

Common variable immunodeficiency

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ABSTRACT

Common variable immunodeficiency (CVID) is a common primary immunodeficiency characterized by a failure in B-cell differentiation with defective immunoglobulin production. Affected patients are uniquely susceptible to recurrent infection with encapsulated organisms and have an increased propensity for the development of inflammatory and autoimmune manifestations. The diagnosis of CVID is commonly delayed and the underlying cause of the disorder is not understood. Replacement antibody therapy reduces the risk of serious infections. However, optimal treatment regimens for the uncommon manifestations associated with this disease, such as granulomatous lymphocytic interstitial lung disease, require further research.

(Am J Rhinol Allergy 27, 260–265, 2013; doi: 10.2500/ajra.2013.27.3899)

Common variable immunodeficiency (CVID) is a heterogeneous disorder characterized by recurrent bacterial infections and impaired B-cell differentiation leading to defective immunoglobulin production. CVID is the most common clinically significant primary immunodeficiency disease. It is not a single disease, but rather a clinical syndrome that represents a family of disorders exhibiting a common phenotype. The age of onset of CVID is variable, presenting in both children and adults. The diagnosis is generally made between 20 and 40 years of age, but up to 20% may present before the age of 20 years.¹ Depending on the ethnicity of the population, it affects an estimated 1 in 25,000–50,000 subjects.^{2–4} The true incidence of CVID may be much higher because the disease is largely underappreciated and underdiagnosed, which is reflected in the common delay in diagnosis of up to 5–10 years.^{1,2,5–8}

PRESENTATION

Nearly all patients present with recurrent upper and/or lower respiratory tract infections including bronchitis, sinusitis, otitis media, and pneumonia. Encapsulated bacteria (*Haemophilus influenzae* and *Streptococcus pneumoniae*) are the most commonly discovered pathogens.^{1,6,8–10} In addition, patients with CVID appear to be particularly susceptible to infections with atypical bacteria such as *Mycoplasma* sp. and *Ureaplasma* sp.^{8–11} Therefore, when deciding on empiric antimicrobial therapy of respiratory tract infections, agents such as macrolides or fluoroquinolones should be considered because they cover both encapsulated and atypical organisms. Pulmonary infections with Gram-negative rods should also be considered, in particular in patients with impaired cellular immunity or longstanding CVID. Opportunistic infections are rare and occur in <10% of patients.^{1,8,12}

Unlike congenital forms of agammaglobulinemia, such as X-linked agammaglobulinemia, T-cell abnormalities are common in patients with CVID and contribute to the more variable clinical manifestations of this disease.^{1,8,12} A subgroup of CVID patients termed late-onset combined immune deficiency is defined by opportunistic infections and/or severe T-cell lymphopenia ($CD4 < 200$ cells/mm³).¹³ This subgroup of patients is also more likely to have a severe clinical phenotype (gastrointestinal disease, granulomatous disease, splenomegaly, and lymphomas).

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Presented at the North American Rhinology and Allergy Conference, February 4, 2013, Puerto Rico

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Gastrointestinal tract infections with pathogens similar to those found in X-linked agammaglobulinemia (*Campylobacter jejuni*, *Salmonella* sp, and *Giardia lamblia*) are also common.^{1,8} The prevalence of hepatitis is also increased in CVID, occurring in ~12% of patients. The prognosis due to hepatitis secondary to infection with hepatitis C is poor and may be rapidly progressive in patients with CVID.^{14,15} Other forms of liver disease such as nodular regenerative hyperplasia are an increasingly recognized complication of CVID.¹

ETIOLOGY

The etiology of the vast majority of cases of CVID is unknown. In a small subset of patients, however, specific molecular defects have been identified. Most of these genetic abnormalities are rare with the exception of mutations in TNFRSF13B, which encodes for transmembrane activator and calcium modulator and cyclophilin ligand (TACI). Mutations in TACI occur in ~8–10% of patients with CVID.^{16,17} Patients with heterozygous mutation in TACI are at high risk to develop CVID, whereas homozygous mutations of TACI always result in CVID.¹⁸ Patients with mutations in TACI are also more likely to have both autoimmune disease and splenomegaly.^{19–21}

Other genetic defects leading to a CVID phenotype include mutations in inducible T-cell costimulator (ICOS), CD19, CD81, CD20, CD21, and B-cell activating factor of the tumor necrosis factor family receptor (BAFF-R).^{16,17,22–28} Some of these genetic mutations are likely to be disease causing (ICOS, CD19, CD20, and CD81) and others (BAFF-R) may require additional genetic contributions to lead to the CVID phenotype.¹² Collectively, mutations in ICOS, CD19, CD81, CD20, CD21, BAFF-R, and TACI account for <10–15% of all cases of CVID.

