Chapter 34
Secondary Immunodeficiencies

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Overview

Individuals who are suffering from frequent or unusual infections often have concerns about how well their immune systems work, knowing that the body's defense against infections is the most important function of the immune system. Immunodeficiency is the word that describe conditions characterized by an abnormal function of the immune system, resulting in an increased risk of developing infectious diseases. In addition, some immunodeficiency disorders are associated with increased risk of cancer and inflammatory conditions. The integrity of anatomical barriers, our skin and the lining of the respiratory and digestive tracts, are part of our immunity. Abnormal barriers are a risk factor for the occurrence of frequent infections.

Immunodeficiencies can be classified into **primary** or **secondary**, according to the cause of the abnormality in the immune system. When a genetic change is the direct cause of the immunodeficiency, it is called a **primary immunodeficiency**. If the immune system is not working properly due to other causes, it is called a **secondary immunodeficiency**.

Secondary immunodeficiencies present with a wide variety of types and severity. They are far more common than primary immunodeficiency diseases (PI). A well-known secondary immunodeficiency is due to the infection by the human immunodeficiency virus (HIV), which leads to the acquired immunodeficiency syndrome (AIDS). Other common causes of secondary immunodeficiency include the use of medications that decrease the immune response, chemotherapy drugs used to treat cancers, and conditions associated with significant loss of proteins in the gut or renal system.

It is important to determine whether an individual with frequent or severe infections has a secondary immunodeficiency. Treatment of the primary problem can lead to subsequent recovery of the abnormal immune function.

Select Causes

HIV infection and other infections

HIV infection targets and destroys CD4 T cells, a subset of immune system cells. These cells are essential to produce an effective immune response. According to the Center for Disease Control and Prevention, there were more than 37 million people living with HIV worldwide in 2017, most of them in Africa. In the U.S., it is estimated that over one million people are HIV infected. Fortunately, advances in prevention, early diagnosis, and effective anti-HIV medications are reducing the incidence of new infections. Individuals with HIV present with a loss of CD4 T cells. Without CD4 T cells, the immune system cannot produce an effective immune response. HIV infected individuals who don't receive treatment suffer from frequent and debilitating infections by other common and uncommon microbes. With the use of anti-HIV medications and control of the virus infection, the immune response usually recovers, and these other severe infections occur less frequently.

In contrast to the persistent immunosuppression associated with HIV infections, infections with other pathogens, for example the viruses that cause influenza and measles, are associated with transient impairment of the immune response. During or shortly after this period of impaired immune responses, these individuals have an increased risk of secondary bacterial infections.

Malignancies

Immunodeficiency occurs in individuals with cancer or malignancies as a result of multiple factors. Besides the effects of anti-cancer medications and radiation therapy on white blood cells, lymphocytes, and neutrophils, malignant conditions might directly compromise the immune function. Decreased serum IgG level in adults might be one of the first signs of the presence of a blood malignancy, such as chronic lymphoma. Chronic lymphocytic lymphoma (CLL) is a blood cancer characterized by the uncontrolled proliferation of

B cells, usually in individuals over 60 years of age. Malignant B cells are immature, and individuals might develop frequent respiratory infections and also autoimmune disorders.

Age: Prematurity, Neonatal Period and Elderly

The immune system starts developing in the first weeks of gestation, with the formation of blood cells and continues to develop even after the baby is born. During the last three months of gestation, maternal antibodies are transferred to the fetus, providing protection in the first few months of life until the newborn's own immune system makes protective antibody levels. A neonate's early immune responses might not be optimal and thus they are at risk of developing some severe infectious diseases.

Infants who are born prematurely are at higher risk for infection because immature barrier function (GI tract, skin), and immaturity of the immune system. These infants also may have decreased levels of maternal antibody because their premature birth prevented some of the transfer of antibody that occurs in late pregnancy.

The immune response in people of advanced age is characterized by decreased ability to generate immune responses to new pathogens. There is also slow tissue repair, of importance to heal skin and mucosal barriers that deter entrance of infectious agents.

Use of Medications That Suppress the Immune System Function

The use of medications to reduce the immune response and the inflammation caused by autoimmunity can increase the risk of infections. The list of these medications, collectively known as immunosuppressive drugs, is long and continues to expand. Immunosuppressive drugs include: corticosteroids, cyclosporine, rapamycin, rituximab, tumor necrosis factor inhibitors, and interleukin inhibitors. Each of these drugs has a different mechanism of action and produce specific effects in the immune system.

