B-cell Defects: A Clinical and Immunological Approach

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Abstract

Primary immune deficiency diseases (PIDs), better known as inborn errors of immunity (IEIs), are a group of heterogeneous diseases with increased susceptibility to infections, autoimmunity, allergy, and malignancies, caused by a defect in the immune system. The latest classification on IEI by International Union of Immunological Societies (IUIS) has described around 416 IEIs. "Predominant antibody deficiencies" contribute to the largest group of IEIs in most of the published cohorts worldwide. B-cell defects/antibody deficiencies would be discussed in this paper, and the reader would be provided with a simplified clinical and immunological approach to these diseases.

Keywords: Agammaglobulinemia, Antibody deficiency, B-cell defect, Hypogammaglobulinemia, Immune deficiency.

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Introduction

Primary immune deficiency diseases (PIDs), better known as inborn errors of immunity (IEIs), are a group of heterogeneous diseases with increased susceptibility to infections, autoimmunity, allergy, and malignancies, caused by a defect in the immune system. The latest classification of IEIs by the International Union of Immunological Societies (IUIS) has described around 416 IEIs.[1] "Predominant antibody deficiencies" contribute to the largest group of IEIs in most of the published cohorts worldwide. B-cell defects/antibody deficiencies would be discussed in this paper, and the reader would be provided with a simplified clinical and immunological approach to these diseases.

B Cells and Immunoglobulins

B cells constitute around 10–20% of peripheral blood lymphocytes. They are produced in the bone marrow and undergo further differentiation in the secondary lymphoid tissues (lymph nodes) into plasma cells and memory cells. Plasma cells produce immunoglobulins or antibodies. When they encounter with the antigen/pathogen in the tissue, IgM antibodies are produced in the initial phase of the immune response. Later, class switching results in the production of either IgG, IgA, or IgE antibody based on the type of infection and the cytokine milieu in the tissue. Defects in β-cell production or function are known to cause "humoral" immune deficiencies.

Clinical Presentation

Children with antibody deficiencies present beyond 6 months of age, as they are protected by maternally transferred IgG in the first 3–6 months of life. Most of them manifest with recurrent sinopulmonary infections caused by encapsulated bacteria (*S. pneumoniae*, *H. influenzae*, etc.). Bronchiectasis is a complication often noted due to delay in the diagnosis. Chronic diarrhea caused by giardiasis is a known presentation. Autoimmune manifestations are noted in 20–30% of patients with common variable immune deficiency (CVID). These include autoimmune hemolytic anemia, thrombocytopenia, and arthritis.

Common β-cell Defects

X-linked Agammaglobulinemia

Previously called "Bruton agammaglobulinemia", X-linked agammaglobulinemia (XLA) is the prototype humoral immune deficiency characterized by absent β cell and agammaglobulinemia.

Etiology: Mutation in the Bruton tyrosine kinase (BTK) gene located on the X-chromosome.

Pathogenesis: Arrest in β-cell development during the Pro-B stage, resulting in severe β-cell lymphopenia, panhypogammaglobulinemia and paucity of secondary lymphoid organs.

Clinical presentation: Recurrent infections in affected boys. Onset >6 months of age.

Common infections: Sinusitis, otitis media, and pneumonia (complication—bronchiectasis).

Other issues: Meningitis, enteroviral encephalitis, and arthritis (caused by mycoplasma and ureaplasma).

"Absent tonsils and non-palpable lymph nodes in young boys with recurrent infections must make one think of XLA."

Organisms: S. pneumoniae, *H. influenzae*, *E. coli*, *S. aureus*, *Klebsiella*, *Giardia*, and *Enterovirus*.

Diagnosis

- Neutropenia may be seen (usually noted in the presence of severe infection)
- Low serum IgG, IgA, and IgM
- Absent β cell (on flow cytometry)
- Low BTK expression on monocytes (flow cytometry)
- Mutation in the BTK gene (Sanger sequencing or next generation sequencing)

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Treatment: Intravenous immunoglobulin (IVIg) 400 mg/kg/month for life.

IgA Deficiency

IgA deficiency—serum IgA <2 standard deviation for age.

Selective IgA deficiency—IgA <7 mg/dL (at or >4 years of age).

Etiology: The basic defect is unknown. In certain families, IgA deficiency is noted in multiple members in successive generations and hence an autosomal dominant pattern of inheritance is suspected.

Drugs causing IgA deficiency: Phenytoin, D-penicillamine, gold, and sulfasalazine.

Clinical presentation: Though IgA deficiency is common in certain populations, it is a mild immune deficiency and patients present with recurrent sinopulmonary infections.

Common infections: Sinusitis, otitis media, and chronic diarrhea (related to giardiasis).

Autoimmune disorders are increased in patients with IgA deficiency.

The following should be noted:

- Children presenting with serious infections and low IgA levels (and normal IgG) must be investigated for IgG2 subclass deficiency.
- Children with IgA deficiency must be followed up as some of them may evolve into CVID (common variable immune deficiency).

Common Variable Immune Deficiency

This is the most common symptomatic immune deficiency in adults. Common variable immune deficiency (CVID) comprises of a group of diseases characterized by low serum immunoglobulins and normal β-cell counts.

