Pearl Title: Primary Antibody Deficiencies (PAD)

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Learning Objective

- Recognize clinical patterns suggestive of Primary Antibody Deficiency (PAD)
- Learn about different presentations of PAD
- Be familiar with the diagnostic methods for PAD.
- Be familiar with common treatments used for PAD.
- Be familiar with complications caused by PAD.
Definition

- Primary antibody deficiency (PAD) syndromes are a group of rare disorders characterized by an inability to produce clinically effective immunoglobulin (Ig) responses.

- Some disorders result from genetic mutations in genes involved in B cell development, whereas others appear to be complex polygenic disorders.
Primary Antibody Deficiencies: Spectrum of disorders

- Selective IgA deficiency
- CVID (Common Variable Immune Deficiency)
- Specific antibody deficiency disorders
- Agammaglobulinemia (Both x-linked and Autosomal recessive)
- Transient hypogammaglobulinemia of infancy
- IgG subclass deficiency
- Selective IgM deficiency
- Hyper IgM syndrome
Selective IgA Deficiency (SIgAD)

- **Prevalence:** 1:400 in the Caucasian population.
- **Definition:** IgA ≤ 7 mg/dl with normal IgG and IgM, normal B-cell numbers, normal specific antibody responses in most patients.
- 2/3 of patients are healthy and asymptomatic.
- **Symptoms** include:
  - **Autoimmune Disorders:** (Idiopathic Thrombocytopenic Purpura, Autoimmune Hemolytic Anemia, Rheumatoid Arthritis, Systemic Lupus Erythematosus, Thyroiditis, and Vitiligo).
  - **Sino-pulmonary Infections:** (Encapsulated bacteria).
  - **Gastrointestinal (GI) Disorders:** (Giardiasis, nodular lymphoid hyperplasia, Celiac Disease, and Inflammatory Bowel Disease).
  - **Allergic Disease:** (Asthma, Allergic Rhinitis, Atopic Dermatitis, and food allergy).
• Very rarely, anaphylactic transfusion reactions to plasma-containing blood products, due to presence of small amounts of IgA in blood products which reacts with anti-IgA antibodies present in such patients.

• In rare cases, Selective IgA Deficiency may progress to CVID

• Symptomatic patients should be followed longitudinally to determine if CVID develops.

• **Treatment**: Treat concomitant disorders, prophylactic antibiotics to reduce risk of infection and occasionally a trial of Immunoglobulin Replacement Therapy (IgGRT), if prophylaxis fails.
IgG Subclass Deficiency

- **Definition:** Absent/very low concentration of one or more IgG subclasses, with normal IgA, IgM and total IgG.

- Four different subtypes: IgG1, IgG2, IgG3, and IgG4

- **Symptoms:** Sinopulmonary/GI infections.

- **Diagnosis:** Total serum IgG, IgA, IgM, and IgE. IgG subclasses (obtained at initial evaluation, and only if vaccine response is impaired) Antibody titers to proteins/polysaccharide antigens like diphtheria, tetanus, *Hemophilus influenzae* type b (Hib), and *S. pneumoniae*

- **Treatment:** Prophylactic antibiotics might be considered. IgGRT reserved for patients with abnormal antibody responses and frequent or chronic infections.
Common Variable Immune Deficiency (CVID)

- Most common symptomatic primary immunodeficiency in adults
- **Prevalence:** 1:10,000 - 1:100,000
- **Etiology:** Impaired B cell differentiation with defective Ig production
- **Symptoms:** Clinically, patients develop recurrent sinopulmonary infections. 20% of patients have non-infectious complications: autoimmunity, chronic lung/GI disease and malignancy.
- **Diagnosis:** Low IgG, IgA and/or IgM **AND** poor responses to protein and polysaccharide vaccines
- **Treatment:** IgGRT is the standard of care in CVID and has led to decrease in infections and improved survival.
## Comparisons in diagnostic criteria of CVID

<table>
<thead>
<tr>
<th>Similarities</th>
<th>European Society of Immunodeficiency (ESID) 2014</th>
<th>International Consensus Document (ICON) 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG must be low</td>
<td>Impaired vaccine responses must be present</td>
</tr>
<tr>
<td></td>
<td>IgA or IgM must be low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other causes of hypogammaglobulinemia ruled out</td>
<td></td>
</tr>
</tbody>
</table>

## Differences

<table>
<thead>
<tr>
<th>Differences</th>
<th>European Society of Immunodeficiency (ESID) 2014</th>
<th>International Consensus Document (ICON) 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients could have normal vaccine responses, but they should have low memory B cells (&lt;70% of normal age range)</td>
<td></td>
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<tr>
<td></td>
<td>Clinical history of increased susceptibility to infections, autoimmunity, granulomatous disorder, unexplained polyclonal proliferation, or positive family history of PAD is required for the diagnosis</td>
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<tr>
<td></td>
<td>Diagnosis is established after the age of 4 years</td>
<td>Onset of symptoms above 2 years of age</td>
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</tbody>
</table>
Specific antibody deficiency

- **Definition:** Normal Ig, normal B-cell numbers, impaired specific antibody responses to polysaccharides vaccines. and *usually*, normal responses to protein based vaccines.