COMPLICATIONS

Acute and chronic infections are a major cause of morbidity in patients with CVID.^{7,12} The occurrence of recurrent upper respiratory tract infections can result in chronic sinusitis and hearing loss. Recurrent lower respiratory tract infections (*i.e.*, pneumonia) may lead to the development of bronchiectasis (Fig. 1), which is reported to be present in up to 20% of patients with CVID.^{29,30} In addition to infectious complications in the lung, parenchymal and interstitial changes may be found leading to both obstructive and restrictive defects (Table 1).

Of particular concern, is a restrictive interstitial lung disease, which on biopsy reveals granulomatous and lymphoproliferative histopathologic patterns (lymphocytic interstitial pneumonitis, follicular bronchiolitis, and lymphoid hyperplasia). The term granulomatous and lymphocytic lung disease (granulomatous lymphocytic interstitial lung disease [GLILD]) has been used to characterize this disorder³⁰ and occurs in ~10–25% of patients with CVID.^{29–35} Progressive pulmonary impairment due to GLILD appears to be an important cause of morbidity and mortality in CVID³⁰ and shows a shortened median survival (13.7 years versus 28.8 years in those without this

Figure 1. (A) High-resolution computed tomography (HRCT) scans showing bronchiectasis related to CVID in the context of a normal chest radiograph (not shown). (B) HRCT scans showing granulomatous lymphocytic interstitial lung disease (GLILD) related to CVID in the context of a normal chest radiograph (not shown).

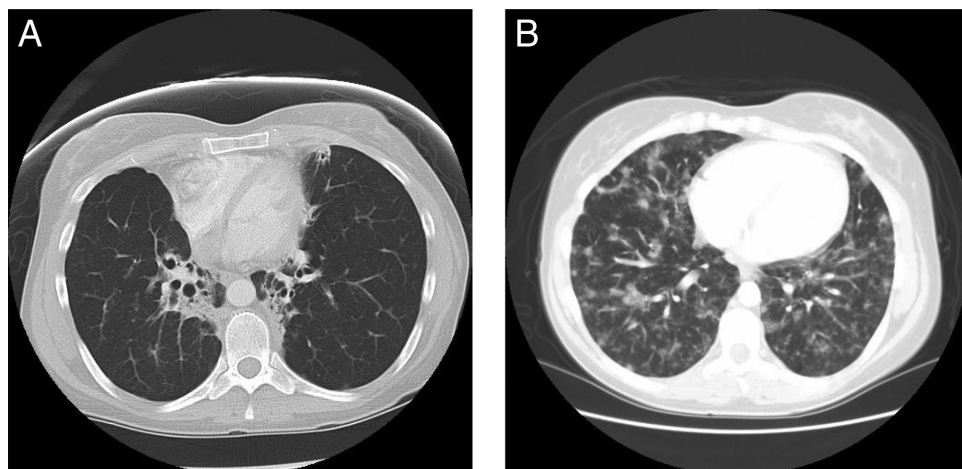


Table 1 Common complications of CVID

Infectious complications	
Upper respiratory tract infections	
Chronic sinusitis	
Hearing loss	
Lower respiratory tract infections	
Bronchiectasis	
Liver disease	
Hepatitis B	
Hepatitis C	
Noninfectious complications	
Autoimmune disease	
Autoimmune hemolytic anemia	
Immune thrombocytopenia	
Autoimmune neutropenia	
Lung disease	
Obstructive	
Bronchiectasis	
Bronchiolitis obliterans	
Restrictive	
GLILD	
Cryptogenic organizing pneumonia	
Gastrointestinal disease	
Malabsorption	
Chronic diarrhea	
Gastritis	
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	
Liver disease	
Nodular regenerative hyperplasia	
Autoimmune hepatitis	
Malignancy	
Non-Hodgkin's lymphoma	

CVID = common variable immunodeficiency; GLILD = granulomatous and lymphocytic interstitial lung disease.

