PEARLS OF LABORATORY MEDICINE

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TITLE: Primary Antibody Deficiency

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Slide 1:

Hello, my name is Joud Hajjar. I am an Assistant Professor of Medicine in Adult Allergy and Immunology at Baylor College of Medicine and Texas Children's Hospital. These slides were prepared by Dr. Maha Syed and myself. Welcome to this Pearl of Laboratory Medicine on "Primary Antibody Deficiency."

Slide 2:

In this pearl, we will take a brief look into the most common Primary antibody deficiencies. On completion, you should be familiar with the following:

- 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.

Slide 3:

Primary antibody deficiency (PAD) syndromes are defined as a group of rare disorders characterized by an inability to produce clinically effective immunoglobulin responses. Some disorders result from genetic mutations in genes involved in B cell development, whereas others appear to be complex polygenic disorders. The prevalence, symptoms, diagnosis and treatments of each of the major humoral immunodeficiencies will be discussed.

Slide 4:

Here is a list of the primary antibody deficiencies that we will be discussing in this presentation.

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

Slide 5:

Selective IgA Deficiency is the most common primary antibody deficiency. Its prevalence in the Caucasian population is 1 in every 400. It probably arises through several pathogenic mechanisms. However, the exact mechanism is not known, it is hypothesized that it is caused by defects in B cells or defective interactions between B and T cells. People with this disorder have absent immunoglobulin A (IgA). IgA protects against infections of the mucous membranes lining the mouth, airways and digestive tract**. From an immune standpoint, patients have very low/undetectable** IgA levels (usually<7 mg/dl) with normal IgM and IgG levels, few patients might have abnormal specific antibody responses. Two-thirds of the patients are healthy and asymptomatic.

Symptomatic patients may present with:

- Autoimmune disorders: (Idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, and vitiligo).
- Sino-pulmonary infections: (Encapsulated bacteria).
- Gastrointestinal Disorders: (Giardiasis, nodular lymphoid hyperplasia, celiac disease, and inflammatory bowel disease).
- Allergic Disease: (Asthma, allergic rhinitis, atopic dermatitis, and food allergy).

Slide 6:

In rare cases, anaphylactic transfusion reactions to plasma-containing blood products such as whole blood, fresh frozen plasma, and immune globulin preparations containing IgA. The mechanism behind this is the presence of antibodies directed against IgA, which can form in some patients with undetectable levels of serum IgA. Reactions occur when anti-IgA antibodies react to small amounts of IgA in plasma or immunoglobulin products.

In rare cases, Selective IgA Deficiency may progress to CVID. In these situations, Symptomatic patients should be followed clinically, and by IG longitudinally to determine if CVID develops.

For Laboratory evaluation, measurement of serum concentrations of IgA, IgG, and IgM is performed. A diagnosis on Selective IgA is confirmed with an isolated deficiency of serum IgA in the presence of normal IgG and IgM.

Treatment may include prophylactic antibiotics to reduce risk of infection and occasionally a trial of Immunoglobulin Replacement Therapy (IgGRT), if patients have specific antibody deficiency, and failed prophylaxis antibiotics.

Slide 7:

IgG Subclass deficiency: The IgG class of antibodies is composed of four different subtypes of IgG molecules: IgG1, IgG2, IgG3, and IgG4. Patients should have persistently low levels of one or two IgG subclasses and a normal total IgG, IgA and IgM.

Pathophysiology is unclear as no specific gene has been identified. Gene deletions, transcription errors and allotypic variations are just some mechanisms by which this disorder may occur.

Patients may present with sinopulmonary infections and Gastrointestinal infections.

Laboratory evaluation include clinical history and physical exam followed by 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 Streptococcus pneumoniae.

Treatment includes Prophylactic antibiotics. IgGRT is reserved for patients with abnormal antibody responses and frequent or chronic infections.

Slide 8:

Common Variable Immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency in adults. Its prevalence varies from 1 in 10,000 to 1 in 100,000. The hallmark of Common Variable Immune Deficiency is poor antibody production (Low IgG, IgA, and/or IgM), and poor responses to protein and polysaccharide vaccines. Clinically patients developed recurrent infections (mainly sinopulmonary). Twenty percent of patients have non-infectious complications: autoimmunity, chronic lung/gastrointestinal disease, and malignancy.

Laboratory evaluation includes the measurement of immunoglobulin levels, the demonstration of impaired responses to vaccinations, and exclusion of other causes of these abnormalities. Immunoglobulin G (IgG) replacement therapy (IGGRT) is the standard of care in CVID and has led to decrease in infections and improved survival.

