

Diagnosing and Treating Common Variable Immunodeficiency



While the outcome for patients with this not-so-common disease has improved, it often takes six to eight years to diagnose, putting them at risk for high-risk complications.

By Ronale Tucker Rhodes, MS

When Tami Slaats's doctor calmly told her she had a primary immunodeficiency disease (PID) known as common variable immunodeficiency (CVID), she assumed he would tell her how this disease could be cured because she heard the word "common."¹ Yet, despite its name, CVID is anything but common; it is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH), which means the disease affects fewer than 200,000 people in the U.S.² The true incidence and prevalence of CVID are difficult to ascertain. But, it is estimated that Tami, who lives in the U.S., is one in 10,000 to 50,000 people who are diagnosed each year in Europe and North America — a figure that is thought to underestimate its prevalence, or the estimated population of people who are managing disease at any given time. A nationwide survey in the U.S. suggests a population prevalence of all diagnosed PIs of approximately one in 1,200, 35 percent of whom are supposed to suffer from CVID.³

What Is CVID?

CVID has been recognized as the most common symptomatic form of antibody deficiency diagnosed in adulthood since it was first described in 1953.⁴ It is the second most common PI (second to selective immunoglobulin A [IgA] deficiency),⁵ but clinically the most significant because of its prevalence, complications, hospitalizations and requirement for lifelong therapy.⁶

The one key characteristic of CVID is an impaired ability to produce antibodies (also called immunoglobulins, or Igs, which are proteins in the body that help ward off infection).³ The medical terms for absent or low blood Igs are agammaglobulinemia and hypogammaglobulinemia, respectively. Deficiencies previously known as late-onset hypogammaglobulinemia and adult-onset hypogammaglobulinemia are now considered part of CVID.⁵ All CVID patients have low serum IgG, and often they have low IgA and/or IgM, as well as an impaired or even absent antibody response to vaccines. In comparison with healthy individuals, the number of B cells and in vitro function may be normal or low, and CD4 and/or CD8 T cell numbers may be normal or low.⁷

The disease affects both genders equally. The onset is typically in young adulthood, but the disorder is found in younger children as well.⁸ A diagnosis of CVID is typically not made until the third or fourth decade of life, but about 20 percent of patients have symptoms of the disease or are found to be immunodeficient in childhood.⁹

Causes of CVID

In 75 percent to 80 percent of cases, the cause of CVID is unknown; however, in 10 percent to 20 percent of cases, a genetic cause has been identified.¹⁰ Most cases are classified as sporadic and occur in people with no apparent history of the disorder in their family. It is believed that sporadic cases probably result from a complex interaction of environmental and genetic factors.¹¹

Recently, studies have shown the involvement of a small group of genes in a few patients. These include inducible co-stimulatory (ICOS) and a few other proteins on B cells, which appear to be causes of autosomal recessive CVID.⁹ When CVID is inherited in an autosomal recessive pattern, the patient inherits a copy of the mutated gene from both parents, but typically, the parents don't show signs and symptoms of the condition. In very rare cases, CVID is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. However, not all individuals who inherit a gene mutation associated with CVID will develop the disease. And, in many cases, affected children have an unaffected parent who shares the same mutation.¹¹

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Approximately 10 percent of affected individuals have a mutation in the TNFRSF13B gene (tumor necrosis factor receptor superfamily, member 13B). The TNFRSF13B gene provides instructions for making a protein called transmembrane activator and calcium modulator and cyclophrenia ligand interactor (TACI). The TACI protein is found on the cell membrane of B cells. When B cells mature, they produce Igs (antibodies) that attach to specific foreign particles and germs, marking them for destruction. More than 25 mutations in the TNFRSF13B gene have been associated with CVID. It is not clear how mutations in the gene prevent normal B cell maturation and antibody production. Some people with TNFRSF13B gene mutations develop CVID, but others do not.¹²

Symptoms of CVID

CVID symptoms vary widely, and they manifest in a range of severity.¹⁰ The degree and type of deficiency of serum Igs, and the clinical course, varies from patient to patient, hence, the word “variable.”⁹

