foreign tissue and are therefore at risk for graft versus host disease (GVHD)
SEVERE COMBINED IMMUNODEFICIENCY

INVESTIGATIONS:
- lymphopenia (<2500 cells/mm$^3$) that is present at birth,
  - condition could be diagnosed in all affected infants if white blood cell counts with manual differential counts were routinely performed on all cord bloods and the absolute lymphocyte count calculated.
- ADA deficiency have the lowest absolute lymphocyte counts
- T cells are extremely low or absent.
- Absence of lymphocyte proliferative responses
- Serum immunoglobulins - diminished to absent
- No antibodies are formed after immunizations.
**TREATMENT:**

- SCID is a true pediatric emergency.
- **Stem cell transplantation is the treatment of choice**
- Without stem cell transplantation, death usually occurs during the 1st year of life.
- If diagnosed within the 1st 3.5 mo of life,
  - HLA-identical or T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cell transplantation
  - No need for pretransplant chemoablation or post-transplant GVHD prophylaxis.
- **Gene therapy - ADA-deficient SCID and X-linked SCID**
  - Serious adverse events occurred in the case of X-SCID.
- **ADA-deficient SCID - Polyethylene glycol conjugated to the bovine-derived enzyme adenosine deaminase (PEG-ADA).**
- Genetic counseling and antenatal screen
WHEN TO SUSPECT IMMUNODEFICIENCY

(1) One or more systemic bacterial infections (sepsis, meningitis)

(2) Two or more serious respiratory or documented bacterial infections such as cellulitis, draining otitis media, pneumonia, lymphadenitis within one year

(3) Serious infections occurring at unusual sites (liver, brain abscess)

(4) Infections with unusual pathogens such as Aspergillus, Serratia, Nocardia, Burkholderia

(5) Infections with common childhood pathogens but of unusual severity
ADDITIONAL CLUES:

- >8 ear infections per yr
- >2 serious sinus infections per yr
- >2 month treatment with antibiotics with poor results
- Failure to thrive with or without chronic diarrhea
- Need for iv antibiotics to treat an infection usually treated with oral antibiotics
<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>T-CELL DEFECT</th>
<th>B-CELL DEFECT</th>
<th>GRANULOCYTE DEFECT</th>
<th>COMPLEMENT DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the onset of infection</td>
<td>Early onset, usually 2–6 mo of age</td>
<td>usually after 5–7 mo of age or later</td>
<td>Early onset</td>
<td>Onset at any age</td>
</tr>
<tr>
<td>Specific pathogens</td>
<td>Mycobacteria, Viruses</td>
<td>Streptococci, staphylococci</td>
<td>staphylococci,</td>
<td>Neisseria,</td>
</tr>
<tr>
<td></td>
<td>Candida, PCP</td>
<td>Haemophilus Campylobacter</td>
<td>Pseudomonas,</td>
<td>Escherichia coli</td>
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<tr>
<td></td>
<td></td>
<td>Enterovirus</td>
<td>Serratia, Klebsiella</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Giardia</td>
<td>Candida;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cryptosporidia</td>
<td>Nocardia, Aspergillus</td>
<td></td>
</tr>
<tr>
<td>Affected organs</td>
<td>FTT, protracted diarrhea, extensive</td>
<td>Sinopulmonary, gastrointestinal,</td>
<td>Skin, Lymphnode,</td>
<td>meningitis,</td>
</tr>
<tr>
<td></td>
<td>mucocutaneous candidiasis</td>
<td>malabsorption, arthritis, enteroviral</td>
<td>Oral cavity,</td>
<td>arthritis,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>meningoencephalitis</td>
<td>Dental, Osteomyelitis</td>
<td>septicemia,</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>sinopulmonary</td>
</tr>
<tr>
<td>Special features</td>
<td>Postvaccination disseminated BCG or</td>
<td>Autoimmunity, lymphoreticular</td>
<td>Prolonged</td>
<td>Rheumatoid</td>
</tr>
<tr>
<td></td>
<td>varicella</td>
<td>malignancy, postvaccination</td>
<td>attachment of</td>
<td>disorders,</td>
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<tr>
<td></td>
<td></td>
<td>paralytic polio</td>
<td>umbilical cord,</td>
<td>glomerulonephritis,</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>poor wound</td>
<td>angioedema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>healing</td>
<td></td>
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</tbody>
</table>
LABORATORY INVESTIGATIONS IN PRIMARY IMMUNODEFICIENCY DISORDER

**Stage 1**

- Initial laboratory screen
  - Full blood count and differential count and platelet count
  - Peripheral smear
  - ESR
- Immunoglobulins including IgE
- HIV screen
- Where indicated a sweat test for cystic fibrosis
- Mantoux test and chest X-ray to exclude tuberculosis
- *Candida skin tests can be used to document presence of delayed-type hypersensitivity*
ESR is normal
chronic bacterial or fungal infection is unlikely

neutrophil count is persistently elevated to extreme levels
absence of any signs of infection
Leukocyte adhesion deficiency

absolute neutrophil count is normal
congenital & acquired neutropenias leukocyte adhesion defects are excluded

absolute lymphocyte count is normal
severe T-cell defect is unlikely

platelet count and size is normal
Wiskott aldrich syndrome is ruled out
STAGE 2 INVESTIGATIONS

- **B-cell-related deficiencies**
  - specific antibody response to universal vaccination with tetanus, diptheria and pertussis protein antigens is performed
  - Response to conjugate pneumococcal vaccine or to polyvalent pneumococcal (pure polysaccharide response) vaccine may also be used in older children
- **B- cell count**
- **Lymphocyte phenotyping**
  - CD3 (total T cells)
  - CD4 (helper T cells)
  - CD8 (suppressor T cells)
  - CD19 (B cell)
  - CD16 + 56 (NK cell)
- **Complement fraction assay (CH50)**
Stage 3 INVESTIGATIONS

- Lymphocyte proliferation studies:
- Chronic granulomatous disease: the neutrophil burst test (flow cytometry)
- Leucocyte adhesion deficiencies – flow cytometric assay of CD 18 or CD 11
STAGE 4 INVESTIGATIONS

- Are available at specialised laboratories
  - Detailed complement fraction studies
  - Bruton’s tyrosine kinase (Btk) assays
  - Neutrophil chemotactic/ phagocytic assays
  - Leukocyte adhesion studies
  - CD40 ligand screening
THANK YOU