Slide 9:

We discuss the similarities and differences in the diagnostic criteria of CVID between the European Society of Immunodeficiency (ESID) 2014, and the International Consensus Document (ICON) 2016. Both require low IgG levels, low IgA and/or IgM and that other causes of hypogammaglobulinemia to be excluded. The ICON requires the presence of impaired vaccine responses, while the ESID forgoes this criterion if the patient had low memory B cells. The age of the diagnosis should be above 2 years for ICON and above 4 years in ESID. The most striking difference is that the ICON criteria allows for CVID diagnosis based on laboratory findings solely, without the presence of clinical symptoms such as recurrent infections, autoimmunity, lymphoproliferation or positive family history, while ESID requires the presence of at least one clinical feature in addition to the laboratory findings to establish the diagnosis of CVID.

Slide 10:

Specific antibody deficiency (SAD) is a primary immunodeficiency disease characterized by normal immunoglobulins, IgA, IgM, total IgG, impaired specific antibody responses (polysaccharides); normal B-cell numbers but with recurrent infection and diminished antibody responses to polysaccharide antigens following vaccination.

Its Prevalence is 5-10% in Children> 2 years. The etiology is unclear, it may be caused by defects such as congenital molecular abnormalities

For subjects aged 6 to 65 years, a normal response is defined as protective antibodies to 70% of the serotypes tested, with at least a 2-fold increase from baseline level.

Symptoms include Recurrent sinopulmonary infections.

Treatment includes prophylactic antibiotics. Vaccination with a conjugate pneumococcal vaccine (Prevnar), while IgGRT should be preserved for patients with severe infections, who fail or unable to tolerate prophylactic antibiotics.

Slide 11:

This table provides values to assess the Polysaccharide vaccine (Pneumovax) response in patients with specific antibody deficiency. Immunization with a polysaccharide pneumococcal vaccine is used to assess immunologic response to polysaccharide antigens in patients over two years of age. Other than being a tool in diagnosis, vaccination enhances immunity to a common respiratory pathogen in patients suffering from recurrent infections. The Pneumovax vaccine response varies depending on the type of phenotype administered.

The value is 1.3 mg/mL is considered to indicate protective specific antibody level.

For patients above the age of 6 years, protective antibodies to 70% of the serotypes is tested, with 2-3-fold increase in the baseline antibody is considered appropriate response.

SAD, indicating impaired antibody response to PneumoVax is classified into mild, moderate and severe.

Severe SAD indicated that patients only have ≤2 protective titers (≥1.3 mcg/mL)

Moderate SAD is diagnosed when patients are able to mount protective antibodies to more than 3 serotypes, but <70% of serotypes for ages above 6 years and <50% for ages less than 6.

Mild SAD indicate that patients have failure to generate protective titers to multiple serotypes or failure to generate of a 2-3-fold increase in 50-70% of serotypes.

Finally, memory SAD indicated that patients had loss of protective antibody levels within 6 to 12 months after vaccination.

Slide 12:

Agammaglobulinemia occurs from failure of B-lymphocyte precursors to mature into B cells and the plasma cells needed to produce immunoglobulins. Its prevalence is 1:379,000 US Live births. It is either X-linked (XLA; Bruton's agammaglobulinemia) due to a mutation in the BTK

gene (85-90% of cases), or autosomal recessive (ARA) due to variations in IGLL1; CD79A gene BLNK, LRRC8, CD79B gene, PIK3R1 and TCF3 gene (10-15% of cases).

Symptoms include upper and lower respiratory tract:

- Encapsulated bacteria (Streptococcus pneumoniae, Hemophilus influenza B)
- Mycoplasma and ureaplasma pneumonia, septic arthritis
- Pseudomonas and Staphylococcus sepsis particularly in the setting of transient neutropenia. Enterovirus infections (polio, Coxsackie, echovirus), chronic diarrhea, meningitis, or fatal disseminated infection.

The definitive diagnosis relies on immunophenotyping by flow cytometry and gene sequencing. For further evaluation, agammaglobulinemia, deficient antibody responses to immunizations and absent/markedly reduced B cells in peripheral blood (CD19, CD20) is seen

Lifetime immunoglobulin replacement therapy is indicated for all patients.

Slide 13:

These images show B cells phenotyping of memory cells in peripheral blood samples. The first plot is from a patient with X-Linked Agammaglobulinemia showing absent $CD19^+$ cells in comparison to the second image on the right, where we see the control have normal $CD19^+$ population.

Slide 14:

Transient Hypogammaglobulinemia of Infancy is a Common immunodeficiency affecting children usually younger than 2 years. IgG is transferred through the placenta from mother, in 3-6 months this IgG wears off, and if the infant's immune system is not mature, the infant develops transient hypogammaglobulinemia. No inherent defects of B-cell maturation or function or defects of specific antibody responses. Low IgG levels and variably low IgA and rarely low IgM levels, normal specific antibody responses in most patients, normal B-cell numbers.