- **Symptoms:** Recurrent sinopulmonary infections.

- **Diagnosis:** IgG, IgG subclasses, IgA, IgM, and IgE. Vaccine response to Tetanus, Diphtheria and PneumoVax®

- **Treatment:** Prophylactic antibiotics, vaccination with conjugated pneumococcal vaccine (Prevnar), IgGRT in severe cases and failure of prophylactic antibiotics.
### Polysaccharide vaccine responses

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Phenotype</th>
<th>Response &lt; 6Yr</th>
<th>Response &gt; 6Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal conjugate</td>
<td>Normal</td>
<td>Normal Response 1.3 mg/mL*</td>
<td>protective antibodies to 70% of the serotypes tested, with at least a 2-fold increase in the titer</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>≤2 protective titers (≥1.3 mcg/mL)</td>
<td>≤2 protective titers (≥1.3 mcg/mL)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>&lt;70% of serotypes are protective (≥1.3 mcg/mL)</td>
<td>&lt;50% of serotypes are protective (≥1.3 mcg/mL)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 70% of serotypes</td>
<td>Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 50% of serotypes</td>
</tr>
<tr>
<td></td>
<td>Memory</td>
<td>Loss of response within 6 to 12 months</td>
<td>Loss of response within 6 to 12 months</td>
</tr>
</tbody>
</table>

* The consensus value in several studies is 1.3 mg/ml, but a value of 1.6 mg/ml has been used in other studies. Original table modified for this publication. From: Orange JS, Ballow M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the basic and clinical immunology interest section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2012; 130:S1
Agammaglobulinemia

- **Prevalence:** 1:379,000 US Live births

- **Etiology:** Failure of B-cells precursors to mature into B-cells, then plasma cells.

- **Genetics:** X-linked in 85-90% of cases, due to a mutation in the BTK* gene, Autosomal recessive in 10-15% of cases due to mutations in IGLL1**, CD79A gene BLNK˟, LRRC8˟, CD79B gene, PIK3R1 and TCF3*** gene.

- **Symptoms** Upper and lower respiratory tract by:
  - Encapsulated bacteria (*Streptococcus pneumoniae, HiB*)
  - *Mycoplasma* and *Ureaplasma* pneumonia, septic arthritis
  - *Pseudomonas* and *Staphylococcus* sepsis particularly in transient neutropenia.
  - Enterovirus infections (*polio, coxsackie, echo virus*), chronic diarrhea, meningitis, and fatal disseminated infection.

- **Diagnosis:** Agammaglobulinemia, deficient antibody responses to immunizations and absent/markedly reduced B cells in peripheral blood (CD19, CD20)

- **Treatment:** Lifetime IgGRT is indicated for all patients.

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* BTK: bruton tyrosine kinase; **IGLL: immunoglobulin lambda like polypeptide; ˟BLNK: b-cell linker; ˟LRRC8: Leucine-rich repeat-containing protein 8; ˟PIK3R1: phosphoinositide-3-kinase regulatory subunit 1; ˟˟TCF3:transcription factor 3;
B cells phenotyping in X-Linked Agammaglobulinemia

Patient

Control
Transient Hypogammaglobulinemia of Infancy

- **Etiology**: IgG is transferred through placenta from mother, and wears off in 3-6 months. Occasionally, infant’s immune system is not mature → transient hypogammaglobulinemia.

- No inherent defects of B-cell or defects of specific antibody responses

- **Symptoms**: Recurrent sinopulmonary or GI infections, candidiasis and sometimes meningitis.

- **Laboratory**: Low IgG, variably low IgA and rarely low IgM, normal specific antibody responses in most patients, normal B-cell numbers

- **Treatment**: Patients with frequent and/or more severe infections are treated with antibiotic prophylaxis or IgGRT till Ig normalizes.
Hyper-IgM syndrome

- **Prevalence**: 1:100,000
- **Genetics**: X-linked (CD40L), or autosomal recessive (CD40, UNG*, AID^)
- **Etiology**: Defects in Class-switch recombination (CSR) of Ig, with or without defects of somatic hypermutation (SHM)
- **CD40 /CD40L Deficiency**: is a combined immunodeficiency because of T cell involvement, severe infections, such as *P jirovecii* pneumonia, severe CMV disease and mucocutaneous candidiasis.
- **Complications**: failure to thrive in infants and liver disease (cirrhosis and cholangiocarcinoma)
Hyper IgM syndrome Cont’d

- **Laboratory**: Low IgG, IgA, and IgE with either normal or elevated IgM, T & B cell defects, neutropenia.