complication).^{1,12,30,36} This noncaseating granulomatous disease is systemic in nature and may be present in the lung, bone marrow, liver, and lymph nodes.³⁷ Consequently, this disease process is often confused with sarcoidosis; but unlike sarcoid, these lesions do not remit spontaneously or resolve with steroid administration.^{30,31} In addition to granuloma, polyclonal lymphocytic infiltration or nonmalignant hyperplasia of the lymph nodes (cervical, mediastinal, and abdominal lymph nodes as well as the spleen) are found in at least 20% of CVID

subjects.^{2,8,30,31,36,38,39} Lymphoid infiltrates can occur in the lungs or other organs such as the liver and kidneys. Enlarged lymph nodes usually show atypical or reactive hyperplasia, with or without preservation of germinal center boundaries.³⁷

Patients with CVID are also at high risk to develop malignancy, which occurs in up to 15% of patients. In particular, the prevalence of non-Hodgkin's lymphomas and gastric carcinoma are increased in CVID and are a major cause of morbidity and mortality.^{1,38,40–42} When lymphomas appear in CVID, they are usually extranodal, B cell in origin, negative for Epstein-Barr virus, and are more common in subjects in the 4th to 7th decades of life.^{1,8,43}

Interestingly, although patients with CVID are unable to make antibodies to foreign antigens, they show a propensity to make autoantibodies; the overall prevalence of autoimmune disease is ~20–25%.^{8,44} They are susceptible to a wide range of autoimmune diseases, but autoimmune thrombocytopenia and autoimmune hemolytic anemia are the most commonly reported cytopenias occurring in 11–12% of subjects.^{1,2,19,45}

The most common gastrointestinal manifestation of CVID is transient or persistent diarrhea, found in 21–57% of patients.^{44,46,47} In addition to bacterial and parasitic infections, chronic gastritis and inflammatory bowel disease are significant problems for patients with CVID.^{1,44} Small bowel enteropathy in CVID resembles celiac disease with short villi, crypt hyperplasia, and intraepithelial lymphocytosis.⁴⁷ This small bowel enteropathy can lead to diarrhea, weight loss, and malabsorption. Large bowel enteropathy resembling Crohn's disease and ulcerative colitis has also been described in CVID,⁴⁷ although it is not clear if these have the same pathogenesis as classic inflammatory bowel disease. Furthermore, a subset of individuals (8% in one cohort)⁷ with CVID exhibit nodular lymphoid hyperplasia on biopsy—most commonly presenting as cholestasis or portal hypertension.^{41,48}

Based on the European Society for Immunodeficiency CVID registry and recently reproduced in additional cohorts,⁴⁹ efforts have been made to divide patients into five distinct phenotypes based on intrinsic disease-related complications: no complications, autoimmunity, polyclonal lymphocytic infiltration, enteropathy, and lymphoid malignancy.² The outcome of individual patients appears to be dependent on the presence or absence of some of these specific complications.² These phenotypes are not exclusive because the lymphoproliferative phenotype (GLILD, splenomegaly, and adenopathy) is frequently accompanied by autoimmune cytopenias, gastrointestinal, and hepatic disease.^{19,30,34,36,47,48,50,51}

As treatments for infection have improved, complications such chronic lung disease, malignancy, and autoimmune disease are now the most common causes of mortality in CVID.^{1,2,30,31,37,42,43} In a recent analysis of 411 subjects with CVID in which 19% had died, the

predominant causes of death included respiratory failure from chronic lung disease, lymphoid or other malignancy, and liver disease.¹ Interestingly, not all complications were shown to be associated with reduced mortality. Risk factors for early mortality included gastrointestinal disease, liver disease, chronic lung disease, and lymphoma whereas autoimmunity and cancer other than lymphoma were not associated with early mortality.

DIAGNOSTIC EVALUATION

The diagnostic criteria for CVID include⁵²

- Decreased serum IgG level, AND decreased serum IgA or IgM
- Decreased ability to make specific antibodies in response to immunizations
- Exclusion of primary immunodeficiencies leading to decreased IgG
- Exclusion of secondary causes of decreased serum IgG
- Greater than 2 years of age

In patients with CVID, IgG levels are reduced by >2 standard deviations from the mean in all patients and <450 mg/dL in 94.2% of patients at diagnosis.² Almost all cases of CVID have a decrease in IgA (usually <5 mg/dL) and reductions in IgM in about one-half of cases.^{1,2,5,6,8,52} Specific antibody responses, which are impaired in CVID, are shown by measuring specific antibodies 3–4 weeks after the administration of a protein (*i.e.*, tetanus, diphtheria toxoid, *H. influenzae* B) and polysaccharide (pneumococcal vaccine) vaccines.⁵³ Early in life CVID is not always discernible from transient hypogammaglobulinemia of infancy or congenital forms of agammaglobulinemia. Therefore, the general consensus is that this diagnosis of CVID should not be made until after a patient reaches the age of 2 years.¹²

