



## Common Variable Immune Deficiency

CHAPTER

2

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## Definition of Common Variable Immune Deficiency

Common Variable Immune Deficiency (CVID) is a disorder characterized by low levels of serum immunoglobulins (antibodies) and an increased susceptibility to infections. The exact cause of the low levels of serum immunoglobulins is usually not known. It is a relatively common form of immunodeficiency, hence, the word “common.” The degree and type of deficiency of serum immunoglobulins, and the clinical course, varies from patient to patient, hence, the word “variable.” In some patients, there is a decrease in both IgG and IgA; in others, all three major types (IgG, IgA and IgM) of immunoglobulins may be decreased. The clinical signs and symptoms also vary from severe to mild. Frequent and unusual infections may first occur during early childhood, adolescence or adult life. In the majority of patients, the diagnosis is not made until the 3rd or 4th decade of life. However, about 20% of patients have symptoms of disease or are found to be immunodeficient under the age of 16.

Due to the relatively late onset of symptoms and diagnosis, other names that have been used for this disorder include “acquired”

agammaglobulinemia, “adult onset” agammaglobulinemia, or “late onset” hypogammaglobulinemia. The term “acquired immunodeficiency” is now used to refer to a syndrome caused by the AIDS virus (HIV) and should not be used for individuals with CVID as these two disorders are very different.

The causes of CVID are largely unknown although recent studies have shown the involvement of a small group of genes in some of the patients (see chapter titled *Inheritance*). Over the past few decades, studies on the cells of the immune system in patients with CVID have revealed a spectrum of lymphocyte abnormalities. Most patients appear to have normal numbers of B-lymphocytes, but they fail to undergo normal maturation into plasma cells capable of making the different types of immunoglobulins and antibodies. Other patients lack enough function from helper T-lymphocytes necessary for a normal antibody response. A third group of patients have excessive numbers of cytotoxic T-lymphocytes, although the role of these cells in the disease is unclear.

## Clinical Presentation of Common Variable Immune Deficiency

Both males and females may have CVID. Some patients have symptoms in the first few years of life while many patients may not develop symptoms until the second or third decade, or even later. The presenting features of most patients with CVID are recurrent infections involving the ears, sinuses, nose, bronchi and lungs. When the lung infections are severe and occur repeatedly, permanent damage to the bronchial tree may occur and a chronic condition of the bronchi (breathing tubes) develops, causing widening and scarring of these structures. This condition is known as bronchiectasis. The organisms commonly found in these infections are bacteria that are widespread in the population and that often cause pneumonia (*Haemophilus influenzae*, pneumococci, and staphylococci). The purpose of treatment of lung infections is to prevent their recurrence and the accompanying chronic damage to lung tissue. A regular cough in the morning that produces yellow or green sputum may suggest the presence of chronic infection or bronchiectasis (widening, scarring and inflammation of the bronchi).

Patients with CVID may also develop enlarged lymph nodes in the neck, the chest or abdomen. The specific cause is unknown, but enlarged lymph nodes may be driven by infection, immune dysregulation, or both. Similarly, enlargement of the spleen is relatively common, as is enlargement of collections of lymphocytes in the walls of the intestine called Peyer's patches.

Although patients with CVID have a depressed antibody response and low levels of immunoglobulin in their blood (hypogammaglobulinemia), some of the antibodies that are produced by these patients may attack their own tissues (autoantibodies). These autoantibodies may attack and destroy blood cells (e.g. red cells, white cells or platelets). Although, most individuals with CVID present first with recurrent bacterial infections, in about 20% of cases the first manifestation of the immune defect is a finding of very low platelets in the blood, or perhaps severe anemia due to destruction of red cells. The autoantibodies may also cause arthritis or endocrine disorders, such as thyroid disease.

## Clinical Presentation of Common Variable Immune Deficiency continued

Some patients with CVID who may not be receiving optimal immunoglobulin replacement therapy may also develop a painful inflammation of one or more joints. This condition is called polyarthritis. In the majority of these cases, the joint fluid does not contain bacteria. To be certain that the arthritis is not caused by a treatable infection; the joint fluid may be removed by needle aspiration and studied for the presence of bacteria. In some instances, a bacterium called *Mycoplasma* may be the cause and can be difficult to diagnose. The typical arthritis associated with CVID may involve the larger joints such as knees, ankles, elbows and wrists. The smaller joints (i.e. the finger joints) are rarely affected. Symptoms of joint inflammation usually disappear with adequate immunoglobulin therapy and appropriate antibiotics. In some patients, however, arthritis may occur even when the patient is receiving adequate immunoglobulin replacement.