- **Treatment**: *PjP* prophylaxis, antibiotics, granulocyte colony-stimulating factor for neutropenia. immunosuppressive regimens for autoimmune manifestations. Hematopoietic cell transplantation could provide a curative option.

- **AID/UNG Deficiency**: Less common form of Hyper IgM. Characterized by recurrent sinopulmonary infections, mostly due to encapsulated bacteria, lymphoid hyperplasia, tonsillar hypertrophy, autoimmunity and malignancy

*AID: Activation-Induced Cytidine Deaminase; ^UNG: uracil-DNA glycosylase;
Normal switched memory B cell

8: (CD19+CD27+) IgD vs IgM

Q1-3

19+27+IgM+IgD+

19+27+IgM-IgD-

19+27+IgM+IgD-

19+27+IgM+IgD+

IgM FITC-A

IgD PE-A

IgM PE-A

IgD FITC-A

IgM FITC-A

IgD PE-A

IgM PE-A

IgD FITC-A

IgM FITC-A
Selective IgM Deficiency

- **Definition**: Absent/very low IgM and normal IgG/IgA.
- Associated with Autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, celiac disease, polymyositis, and Hashimoto’s thyroiditis.
- **Symptoms**: Sinopulmonary infections, most commonly seen in children. Adults present with allergies and autoimmunity in addition to these infections.
- **Laboratory**: Low or absent IgM and normal IgA, IgG, normal or impaired response to vaccines. Ruling out other conditions causing low IgM.
- **Treatment**: No commercially available highly enriched IgM preparation. Treatment with IgGRT maybe considered in those with selective antibody deficiency and recurrent infections.
Laboratory evaluation of Humoral Immune Deficiency

- Targeted History & Physical exam for recurrent infections and autoimmunity
- Quantitative serum Ig (age and sex matched controls)
- Measurement of Antibody production
  - Polysaccharide vaccine, PneumoVax®
  - Protein based: Tetanus, Diphtheria
  - 4 week post-immunization level within protective range, cut off varies with each vaccine. (See Orange et al. 2012)
- Peripheral blood lymphocyte subset analysis
### Selected CD markers used in PAD diagnosis

<table>
<thead>
<tr>
<th>T-cells</th>
<th>CD3</th>
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<tbody>
<tr>
<td>CD4</td>
<td>CD4 (CD3⁺CD4⁺)</td>
</tr>
<tr>
<td>CD8</td>
<td>CD8 (CD3⁺CD8⁺)</td>
</tr>
<tr>
<td>B-Cells</td>
<td>CD19 (CD3⁻CD19⁺)</td>
</tr>
<tr>
<td>Memory B-cell</td>
<td>CD19⁺CD27⁺</td>
</tr>
<tr>
<td>Non-switched memory B-cells</td>
<td>CD19⁺CD27⁺IgM⁺IgD⁺</td>
</tr>
<tr>
<td>Switched memory B-cells</td>
<td>CD19⁺CD27⁺IgM⁻IgD⁻</td>
</tr>
<tr>
<td>Transitional B cells</td>
<td>CD19⁺CD38⁺bright</td>
</tr>
<tr>
<td>Activated/autoimmune B cells</td>
<td>CD19⁺CD38⁻/lowCD21⁻/low</td>
</tr>
</tbody>
</table>
Figure 1. Evaluation of PAD*

- Recurrent sinopulmonary infection
- Infections + autoimmunity
- Infections + malignancy

**Check IgG, IgA, IgM Concentration**

- **Normal**
- **Low**

**Assess vaccine response**

- Normal response
- Poor Response

- **Evaluate periodically/Reassess secondary causes**
- **Specific Antibody Deficiency**
- **Low IgG, IgA, IgM**

**Other Causes for Hypogammaglobulinemia**

- **Yes**
- **No**

**Secondary Hypogammaglobulinemia**

- **Yes CVID**

*PAD: Primary antibody deficiency; **CVID: common variable immune deficiency*
References

1. Immune Deficiency Foundation website: http://www.primaryimmune.org/
2. https://Uptodate.com
11. Yong PF, Thaventhiran JE, Grimbacher B A rose is a rose is a rose," but CVID is Not CVID common variable immune deficiency (CVID), what do we know in 2011 Adv Immunol 111:47-107, 2011.
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