

# COMMON VARIABLE IMMUNODEFICIENCY



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**DEFINITION:** Common Variable Immunodeficiency (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 also the clinical course, also 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 occur first during early childhood, adolescence or adult life. In the majority of patients, however, the diagnosis is not made until the 3rd or 4th decade of life.

Because of 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 virus) and therefore should not be used for individuals with Common Variable Immunodeficiency (CVID). These two disorders are very different.

Most individuals with CVID present first with recurrent bacterial infections and, when tested, have markedly decreased serum immunoglobulin levels and impaired antibody responses. The causes of CVID are largely unknown. 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 the helper T-lymphocytes necessary for a normal antibody response. A third group of patients have excessive numbers of cytotoxic T-lymphocytes.

**CLINICAL PRESENTATION:** Both males and females may have Common Variable Immunodeficiency (CVID). Although some patients have symptoms in the first few years of life, many patients may not develop symptoms until the second or third decade, or 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 the lung infections is to prevent their recurrence and the accompanying chronic damage to lung tissue. Regular cough in the morning that produces yellow or green sputum suggests 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.

Some patients with CVID who may not be receiving optimal gamma globulin therapy may also develop a painful inflammation of one or more joints. This condition is called polyarthritis. Although in the majority of the cases, the joint fluid does not contain bacteria, in order 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 gamma globulin therapy and appropriate antibiotics. In some patients, however, arthritis may occur even when the patient is receiving adequate gamma globulin 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.

Although patients with CVID have a depressed antibody response and low levels of gamma globulin in their blood (hypogammaglobulinemia), some of the antibodies 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), or they may cause endocrine disorders, such as thyroid disease or diabetes.

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:** Common Variable Immunodeficiency (CVID) is suspected in children and adults who have a history of recurrent infections involving ears, sinuses, bronchi, and lungs. The diagnosis is confirmed by finding a low level of serum immunoglobulins, usually including IgG, IgA and IgM. The latter two immunoglobulin classes may be completely absent in some patients or normal in others. 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 to decide if the patient will benefit from

gamma globulin treatment.

The number of T-lymphocytes may also be determined and their function tested in samples of blood. Normally, approximately 5-10% of the blood lymphocytes are B-lymphocytes and 60-70% are T-lymphocytes. With special laboratory techniques, it is possible to determine if B-lymphocytes produce antibody in a test tube (tissue culture), and if T-lymphocytes help the B-lymphocytes in this task.

**INHERITANCE:** Because of the non-uniform nature of Common Variable Immunodeficiency (CVID), a clear pattern of inheritance has not been defined. In some instances, however, 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 on *Selective IgA Deficiency*).

**TREATMENT:** The treatment of Common Variable Immunodeficiency (CVID) is similar to that of other disorders characterized by low levels of serum immunoglobulins. In the absence of a significant T-lymphocyte defect, gamma globulin treatment almost always brings improvement of symptoms. Gamma globulin 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 on *Specific Medical Therapy*).

Patients with chronic sinusitis or chronic lung disease may 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 gamma globulin.

**EXPECTATIONS:** Gamma globulin replacement combined with antibiotic therapy have greatly improved the outlook of patients with Common Variable Immunodeficiency (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 gamma globulin therapy and how successfully infections can be prevented in the future by using gamma globulin and antibiotic therapy.