Corticosteroids, such as hydrocortisone and prednisone, have been used for decades to control inflammation. The immune suppressing effects of corticosteroids occurs with oral prolonged and high doses. In order to reduce the immunosuppressive effects, corticosteroids may be administered with limited schedules or topically, such as skin or inhaled, to achieve minimal systemic absorption.

Medications That May Decrease the Serum Immunoglobulins and/or Suppress the Immune Function

- **Systemic corticosteroids**
- **Chemotherapeutic agents**
  - Cyclophosphamide
  - Methothrexate
  - Mycophenylate
- **Immunosuppressants**
  - Cyclosporine
  - Rapamycin
  - Tacrolimus
- **Immunosuppressive biological agents**
  - Rituximab
  - Adalimumab
- **In some individuals anti-seizure medications**
  - Phenobarbital
  - Hydantoin
  - Carbamazepine
  - Valproic acid
- **Other medications**
  - D-Penicillamine
  - Gold therapy
  - Captopril

Conditions Leading to Loss of Proteins

Immunoglobulins (Ig) are proteins that can be lost through the gastrointestinal tract and kidneys resulting in low serum IgG levels. If the production of antibodies is not affected, increased susceptibility to infections is variable. Chronic or recurrent diarrhea and other gastrointestinal diseases can lead to protein loss in the stool, a condition called protein losing enteropathy. In some kidney diseases, protein is lost in urine. Individuals with low serum levels of albumin and IgG should be evaluated for these possibilities—protein-losing enteropathy or nephrotic syndrome. Treatment of these conditions can reduce the loss of serum IgG and antibodies in the stool or urine.

Malnutrition

Malnutrition is a leading cause of immunodeficiency worldwide, though uncommon in the U.S. and other countries. Severe restriction of protein and calorie intake result in inadequate cell metabolism that affect

all body functions, including the immune system response. Shortage of nutrients limits lymphocyte proliferation in response to antigens and reduces production of antibodies. Lymphocyte proliferation and antibody production are fundamental for an effective immune response. Specific vitamins, like vitamin A, and minerals that play essential roles in cell metabolism and function are also of significance for the normal function of the immune system. Malnutrition affects the integrity of the skin and mucosa, which may serve as ports of entry for pathogens. A balanced diet is essential for the immune system. An immunodeficiency secondary to malnutrition may be reversed with adequate nutrition.

Abnormal Barriers as a Risk Factor for Frequent Infections: Allergy Inflammation

Skin and mucosal tissues are considered integral components of the immune system. Disruptions of these barriers increases susceptibility to infections. One of the most common conditions associated with frequent infections is allergic disease. Although the allergic response depends on the immune system, it is an unwanted response and not an immunodeficiency. Allergic individuals have sensitivity to specific substances in the environment collectively called allergens, such as grass pollen, dust mite or cat hair. Exposure to environmental allergens might result in local inflammation of the nose, throat, lungs, eyes, and skin. This inflammation produces swelling of tissues and production of secretions that increases the risk of recurrent upper respiratory infections.

Diagnosis and Treatment

When an individual is found to have an abnormality in the immune system, the next step is to find whether there is a factor that can explain it. Secondary immunodeficiencies are common and often can be treated. A complete clinical history and physical exam is usually revealing of potential factors affecting the immune system, such as prolonged use of corticosteroids. Routine urine and blood testing might also be useful. For example, excessive loss of protein found in urine might explain low serum levels of IgG. It is also important to keep in mind that both a primary and a secondary immunodeficiency can occur at the same time.

Once the cause of a secondary immunodeficiency is defined, the main objective of the medical management is to treat this cause, when possible. For example, measures to control protein loss in stools. While this specific treatment is initiated, other objectives of management include treating current infections and using preventive measures to reduce the risk of further infections. Preventive measures to consider include: Ig replacement therapy when there is antibody deficiency, antibacterial and antifungal prophylaxis for recurrent bacterial infections and fungal infections, respectively. If the cause of the secondary immunodeficiency cannot be treated or is persistent, periodic follow up visits are recommended to ensure prompt diagnosis and treatment of infections.

Select Common Causes of Secondary Immunodeficiencies

- Recurrent use of corticosteroids, or other immunosuppressive medications
- Use of monoclonal antibodies targeting the immune system, such as rituximab (anti-B cells)
- Immunoglobulin losses via the gastrointestinal or urinary tract
- Malignancies
- Human immunodeficiency virus (HIV) infection