

Chapter 3

Common Variable Immune Deficiency Phenotypes

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Common Variable Immune Deficiency (CVID) is one of the most frequently diagnosed forms of primary immunodeficiency diseases (PI). While children may have this immune defect, it is usually diagnosed in adults. CVID is characterized by low levels of serum immunoglobulins and also lack of specific antibodies in response to vaccines. Lack of antibody protection leads to increased susceptibility to infections. Genetic causes are found in some (approximately 30%), but for a large majority the causes are not well understood.

Overview

CVID is a relatively frequent form of primary immunodeficiency, found in about 1 in 25,000 persons; this is the reason it is called common. The degree and type of deficiency of serum immunoglobulins, and the clinical course, varies from person to person, hence, the word variable. An additional characteristic is a decreased IgA and/or IgM level, or a low level of all three major types of immunoglobulins (IgG, IgA, and IgM). In some individuals, there are defects of the T cells, and this may also contribute to increased susceptibility to infections as well as autoimmunity, granulomatous disease, and cancer.

To be sure that CVID is the correct diagnosis, there must be evidence of a lack of specific antibodies (measured antibodies in response to vaccines) and other possible causes of these immunologic abnormalities must be excluded, such as loss in the gastrointestinal tract or urine. Frequent and/or unusual infections may first occur during early childhood, adolescence or adult life. As mentioned earlier, some people with CVID also have an increased incidence of autoimmune or inflammatory conditions, granulomas and an increased susceptibility to cancer when compared to the general population. Sometimes it is the presence of one of these other conditions that prompts an evaluation for CVID.

Although CVID is a distinct diagnosis, some may confuse it with other antibody deficiencies. The medical terms for absent or low blood immunoglobulins are agammaglobulinemia and hypogammaglobulinemia, respectively. Due to the late onset of symptoms and diagnosis, other names that have been used in the past include acquired agammaglobulinemia, adult onset agammaglobulinemia, or late onset hypogammaglobulinemia. The term “acquired immunodeficiency” refers to a syndrome caused by the human immunodeficiency virus (HIV) and should not be used for individuals with CVID, as these disorders are very different.

Clinical Features

Both males and females may have CVID. In many, the diagnosis is not made until the third or fourth decade of life. About 20% of people with CVID, however, have symptoms of the disease or are found to be immunodeficient in childhood. Because the antibody arm of defense (the humoral immune system) is slow to mature, the diagnosis of CVID is generally not made until after the age of 4.

The usual presenting features of CVID are recurrent infections involving the ears, sinuses, bronchi (breathing tubes), and lungs (respiratory tract). When the lung infections are severe and occur repeatedly, permanent damage with widening and scarring of the airways, a condition termed bronchiectasis, may develop.

The organisms most commonly found in sinus and lung infections are bacteria that are widespread in the population and that often cause pneumonia (*Haemophilus influenzae*, *Streptococcus pneumoniae*) even in people who do not have CVID. The purpose of treatment of lung infections is to prevent their recurrence and to prevent the accompanying chronic and progressive damage to lung tissue. A regular cough in the morning and the production of yellow or green sputum (a mixture of saliva and mucus) may suggest the presence of chronic bronchitis or bronchiectasis.

Individuals with CVID may also develop enlarged lymph nodes in the neck, chest, or abdomen. Enlarged lymph nodes may be caused by infection, an abnormal immune response, or both. Similarly, enlargement of the spleen is relatively common, as is enlargement of Peyer's patches, which are collections of lymphocytes in the walls of the intestine.

In some cases, other collections of inflammatory cells called granuloma (comprised of white blood cells including monocytes and macrophages) can be found in the lungs, lymph nodes, liver, skin, or other organs. Granuloma may form in response to an infection, but the cause of their collection in tissues in CVID is not really known.

Although people with CVID have depressed antibody responses and low levels of immunoglobulins in their blood, some of the antibodies they produce may attack their own tissues (autoantibodies). These autoantibodies may attack and destroy blood cells, like 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 deficiency is a finding of very low platelets in the blood or less commonly, severe anemia due to destruction of red cells. Autoantibodies may also cause other diseases such as arthritis or endocrine disorders, like thyroid disease.

Gastrointestinal (GI) complaints, such as abdominal pain, bloating, nausea, vomiting, diarrhea, and weight loss, can also be associated with CVID. Approximately 21% of people with CVID may have significant GI problems. Careful evaluation of the digestive organs may reveal a reduced ability to absorb fat and certain sugars or inflammatory bowel disease. If a small biopsy (sample) of the bowel mucosa (tissue) is obtained, characteristic changes may be seen. These changes are helpful in diagnosing the problem and treating it. In some

people with digestive problems, the detection and eradication of infections due to bacteria, parasites, or viruses may help eliminate the GI symptoms.

Some people with CVID, particularly those who have not received the ideal immunoglobulin (Ig) 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, if tested, 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, like the finger joints, are more rarely affected. Symptoms of joint inflammation may disappear with adequate Ig replacement therapy and appropriate antibiotics. In some, however, arthritis may occur even when the individual is receiving adequate Ig replacement therapy.

Finally, people with CVID may have an increased risk of cancer, especially cancer of the lymphoid system or possibly the gastrointestinal tract. However in a recent study of cancer incidence of people with PI enrolled in the United States Immunodeficiency Network (USIDNET) patient registry, of the four most common malignancies in men and women (lung, colon, breast, and prostate cancers), there was no significant increase of these cancers in people with PI versus the age-adjusted population.

