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Antibody Deficiency Disorder

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Introduction

Antibodies or immunoglobulins (Ig) play an important role in the immune system mechanisms of defense. They fight off extracellular pathogens, for instance, bacteria and can neutralize viruses when they are in the bloodstream and other body fluids. Normal individuals have 5 classes of immunoglobulins, which are IgM, IgG, IgA, IgD and IgE and immunoglobulin subclasses including IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. Sometimes an antibody deficiency disorder takes place. It can happen due to several causes including a genetic absence of an important enzyme in B-cell development that renders immature B cells that are unable to proliferate into mature Ig-producing B cells or may be caused when T lymphocytes do not signal B lymphocytes or are idiopathic.

The most common antibody deficiency disorders include:

- X-linked agammaglobulinemia (Bruton disease)
- Transient hypogammaglobulinemia of newborn
- Selective Ig immunodeficiencies, for example, IgA selective deficiency
- Super IgM syndrome
- Common variable immunodeficiency disorder

Etiology

X-linked Agammaglobulinemia (Bruton Disease)

It is seen in boys. It is due to a failure of pre B cells to differentiate into mature B lymphocytes as caused by a mutation in the gene that encodes for a tyrosine kinase protein needed for further differentiation.

Transient Hypogammaglobulinemia of Newborn

It is a physiological reaction of the body after the maternal antibody disappearance about 4 to 6 months of age. The child is susceptible to recurrent infections similar to those seen in X-linked agammaglobulinemia. Once the child's immune system matures and makes antibody, this problem is corrected.

Selective Ig Immunodeficiencies (IgA selective deficiency)

Normally, antibodies switch from IgM to other classes including IgG and IgA. Sometimes there is malfunctioning in heavy-chain gene switching and causes this problem.

Super IgM Syndrome

In this disease the gene encoding the CD40 ligand on T cells is anomalous. That creates that B and T-lymphocyte cooperation in the immune response be compromised. The failure to interact with CD40 results in an inability of the B cell to switch from the production of IgM to the other classes of antibodies.

Common Variable Immunodeficiency Disorder

It expresses in the second or third decade of life or later. It has an unknown etiology.

Epidemiology

Data have shown that the most prevalent immunodeficiency disorders are the antibody deficiencies. These have been

documented in many countries. For instance, in Singapore, 39 patients were diagnosed with immunodeficiency between 1990 and 2000 and the 41% were antibody deficiency. Similarly, in South Africa (51%), Korea (53.3%) and Taiwan (46%) reported this problem. In Denmark, medical records were reviewed and identified a CVID prevalence of 1:26,000, a peak in the fourth decade and the frequency of respiratory infections was 98%. Other problems such as bronchiectasis (36%) and splenomegaly (22.4%) were reported.

Pathophysiology

Antibodies or immunoglobulins protect against extracellular microorganisms such as bacteria. They are produced by plasma cells, which are the product of the differentiation of mature B lymphocytes. Antibody deficiencies may occur due to lack of B-cells maturation, missing enzymes or failure of T-cell stimulatory signals for appropriate antibody production. In transient hypogammaglobulinemia of infancy, recurrent bacterial infections occur in children until their immune system matures.

Histopathology

X-linked agammaglobulinemia lacks germinal centers, and lymphoid architecture is grossly altered. Hyper-IgM syndrome results in elevated IgM concentrations along with IgG and IgA-selective immunodeficiency. The gallbladder in these patients shows alterations in submucosa that consists of cells with eccentric nuclei and pink-staining cytoplasm. These cells produce large quantities of IgM. Several immunodeficiencies can manifest lymph nodes with multiple B-cell follicles of variable sizes and proliferation centers when immunohistochemical staining for CD21 and CD79a is used.

History and Physical

In antibody immunodeficiency disorders, there is a history of:

- Recurrent bacterial infections
- Fever
- Opportunistic infections
- Frequent use of antimicrobials without noticeable improvement

The physical findings include:

- Bacteremia
- Sinus and lung infections like pneumonia
- Otitis media
- Meningitis
- Septicemia
- Arthritis
- A cough
- Malaise
- Intestinal malabsorption
- Bronchiectasis
- Recurrent tonsillitis
- A sore throat
- Purulent conjunctivitis
- Pyodermitis

- Failure to thrive
- Diarrhea
- Low set ears and facial dysmorphisms
- Recurrent abscess
- Septic shock
- Asthenia
- Anorexia
- Loss of weight
- Aphthous stomatitis
- Urinary sepsis
- Denture abnormalities and periodontitis

Evaluation

The immunological investigation of a patient with antibody deficiency includes the assessment of both B and T lymphocytes and other investigations as follow:

Quantitative Serum Immunoglobulins

- IgG
- IgM
- IgA

IgG Sub-Classes

- IgG1
- IgG2
- IgG3
- IgG4

B-cell Quantitative Assessment

- Levels of CD19
- Levels of CD20
- Levels of CD21
- Levels of CD81
- Levels of CD 225

