

Common Variable Immunodeficiency

A Clinical Overview

Often appearing as recurrent or recalcitrant infections, the diagnosis of common variable immunodeficiency (CVID) is often missed. Patients remain untreated for long periods of time, resulting in complications. Arm yourself with expert information about this rare genetic disorder.

Deborah Johnson, DNP, FNP-BC

Deborah Johnson is an Adjunct Professor of Nursing at Spring Arbor University, Spring Arbor, Michigan.



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A 60-year-old woman with a recent history of air and cruise ship travel presented with symptoms consistent with acute sinusitis. She had a 34-pack-year history of cigarette smoking but had quit at age 50. Her medical history was significant for hypothyroidism, hypertension, coronary artery disease, mild asthma, and COPD. Past surgical history included coronary artery bypass, abdominal hysterectomy, and cholecystectomy. Her medications included inhaled bronchodilators, thyroxin, hydrochlorothiazide, nitrates, β -blockers, and calcium channel blockers.

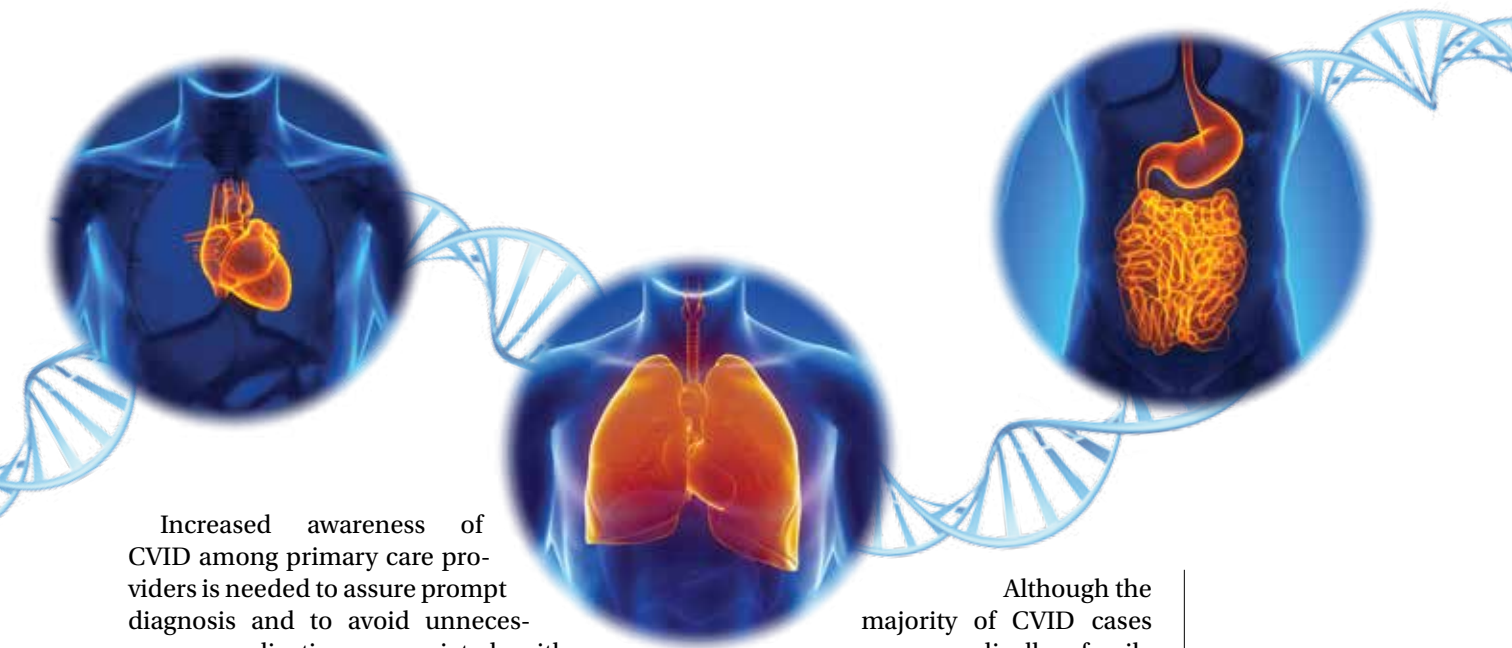
Over the next five years, she presented with frequent episodes of respiratory illness for which she received multiple courses of antibiotics, inhaled bronchodilators, and oral as well as inhaled corticosteroids. She consequently became increasingly sensitized to multiple antibiotic classes and was frequently hospitalized for the treatment of her respiratory illnesses.