Diagnosis

CVID should be suspected in children or adults who have a history of recurrent bacterial infections involving ears, sinuses, bronchi, and lungs. The characteristic laboratory features include low levels of serum immunoglobulins, including IgG, often IgA and sometimes IgM. Another part of the diagnosis of CVID is to determine if there is a lack of functional antibody. This is done by measuring serum levels of antibody that are specific to vaccine antigens such as Tetanus/ Diphtheria, or pneumococcal polysaccharide. People with CVID have very low or absent antibody levels to most of these vaccines.

Immunization with killed vaccines is used to measure antibody function, and this functional testing is crucial prior to beginning treatment. These tests also help the healthcare providers decide if the individual will benefit from Ig replacement therapy and are

often essential in obtaining insurance authorization for this therapy. The number of B and T lymphocytes may also be determined and their function can be tested in laboratories. Recent studies have also shown that examining the maturity of the B cells in the blood by looking at the surface receptors (B cell memory markers) can help in predicting the relative severity of the immune deficiency.

Genetics and Inheritance

People with CVID usually have normal numbers of the cells that produce antibody (B cells), but these cells fail to undergo normal maturation into plasma cells, the cells capable of making the different types of immunoglobulins and antibodies for the blood stream and secretions.

The genetic causes of CVID are largely unknown, although recent studies have shown the involvement of an increasing number of genes in select people. These include genes that regulate immune functions, B cell surface proteins that help cells signal properly when a foreign substance is identified, and genes important in B cells activation. Until recently, the majority of the genes identified caused autosomal recessive CVID (See Inheritance Chapter), but increasingly autosomal dominant inheritance has been reported (one copy of an abnormal gene leading to variable expression). In these cases, other family members with the same genetic abnormality may not have any medical symptoms. As these are very rare gene defects for the most part, genetic testing is not required for most individuals with CVID. Particularly in those with inflammatory or autoimmune complications, however, genetic studies have been helpful in guiding additional individualized therapies.

Treatment

The treatment of CVID is similar to that of other disorders with low levels of serum immunoglobulins. In the absence of a significant T lymphocyte defect or organ damage, Ig replacement therapy almost always brings improvement of symptoms. Immunoglobulin is extracted from a large pool of human plasma; it consists mostly of IgG and contains all the important antibodies present in the normal population. (See Immunoglobulin Replacement Therapy Chapter.)

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

infections are suspected, antibiotics specific for those organisms may be indicated. If bronchiectasis has developed, a daily pulmonary regimen (chest physiotherapy and postural drainage) may be needed to mobilize the secretions from the lungs and bronchi and make them easier to cough up.

When individuals with CVID are on Ig replacement therapy, routine immunizations are not required because the Ig solutions contain protective antibodies against these. Exceptions may be the new killed shingles vaccine, the human papilloma virus vaccine (HPV), and the annual viral influenza vaccine.

Those with GI symptoms and malabsorption should be evaluated for the presence of *Giardia lamblia*, rotavirus, *Campylobacter*, norovirus, bacterial overgrowth, and other GI infections. In some cases, inflammatory bowel disease is found. This is an autoimmune condition that can be treated by the medications normally prescribed for individuals who are not immunodeficient, including the newer biologic drugs. Maintaining a balance between the immunosuppression used to control the autoimmune process while avoiding compounding the defects of the underlying PI requires close cooperation between the individual and the various specialists involved in their care. (See Autoimmunity in Primary Immunodeficiency Chapter.)

If autoimmune or inflammatory disease, granulomas, or tumors develop, the treatment is usually the same as would be given to a person with a normal immune system. When people with CVID, however, have these complications, there is a tendency for them to be less responsive to therapy. Regular checkups including lung function are recommended.

Most individuals with CVID carry out most if not all normal activities. Regularly scheduled and careful follow-up is still mandatory as new problems may arise or evolve over time. In general, those who are stable are seen at least yearly, but with added questions or when other conditions arise, shorter intervals such as three to six months are needed. In addition to addressing routine questions and checking blood counts, metabolic panels, and Ig levels, monitoring for weight changes is important, as Ig doses may need to be adjusted. There is no current consensus on how best to monitor for lung disease. Chest X-rays are not able to show the same level of detail as a CT scan, but there is a lower radiation exposure with a chest x-ray. For more frequent follow-up of those with chronic cough and/or known lung damage, complete lung

functions including carbon monoxide (CO) diffusion is useful, with possible chest CT at 3-4 year intervals. Monitoring for autoimmunity is usually accomplished through routine blood counts and general medical oversight which will reveal characteristic symptoms. GI diseases will be similarly evident with complaints of diarrhea and, often, weight loss. Routine endoscopy is not required although people with suggestive GI symptoms should have appropriate upper and/or lower endoscopy (colonoscopy) with examination for H pylori, pathogenic bacteria or viruses, or other mucosal changes. Loss of height may reflect loss of bone density; this requires attention to vitamin D, calcium, and other standard therapies. Evaluation of enlarged lymph nodes is not simple. When new lymph nodes appear and persist, biopsy may be required, but most commonly these reflect simply reactive changes that are not clinically significant.

Expectations

Ig replacement therapy combined with antibiotic therapy has greatly improved the outlook of people with CVID. The aim of the treatment is to keep the individual free of infections and to prevent the development of chronic inflammatory changes in tissues. The outlook for people with CVID depends on how much damage has occurred to lungs or other organs before the diagnosis is made and treatment Ig replacement therapy started, as well as how successfully infections can be prevented in the future by using these therapies. The development of autoimmune disease, inflammatory problems, granulomas, and/or malignancy can have a significant impact on the quality of life. These diagnoses often require additional therapies.

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