The major characteristics of CVID are bacterial and viral infections. The most common infections are sinopulmonary and include *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Klebsiella pneumoniae* and, sometimes, mycoplasma infections. Recurrent sinopulmonary infections can begin any time, but more commonly, they are preceded by a long period in which infection frequency and severity are normal or near normal.¹³

Individuals may also experience meningitis or other systemic bacterial infections, recurrent eye or skin infections or gastrointestinal (GI) symptoms related to compromised immune/gut homeostasis, including chronic diarrhea, malabsorption or bloating. Twenty percent of CVID patients experience infections and inflammation with associated malabsorptive symptoms. Forty percent of dyspeptic individuals with CVID experience *H. pylori* infection. And, 2 percent to 3 percent of CVID patients experience chronic gut inflammation and associated malabsorption, which is not responsive to a gluten-free diet.¹³

Complications of CVID

In addition to the recurring symptoms caused by CVID, there are many problematic complications that often occur in CVID patients, many of which are due to a diagnostic delay, including chronic lung disease, granuloma formation, lymphoid hyperplasia and infiltrative disease, GI disease, autoimmunity and the development of cancer. Indeed, these causes appear to be the major cause of morbidity and death in patients with CVID.⁶

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Infections of the respiratory tract are the most common symptom of CVID, occurring in up to 73 percent of patients. Continued respiratory tract disease can lead to chronic lung damage, and in the more severe cases, it necessitates continuous oxygen treatment and/or heart or



lung transplantation. The question is whether the damage is due to infections prior to diagnosis, continued low-grade infections that are not adequately addressed by treatment or a combination of the two.⁶

Granuloma formation, caused by lymphoid aggregates within the tissues, occurs in approximately 25 percent of patients with CVID. These granulomata resemble those found in both sarcoidosis and Crohn’s disease, which can affect several organs. Granuloma formation may commonly manifest in skin and subcutaneous tissues, the GI tract and lungs.¹⁴ In some patients with granuloma formation, it is accompanied with an intense lymphoid infiltration, which leads to what is known as granulomatous lymphocytic interstitial lung disease. One study of CVID patients with interstitial lung disease reported a median survival of 13.7 years compared with 28.8 years in those without this complication.⁶

There also is an increased incidence of malignancy. Cervical, mediastinal and abdominal lymphoid hyperplasia and enlarged spleen are found in at least 20 percent of CVID patients. Lymphoid infiltrates occur in lung or other organs such as the liver or kidneys.⁶ These patients are also susceptible to lymphomas. In one study, it was found that nearly 8 percent of patients developed non-Hodgkins lymphoma, another 1 percent to 2 percent had Hodgkins lymphoma, and other individuals had 24 different cancers, including breast cancer, prostate cancer, squamous cell carcinoma, melanoma and basal cell carcinoma.¹³

The GI tract is the largest immune organ in the body, so

it is expected that an immunodeficiency will affect it in some way. GI complications for CVID patients are variable, and tend to mimic known diseases such as celiac, pernicious anemia and inflammatory bowel disease. Many studies confirm a high prevalence of inflammatory, malignant and infectious GI disorders in CVID patients, which are thought to be caused by T-cell-mediated defects.⁵

Up to 25 percent of CVID patients develop autoimmune disorders, mainly immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA) or both (Evans syndrome), and more rarely, autoimmune neutropenia. CVID patients with ITP or Evans syndrome tend to be younger than those who develop AIHA. Other autoimmune diseases that occur in CVID patients include pernicious anemia, rheumatoid arthritis, Sjögren's syndrome, vasculitis, thyroiditis, alopecia, vitiligo, hepatitis, primary biliary cirrhosis, uveitis, sicca syndrome and systemic lupus erythematosus.⁶

Diagnosing CVID

Currently, there is a six- to eight-year delay in diagnosing CVID, which puts patients at considerable risk since the prevention and control of long-term complications such as bronchiectasis critically depend on early diagnosis and treatment.³ Most patients are diagnosed with CVID between the ages of 20 years and 40 years, but approximately 20 percent are diagnosed under age 20. Generally, physicians are reluctant to diagnose CVID in young children (under age 4) because physiologic immaturity can mimic the disease in the early years; also, this period of delay allows other diagnostic considerations to be explored.¹⁵