Common variable immunodeficiency disorders (collectively known as CVID) are the most common clinically significant immunodeficiency diseases among adults.¹ Manifesting clinically as frequent, unusually severe or recalcitrant bacterial infections of the ear, sinus, respiratory tree, and/or gastrointestinal tract, CVID is genetically induced.² Additionally, these disorders can predispose individuals to autoim-

mune conditions and to cancers involving B lymphocytes.³ Often thought to be a disease of younger people, CVID can occur across the age span.⁴

The immune dysfunction that characterizes CVID is believed to result from underlying genetic defects that affect the differentiation of B cells, leading to faulty immunoglobulin (Ig) synthesis. Recent advances that allow the detection of multiple novel susceptibility loci for CVID have dramatically increased our understanding of the pathophysiology and pathogenesis of this disorder.⁵ These advances are being used to refine the diagnostic parameters of CVID and in the future may help clinicians tailor treatment protocols to specific genetic defects.^{5,6}

Although considered rare, CVID is often unrecognized; the incidence is likely much higher than the current estimates of 1:10,000 to 1:50,000.⁷ About 13% to 23% of individuals with chronic sinusitis are thought to be affected by CVID.⁸ While it is most commonly diagnosed during the second and third decades of life, it can be diagnosed at any time during the lifespan.⁴ A high burden of disease is associated with this disorder, as hospitalizations and costly, aggressive treatment regimens are needed to manage the resultant bacterial infections and sequelae.²



Increased awareness of CVID among primary care providers is needed to assure prompt diagnosis and to avoid unnecessary complications associated with delayed treatment. The diagnostic workup is complex, and referral to immunology for specific diagnosis and treatment is strongly advised. Recognition is the first step, and primary care providers must include primary immunodeficiency disorders, including CVID, in their differential to avert a missed diagnosis and to ensure optimal treatment.⁹

CLINICAL MANIFESTATIONS/ PATIENT HISTORY

Frequent and severe infections are a hallmark of CVID. The most common types of infections seen in CVID are sinusitis, conjunctivitis, otitis media, bronchitis, pneumonia, and gastroenteritis.¹⁰ These primary bacterial infections can disseminate, causing septicemia and/or central nervous system infection.¹¹ The usual infectious pathogens are encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, but atypical infections due to organisms such as *Pneumocystis carinii* and *Mycoplasma pneumoniae* also occur in some patients.^{12,13}

Ten percent to 40% of cases of chronic diarrhea are the result of CVID.^{4,10} Common causative organisms include *Giardia*, salmonella, *Shigella*, and *Campylobacter*.¹⁰ Patients with CVID are also susceptible to fungal and mycobacterial infections, but with the exception of herpes simplex and herpes zoster, viral infection is uncommon.¹⁴ CVID also predisposes patients to a myriad of autoimmune, granulomatous, and malignant diseases.¹⁵

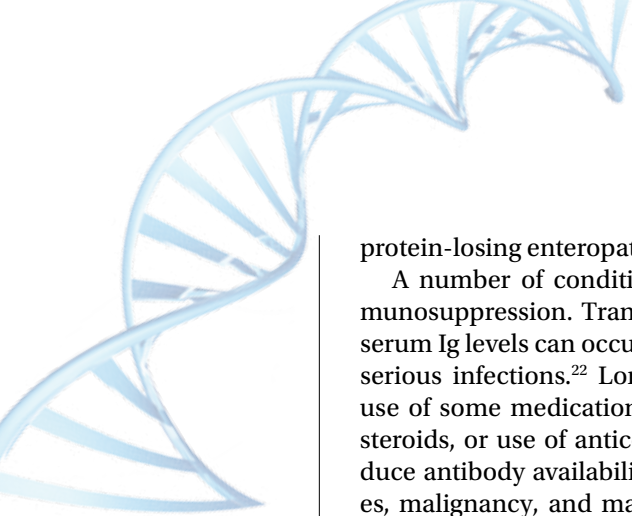
Although the majority of CVID cases occur sporadically, family history is helpful in securing the correct diagnosis.¹⁵ Known immunodeficiency, unusual susceptibility to infections, autoimmune diseases, hematologic malignancy, or death caused by infection in other family members should increase the provider's index of suspicion for CVID.¹⁶

Many genetic defects have been implicated in CVID, yet the wide phenotypic expression found even in persons with similar genetic profiles implies that CVID has a complex genetic transmission pattern.¹⁵ Known or suspected consanguinity in parents or grandparents increases the risk for CVID.⁶