Antibody Activity

Detection of isohemagglutinins (IgM)

- Anti-type A blood
- Anti-type B blood

IgG antibodies (post-exposure)

- Rubella
- Measles
- Varicella Zoster

IgG antibodies (post-immunization)

- Tetanus toxoid
- Diphtheria toxoid
- Pneumococcal polysaccharide
- Polio

Other assays

- Serum protein electrophoresis

Blood Lymphocyte T Subpopulations

- Total lymphocyte count
- T lymphocytes (CD3, CD4, and CD8)
- CD4/CD8 ratio

Lymphocyte Stimulation Assays

- Phorbol ester and ionophore
- Phytohemagglutinin
- Antiserum to CD3

Phagocytic Function

Nitroblue tetrazolium (NBT) test (before and after stimulation with endotoxin)

- Unstimulated
- Stimulated

Neutrophil mobility

- In medium alone
- In the presence of chemoattractant

Microbiological Studies

- Stool (testing for bacterial infection)
- Sputum (bacterial culture)
- Cerebrospinal fluid (culture, chemistry, and histopathology)
- Blood culture

Levels of Cytokines

- IL-1
- IL-2

- IL-4
- IL-5
- IL-6
- IL-13
- IL-17
- IL-22

Other Investigations

- Complete blood cell count
- Blood chemistry
- Chest x-ray
- Diagnostic ultrasound
- CT scan
- Fluorescent in situ hybridization (FISH)
- DNA testing

Treatment / Management

Antibody deficiency after diagnosis can be received intravenous immunoglobulin (IVIG) replacement therapy that is mostly IgG, but it may be enriched with IgM and IgA. It can be applied intravenously or intra-subcutaneously. Other medications used include antimicrobials such as broad-spectrum antibiotics and metronidazole, which may be used if anaerobes bacteria are suspected. Transfer factor is used if an underlying T-cell failure is suspected.

Bone marrow transplantation (BMT) and gene therapy, which remain experimental, can be the solution for those deficiencies caused by genetic abnormalities, for instance, the use of BMT in X-linked agammaglobulinemia. In case of septic shock treatment with steroids is reserved. Nutritional supplements can be administered including vitamins A, C, E and B6, iron, zinc, selenium, and copper.

Differential Diagnosis

The most important differential diagnosis includes the following: X-linked agammaglobulinemia characterizes by recurrent bacterial infections in boys, and genetic studies may reveal the presence of Bruton's tyrosine kinase (BTK) mutations. Transient hypogammaglobulinemia of newborn presents in newborns above the age of 4 months, and characterizes by recurrent pneumonia, meningitis, otitis media and other problems that resemble Bruton's disease. It is a physiological defect in the immune system caused by maternal IgG disappearance and corrected soon but requires treatment. In super-IgM syndrome, recurrent bacterial infections occur, but the cause of this illness is a mutation in the gene encoding for CD40 on T lymphocytes that causes a failure in T and B lymphocyte cooperation. Common variable immunodeficiency presents with recurrent bacterial infections including sinopulmonary problems but later in life (second-fourth decade), and the diagnosis is made once all causes of immunodeficiency have been ruled out.

Antibody deficiency may present in other diseases including:

- Multiple myelomas
- Burns
- Severely combined immunodeficiency disorders (SCID)
- Immunodeficiency with ataxia-telangiectasia
- DiGeorge syndrome

- Lymphomas
- Acute leukemia and others lymphoproliferative disorders
- Malnutrition
- Interleukin-12 receptor deficiency
- HIV/AIDS
- Use of immunosuppressors
- Systemic lupus erythematosus
- Bare leukocyte syndrome
- Organ transplantation recipient
- Sarcoidosis
- Amyloidosis
- Interferon-gamma (IFN-gamma) receptor deficiency
- Chronic granulomatous disease
- Wiskott-Aldrich syndrome
- Obesity
- Chronic renal failure
- C3 deficiency
- Toll-like receptor deficiency and other innate immune system-related deficiencies
- X-linked lymphoproliferative (XLP) syndrome
- Zinc deficiency
- TRAF3 adaptor molecule deficiency
- WHIM syndrome
- UNC93B deficiency
- Down syndrome
- Hemoglobinopathy

Prognosis

Antibody deficiency disorders have a better prognosis if they can be treated with intravenous immunoglobulins (IVIG) or subcutaneous infusions once a week. The use of broad-spectrum antibiotics can improve life expectancy. X-linked agammaglobulinemia has a poor prognosis that can improve if bone marrow transplantation is successfully practiced. Transient hypogammaglobulinemia of infancy has the best prognosis because it is due to an immaturity of the neonate's immune system and is correct once their immunoglobulin synthesis starts.

Questions

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