Symptoms include recurrent sinopulmonary or GI infections, candidiasis, and sometimes meningitis.

Diagnosis includes low IgG, IgA, IgM, normal specific antibody responses in most patients and normal B-cell numbers

Patients with frequent and/or more severe infections are treated with antibiotic prophylaxis or immunoglobulin replacement therapy until immunoglobulins normalize.

Slide 15:

Hyper-IgM is a heterogeneous group of genetic disorders resulting in defects of immunoglobulin class switch recombination (CSR), with or without defects of somatic hypermutation (SHM). Its Prevalence is 1 in 100,000. It could be either X-linked (CD40L), or autosomal recessive (CD40, UNG, AID).

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 include failure to thrive in infants and liver disease (cirrhosis and cholangiocarcinoma)

Slide 16:

Laboratory evaluation includes low IgG, IgA, and IgE with either normal or elevated IgM. Patients might have neutropenia. The major finding is absence of class witched B cells ($CD19^{+}IgM^{-}IgD^{-}$), an example will be shown on the next slide.

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

Activation-Induced Cytidine Deaminase/ uracil-DNA glycosylase deficiencies are less common forms of Hyper IgM and are characterized by recurrent sinopulmonary infections, mostly due to encapsulated bacteria, lymphoid hyperplasia, tonsillar hypertrophy, autoimmunity and malignancy.

Slide 17:

This plot shows the appearance of Normal switched memory B cell on peripheral blood analysis, which is usually absent in patients with HIGM syndrome.

Slide 18:

Selective IgM deficiency (SIgMD) is a rare immune disorder with absent/very low immunoglobulin M (IgM), and normal IgG and IgA antibodies. Its etiology is unclear and maybe caused by B-cell defects, disordered T cell help, and possibly, chromosomal defects.

It is associated with Autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, celiac disease, polymyositis, and Hashimoto’s thyroiditis.

Clinical features: sinopulmonary infections such as otitis media, chronic sinusitis, bronchitis, etc. Infectious manifestations are most commonly seen in children. Adults present with associated allergic and autoimmune in addition to these infections. Allergic diseases include rhinitis and sinusitis.

Diagnosis: low or absent IgM and normal antibody levels. Ruling out other conditions causing low IgM levels.

Treatment: There is no commercially available highly enriched IgM immunoglobulin preparation. Treatment with immune globulin therapy may be considered in those with selective antibody deficiency.

Slide 19:

In this slide, we discuss the laboratory evaluation of Humoral Immune Deficiency.

This should begin with a targeted history & physical exam for recurrent infections and autoimmunity. Following laboratory evaluations should be considered:

- Quantitative serum Ig (age and sex-matched controls)
- Measurement of Antibody production
- Polysaccharide vaccine, PneumoVax®
- Protein based: Tetanus, Diphtheria

The measurement of quantitative Antigen-specific Ig titer pre- and post-immunization will give important clues. 4-week post-immunization level should be within protective range, cut off varies with each vaccine.

Peripheral blood lymphocyte subset analysis should additionally be considered.

Slide 20:

These tables provide a summary of some of the CD markers that we use in diagnosing patients with PAD. T cells are CD3+, and they are either CD4 or CD8. CD19 is the marker for B cells, and CD27 marker on B cells indicates that those cells encountered antigen and became memory B cells. CD19CD27 which express both IgD and IgM did not class switch, and when IgD and IgM expression is lost, this indicated that those B cells have undergone class switching, to produce IgA, IgG or IgE. CD19+CD38+bright are transitional B cells, while $CD19^{+}CD38^{-/low}CD21^{-/low}$ are autoreactive B cells that might be expanded in patients with CVID and autoimmunity

Slide 21:

This figure summarizes the evaluation algorithm of PAD.

Patients with Recurrent sinopulmonary infection or infections + autoimmunity or infections + malignancy, should have IgG, IgA and IgM levels evaluated. For patients with normal levels assess the vaccine response. For normal response evaluate periodically/Reassess for secondary causes. A poor vaccine response, with normal IG levels implies selective antibody deficiency (SAD).

For patients with low levels, other causes of hypogammaglobulinemia should be ruled out such as protein-losing enteropathy, proteinuria or medications causing hypergammaglobulinemia such as steroids/antiepileptics. If none of those causes are confirmed, treatment should be directed to the underlying causes, and those patients are considered to have secondary hypogammaglobulinemia. Otherwise, the next step should be to assess vaccine responses. Low levels of IgG, IgA, IgM + Poor response might suggest diagnosis of CVID, if the other criteria that we have discussed earlier are met.

Slide 22: References

Slide 23: Disclosures

Slide 24: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory medicine on "Primary Antibody Deficiency."