Although these family history elements occur infrequently, they increase the likelihood of severe opportunistic infection, which can cause organ damage or even death.^{1,17} Being alert for these elements of family history can help to avoid delays in diagnosis and treatment and eventual organ damage.²

DIFFERENTIAL DIAGNOSIS

When considering the differential diagnosis for the primary features of CVID, other etiologies that should be considered include allergies, environmental exposures, uncontrolled gastroesophageal reflux disease, structural abnormalities of the upper respiratory tract, and celiac disease.^{5,10,18,19} Far less common but still worthy of consideration are other genetic conditions, such as primary ciliary dyskinesia, cystic fibrosis, thymic dysfunction or carcinoma, and



protein-losing enteropathies.^{20,21}

A number of conditions can cause immunosuppression. Transient reductions in serum Ig levels can occur in the presence of serious infections.²² Long-term, high-dose use of some medications, such as corticosteroids, or use of anticonvulsants may reduce antibody availability. Chronic illnesses, malignancy, and malnutrition can also play a role in immunosuppression.¹⁹ CVID shares features with a large number of primary immune diseases, and these as well as other causes of hypogammaglobulinemia must be excluded before the diagnosis of CVID can be made.¹

DIAGNOSIS

While infectious disease is a common reason patients seek medical care, few patients presenting with one will have CVID. Nevertheless, immunologic evaluations should be performed and appropriate referral to an immunology specialist is strongly recommended when more than one severe infection arises in a year's time; when a pattern of severe or unusual infections presents over a period of time; when bronchiectasis is present; or when infections do not resolve with conventional treatment.¹⁶ In addition, the physical findings noted in the Table, when combined with a history of recurrent infections, autoimmune disorders, or lymphocytic malignancy, should prompt evaluation for CVID.^{10,16,18,23}

The diagnosis of CVID requires testing for low serum levels of total IgG, IgG subclasses, IgA, and IgM. In CVID, IgG and IgA levels will be reduced, and occasionally IgM levels will also be diminished.²⁴ Unless an active infection is present, there will be no change in the patient's routine blood tests, such as the complete blood count and total complement levels.

The diagnosis is also based on demonstration of a deficient antibody

response to protein (tetanus) and polysaccharide (pneumonia) vaccine antigens.²¹ A minimal reaction to these vaccines should prompt referral to an immunology specialist for additional testing and a plan of care.²⁵ However, whenever the index of suspicion for CVID is high, prompt referral to immunology should not be delayed to perform further testing.¹⁶

TREATMENT/MANAGEMENT

IgG replacement therapy, which treats the underlying pathophysiology of CVID by supplementing one of the deficient antibodies, is the standard treatment for CVID. IgG is considered a blood product since it is made from human plasma. Patients may experience untoward reactions to IgG replacement therapy, similar to transfusion reactions; such reactions commonly include back pain, low-grade fever, muscle and joint discomfort, and fatigue. These unpleasant effects can be minimized with the prophylactic use of antihistamines, antipyretics, or even glucocorticoids.²⁶

Although IgG replacement therapy has high upfront costs, it increases patients' well-being considerably by preventing multiple or recurrent infections and the resultant hospitalizations for antibiotic therapy.²⁷ Home infusion of IgG can minimize costs as well as increase patient autonomy.²⁸ With home infusions, IgG is administered via a multisite subcutaneous route using a slow-infusion mechanical pump. Subcutaneous infusions generally take four to six hours, depending on the number of sites used. Some patients can infuse while they sleep, which increases patient satisfaction with the treatment.²⁷

A significant problem associated with CVID is the overuse of antibiotic therapy. Although it is a common practice to combine prophylactic antibiotics with IgG therapy in this population, this practice is not based on evidence.²⁹ Prophylactic antibiotic regimens are generally extrapolated from protocols to treat recurrent and prolonged infections in a non-CVID population.³⁰ Although infection must be actively treated, care should be taken to avoid excessive use of antibiotic therapy, lest this practice con-

CVID Resources

Trustworthy sources to guide the primary care provider's decision-making process when caring for patients with CVID include:

- European Society for Immunodeficiencies
www.esid.org/
- Immune Deficiency Foundation
www.primaryimmune.org
- Online Mendelian Inheritance in Man
www.ncbi.nlm.nih.gov/omim

TABLE
Physical Signs Suggestive of CVID in Patients with Appropriate History

Abdomen	Abdominal pain, chronic or bloody diarrhea, organomegaly (spleen or liver)
Head and neck	Alopecia areata and alopecia, lymphadenopathy
Respiratory tract	Bronchiectasis, cough, dyspnea, lung infiltrates, pleuritic chest pain
Skin	Actinic keratosis, atopic dermatitis, eczema, extensive warts or mollusca, hyperpigmentation, petechiae, skin cancers, vitiligo
Systemic	Signs of malnutrition, weight loss

Abbreviation: CVID, common variable immunodeficiency.