Physicians should suspect a PI in children or adults who have a history of recurrent bacterial infections involving ears, sinuses, bronchi and lungs.⁹ CVID is primarily diagnosed by testing for low serum IgG concentration, which ranges from profoundly reduced (less than 100 mg/dL) to just below the normal range in adults (800 mg/dL to 1,200 mg/dL). Those with the disease also don't mount an antibody response to the pneumococcal vaccine. Other abnormal laboratory studies that would suggest a CVID diagnosis include reduced serum concentrations of other Igs, especially IgA or IgM, and reduced numbers of switched memory B cells as assessed by peripheral B-cell immunophenotyping. For some inherited causes of CVID, testing for loss of protein expression and/or molecular genetic testing to identify causative mutations is possible.¹³

The diagnosis of CVID requires low serum IgG, low serum IgA and/or IgM and decreased response to the pneumococcal vaccination. A normal response to the pneumococcal vaccine is greater than 50 percent for children 2 years old to 5 years old and greater than 70 percent for individuals 6 years old to 65 years old.

Treating CVID

To prevent recurrent sinopulmonary infections and chronic lung disease, immune globulin (IG) replacement therapy is given either intravenously (IVIG) or subcutaneously (SCIG). Generally, IVIG is dosed at 500 mg/kg every three to four weeks. SCIG also can now be performed with a variety of dosing schedules, from every two weeks, weekly and even semi-weekly, to suit the preference of the patient.¹⁶

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Prophylactic antibiotics may help patients with chronic sinusitis or chronic lung disease. Antibiotics also may help control GI tract complications. For those with bronchiectasis, physical therapy and postural drainage will remove the secretions from the lungs and bronchi.¹⁶

Other complications of CVID are most often prescribed the standard treatments. However, higher doses of IG therapy are often prescribed to treat chronic lung disease, lymphoid interstitial disease, granuloma and some autoimmune disorders.⁶

For all patients, regularly scheduled follow-up is mandatory since new problems may arise and evolve over time. Stable patients should be seen at least yearly, while those with complications should be seen at shorter intervals such as every three to six months.⁶ During these visits, several surveillance methods can be performed, including periodic complete blood cell counts and differential white blood cell counts to detect lymphoma, annual pulmonary function testing (beginning in children at age 8 years to 10 years), high-resolution CT scans every two to three years to follow progression of lung disease, biopsy of enlarged lymphoid tissue, and other imaging

techniques for the assessment of granulomatous disease and GI complications.¹³

Allogeneic stem cell transplantation (ASCT) has occasionally been reported as treatment in cases of occurring malignancy in CVID patients, but the outcome of ASCT as a potentially curative approach in CVID with poor prognosis is unknown. In a study on the feasibility and outcome of ASCT in four patients suffering from severe CVID, one patient died after three months due to overwhelming hemorrhagic pneumonia. However, at the time the study was reported on, the other three patients had survived between 4.5 years and 7 years. One patient is cured from his lymphoma and the underlying CVID; he is free of recurrent infections, has normalized his serum Ig levels (except IgA) and responds for the first time to vaccines. In the other two patients, ASCT reached the end point of resolving the lymphoproliferative disease in one, and reducing the steroid dose with stabilization of pulmonary disease in the second, but had little effect on the underlying immunodeficiency. The researchers note that the importance of the study lies in the evidence that CVID can be cured in selected patients.¹⁷

IVIG in high doses can be a very effective treatment.

Improving CVID Outcomes

The outcome for CVID patients has greatly improved over the years, and the majority of patients can expect to have stable lifestyles. However, diagnosis is still delayed six to eight years after characteristic symptoms, which poses a high risk of long-term and severe complications from CVID. Therefore, one of the most important goals is to reduce the time it takes to diagnose the disease. Certainly a greater awareness about the disease can help. For the low percentage of at-risk individuals who have relatives with CVID, clinical surveillance may allow timely intervention and improve outcome. On a case-by-case basis, molecular genetic testing for early identification of at-risk family members may improve diagnostic certainty.¹³ ■

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