Some patients with CVID report gastrointestinal complaints such as abdominal pain, bloating, nausea, vomiting, diarrhea and weight loss. Careful evaluation of the digestive organs may reveal

malabsorption of fat and certain sugars. If a small sample (biopsy) of the bowel mucosa is obtained, characteristic changes may be seen. These changes are helpful in diagnosing the problem and treating it. In some patients with digestive problems, a small parasite called *Giardia lamblia* has been identified in the biopsies and in the stool samples. Eradication of these parasites by medication may eliminate the gastrointestinal symptoms.

Finally, patients with CVID may have an increased risk of cancer, especially cancer of the lymphoid system, skin and gastrointestinal tract.

Patients with CVID do not have physical abnormalities unless complications have developed. Some patients with CVID may have an enlarged spleen and lymph nodes. If chronic lung disease has developed, the patient may have a reduced ability to exercise and decreased vital capacity (the maximum amount of air that can be taken into the lung voluntarily). Involvement of the gastrointestinal tract may, in some instances, interfere with normal growth in children or lead to weight loss in adults.

## Diagnosis of Common Variable Immune Deficiency

CVID is suspected in children or adults who have a history of recurrent infections involving ears, sinuses, bronchi, and lungs. The diagnosis is confirmed by finding low levels of serum immunoglobulins, including IgG, IgA and usually IgM. Patients who have received complete immunizations against polio, measles, diphtheria and tetanus will usually have very low or absent antibody levels to one or more of these vaccines. Immunization with other vaccines, such as the

pneumococcal vaccine, is done to define the degree of immunodeficiency. In some instances, these tests help the physician decide if the patient will benefit from immunoglobulin replacement therapy. The number of T-lymphocytes may also be determined and their function tested in samples of blood. With special laboratory techniques, it is possible to determine if B-lymphocytes produce antibody in a test tube (tissue culture) and if T-lymphocytes have normal functions.

## Genetics and Inheritance of Common Variable Immune Deficiency

Due to the unclear genetic nature of CVID, a clear pattern of inheritance has not been defined. In some instances, more than one family member is found to be deficient in one or more types of immunoglobulins. For example, it is not unusual for one family member to have CVID while another may have selective IgA deficiency (see chapter titled *Selective IgA Deficiency*).

In the past few years, mutations in several different genes have been found to be associated with CVID. These include inducible co-stimulatory

(ICOS) in one family and a protein on B-cells (CD19) in several families as causes of autosomal recessive CVID. Mutations in a cell receptor (TACI) for two factors (BAFF or APRIL) needed for normal growth and regulation of B-cells have also been found in about 10% of patients with CVID. A causative role of these mutations in the immune defect is not yet clear since some of these mutations can be found in people with normal immunoglobulins.

## Treatment for Common Variable Immune Deficiency

The treatment of CVID is similar to that of other disorders characterized by low levels of serum immunoglobulins. In the absence of a significant T-lymphocyte defect or organ damage, immunoglobulin replacement therapy almost always brings improvement of symptoms. Immunoglobulin is extracted from a large pool of human plasma consisting mostly of IgG and containing all the important antibodies present in the normal population (see chapter titled *Specific Medical Therapy*).

Patients with chronic sinusitis or chronic lung disease may also require long-term treatment with broad-spectrum antibiotics. If mycoplasma

or chlamydia infections are suspected, antibiotics specific for those organisms may be indicated. If bronchiectasis has developed, physical therapy and daily postural drainage are needed to remove the secretions from the lungs and bronchi.

Patients with gastrointestinal symptoms and malabsorption are evaluated for the presence of *Giardia lamblia*, rotavirus and a variety of other gastrointestinal infections.

Most patients with immunodeficiency and arthritis respond favorably to treatment with immunoglobulin replacement therapy.

## Expectations for Common Variable Immune Deficiency Patients

Immunoglobulin replacement therapy combined with antibiotic therapy has greatly improved the outlook of patients with CVID. The aim of the treatment is to keep the patient free of infections and to prevent the development of chronic lung disease. The outlook for patients with CVID depends on how much damage has occurred

to their lungs or other organs before diagnosis and treatment with immunoglobulin replacement therapy and how successfully infections can be prevented in the future by using immunoglobulin and antibiotic therapy.