Note: Appropriate history includes recurrent infections, autoimmune disorders, or lymphocytic malignancy.

Sources: Kakkas. *Hosp Chron.* 2016¹⁰; De Vries. *Clin Exp Immunol.* 2012¹⁶; Fasano. *N Engl J Med.* 2012¹⁸; Verma. *Drugs Aging.* 2013.²³

tribute to the development of more virulent, resistant organisms and create increased risk for this patient population.³⁰ Daily vitamin D supplementation (1,500-1,600 IU/d) is helpful to limit respiratory tract infections in immunodeficient patients without IgG supplementation who have 25(OH)D levels less than 75 nmol/L.³¹

Infections in persons with CVID can be severe and may lead to organ-system compromise, requiring aggressive therapy aimed at supporting the function of the affected organ systems. For example, patients with CVID can develop unrelenting vomiting and diarrhea, which may require inpatient admission for rehydration and stabilization until the infection can be treated adequately.³²

Treatment options remain limited for the subset of CVID patients who develop severe complications, such as interstitial lung disease or neoplasms. These complications are associated with a significant increase in patient mortality, and allogeneic hematopoietic stem cell transplantation may be indicated for patients who develop them. This potentially curative treatment is being explored in ongoing research trials.³³

Immunization of immunodeficient patients and their close contacts is a complicated but important process to ensure maximum protection from vaccine-preventable diseases; however, care must be taken to limit untoward reactions, such as transmission of disease via live agent vaccines.²¹ In

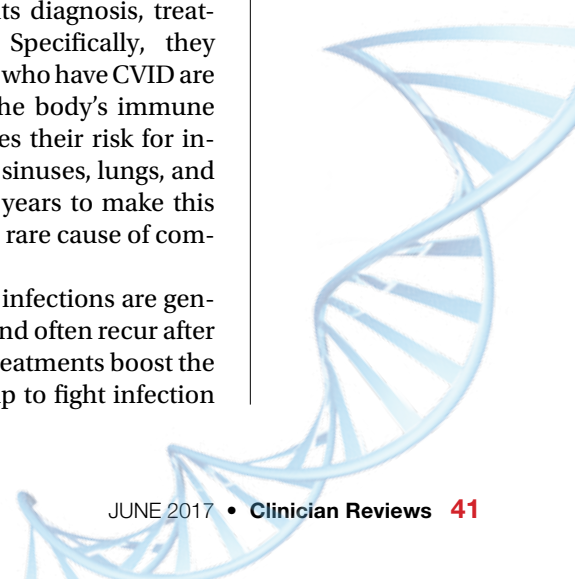
general, when CVID is suspected or there is a family history of immune deficiency, inactivated vaccines should be given on schedule, but live-attenuated vaccines should be delayed until the evaluation is complete, because of the risk for disseminated infection. Specific guidance on this important aspect of patient care can be found in the Immune Deficiency Foundation's vaccination recommendations.³⁴

PATIENT EDUCATION

Scrupulous hand hygiene, careful avoidance of infectious exposures, watchful food handling and preparation, and lifestyle choices that support good general health are key elements of self-care for patients who have CVID. Preventive measures serve this population well by helping to reduce some of the complications of this serious disease.

Patients with CVID should understand key aspects regarding its diagnosis, treatment, and prognosis. Specifically, they should know that people who have CVID are born missing some of the body's immune defenses, which increases their risk for infection, especially of the sinuses, lungs, and gut. Sometimes it takes years to make this diagnosis, because it is a rare cause of common symptoms.

In people with CVID, infections are generally harder to resolve and often recur after antibiotic therapy. IgG treatments boost the immune system and help to fight infection



as well as limit complications. Most people with CVID lead relatively normal, healthy lives. The disorder is not contagious.

The patient was referred to immunology, and a diagnosis of CVID was made. She was successfully treated with subcutaneous IgG replacement therapy. She died due to overwhelming sepsis after an episode of pneumonia at age 84.

CONCLUSION

The secret to prompt detection of CVID is adding it to the differential diagnosis of recurrent infections. Timely recognition and appropriate referral prevent serious complications, since successful treatment options are available. **CR**

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