Etiology: Most patients do not have an identified genetic defect. Underlying genetic defect with autosomal recessive or dominant inheritance has been identified in 10% of the cases. Genes—ICOS, BAFF-R, CD19, CD20, CD21, CD81, TACI, etc.

Pathogenesis: Though β-cell are present in normal numbers, they fail to differentiate into antibody-producing plasma cells.

Clinical presentation: Onset in adolescents and adults. It is prudent to remember that a majority of the patients with CVID would first present to adult physicians, gastroenterologists, and pulmonologists.

- Common infections—sinusitis, otitis media, pneumonia, diarrhea.
- Recurrent pneumonia leads to bronchiectasis.
- Increased predisposition to autoimmune disorders—autoimmune hemolytic anemia, immune thrombocytopenia, arthritis, alopecia areata, pernicious anemia.
- Increased risk of lymphoma and gastric carcinoma.
- Noncaseating granulomas affecting lung, liver, spleen, and skin can be seen.

Organisms: S. pneumonia, *H. influenza*, *Mycoplasma*, *Giardia*, *Norovirus*, etc.

Diagnosis

- Recurrent infections/autoimmunity and
- Low IgG and low IgA or low IgM and
- Exclusion of other causes of hypogammaglobulinemia

Immunological phenotype: Hypogammaglobulinemia with normal β-cell counts.

The following features further favor the diagnosis of CVID:

- Reduced class switch memory β cell.
- Low postvaccination titers (antipneumococcal, anti-tetanus, antidiphtheria, etc.).
- Low isohemagglutinin titers (anti-A and anti-B titers)

Treatment—IVIg 400 mg/kg/month for life.

IgG2 Subclass Deficiency

Four IgG subclasses: IgG1, IgG2, IgG3, and IgG4.

IgG2 protects against polysaccharides (encapsulated bacteria).

Etiology: Unknown.

Clinical presentation: Recurrent infections with encapsulated bacteria (*S. pneumoniae*, *H. influenza*, etc.).

Diagnosis: Low IgG2 levels for age.

Total IgG is normal or elevated (due to compensatory increase in other IgG subclasses).

Clinically significant IgG2 deficiency = IgG2 subclass deficiency + poor vaccine response

Only clinically significant IgG2 deficiency warrants treatment.

Treatment

- Antibiotic prophylaxis (co-trimoxazole),
- Vaccination (pneumococcal conjugate vaccine PCV13 followed by PPSV23).
- Despite these measures, if there are ongoing infections, consider IVIg 400 mg/kg/month.

Patients with IgA deficiency and significant infections must be investigated for IgG2 deficiency.

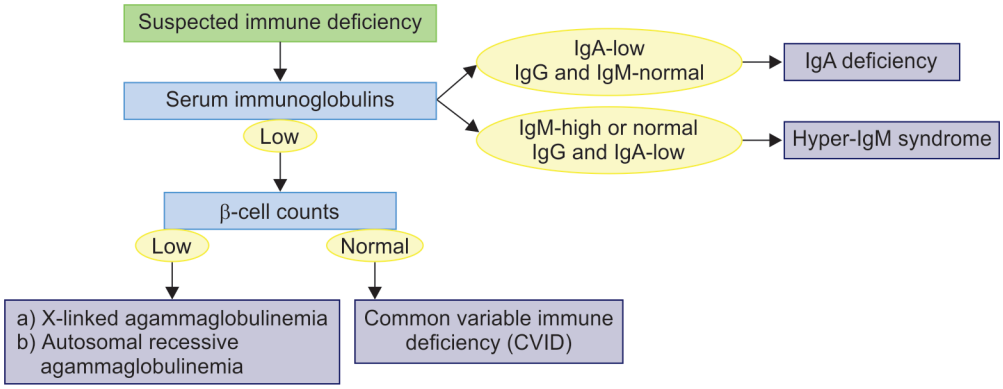
Laboratory Approach

Complete blood counts along with absolute neutrophil and lymphocyte counts provide valuable clues to the underlying PID. Patients with X-linked agammaglobulinemia and hyper-IgM syndrome may present with neutropenia. Antibody production by β cells can be estimated by the measurement of serum immunoglobulins, which are a useful screening test for β-cell defects. Serum immunoglobulins must always be interpreted keeping age-appropriate norms in mind. A simplified laboratory approach is provided in Flowchart 1.

Treatment

Children and adults with agammaglobulinemia or hypogammaglobulinemia must be treated with replacement IVIg for life. A dose of 400 mg/kg/month has been recommended. Dose must be titrated and individualized targeting freedom from

Flowchart 1: A simplified algorithm for investigating a suspected case of β-cell disorder



infections. In the presence of bronchiectasis, doses as high as 800–1,000 mg/kg/month may be needed.

Conclusion

B-cell defects/antibody deficiencies form the most common group of PIDs. Children and adults presenting with recurrent sino-pulmonary infections and chronic or recurrent gastrointestinal infections must be investigated for β-cell defects. Patients with β-cell defects are at increased risk of autoimmune diseases and malignancies. Serum immunoglobulin estimation is a readily available, cost-effective tool to screen for β-cell defects.

Reference

1. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2019 Update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 2020;40(1):24–64. DOI: 10.1007/s10875-019-00737-x.