Exclusion of other secondary causes of hypogammaglobulinemia is especially important in patients with isolated low IgG (Table 2).^{2,12,54–56} Protein loss from protein losing enteropathy or nephrotic syndrome can present as hypogammaglobulinemia and is not uncommon. Chronic oral corticosteroid use can also lead to reduced IgG levels and is a common cause of hypogammaglobulinemia in patients with severe asthma or chronic obstruction pulmonary disease. The decrease in serum IgG occurs is relatively selective with a relative sparing of the IgA and IgM and normal specific antibody production.^{57,58} The magnitude of the reduction of serum IgG after corticosteroid therapy is dependent on the dose and duration of steroid therapy. Although corticosteroid therapy typically does not reduce serum IgG to <400 mg/dL, reduction below this level may be seen in patients receiving high doses of corticosteroids over a long period of time.^{57,58} Other common medications associated with hypogammaglobulinemia include rituximab, azathioprine, sulfasalazine, and several anticonvulsants (carbamazepine, levetiracetam, oxcarbazepine, and phenytoin).^{59–63}

The physical examination of a patient with a suspected CVID requires an in-depth focus on the involved organ systems. The chest examination often may reveal wheezing, rhonchi, or crackles in patients with CVID-associated lung disease. The clinician should observe specifically for clubbing or cyanosis and use of accessory muscles for respiration. Careful periodic examination of the lymph nodes (cervical, axillary, or inguinal) and spleen is important, because patients with CVID also frequently have adenopathy and splenomegaly, which can be quite profound.

Laboratory evaluation would include quantitative immunoglobulins (IgG, IgA, and IgM) and functional antibody testing. Flow cytometry should enumerate the total numbers of T cells, T-cell subsets (CD4 and CD8), B cells, B-cell subsets, and NK cells. B-cell subset analysis should include the percentage of total memory B cells, switched memory B cells, and CD21(lo) B cells.^{31,64–67}

B-cell numbers are variable in CVID, and if reduced may indicate a poorer prognosis.^{1,8} Low numbers of switched memory B cells (CD27[+]IgM[–]IgD[–]) in the peripheral blood are frequently found in patients with a more severe phenotype of CVID (*e.g.*,

Table 2 Causes of hypogammaglobulinemia to exclude before diagnosis of CVID

Other primary immunodeficiency
X-linked agammaglobulinemia
XLP
Hyper-IgM syndrome
Secondary causes
Medications (corticosteroids, azathioprine, cyclosporine, d-penicillamine, gold, sulfasalazine, carbamazepine, levetiracetam, oxcarbazepine, and phenytoin)
Protein loss <i>via</i> gastrointestinal tract, lymphatics, or kidneys
B-cell lymphomas
Bone marrow failure

CVID = common variable immunodeficiency; XLP = X-linked lymphoproliferative disease.

GLILD)^{31,68} and may portend a worse prognosis. T-cell abnormalities occur in ~40% of patients and include anergy, T-cell lymphopenia, and poor proliferative responses to mitogens and antigens.

At initial evaluation sinus, chest, abdomen, and pelvis CT should be performed. Sinus CT is helpful in evaluation of sinus disease and in deciding if any additional antibiotic treatments may be of benefit. Abdominal CT scans are used to assess spleen size, and/or the presence of intraabdominal and retroperitoneal adenopathy. Because of the complexity of the pulmonary pathology in patients with CVID, in addition to high-resolution computed tomography (HRCT) scans of the chest, x rays, and full pulmonary function tests (including lung volumes, spirometry and diffusion capacity) should be obtained as part of the initial evaluation. HRCT scan of the chest is much more sensitive than a standard chest radiograph in detecting pulmonary parenchymal abnormalities such as interstitial lung disease or bronchiectasis.

Serologic assays that measure specific antibody are inappropriate to identify pathogens responsible for infection in patients with CVID. Diagnosis of specific pathogens in this patient population must be made by culture, polymerase chain reaction, or other direct methods of pathogen detection. Screening for human immunodeficiency virus and hepatitis B and C should be performed at the initial evaluation by polymerase chain reaction. Abnormalities in liver function tests are not uncommon and may be abnormal in as high as 43% of patients.^{51,69}

TREATMENT

The primary treatment of CVID is antibody replacement with either i.v. or subcutaneous immunoglobulin with an initial dose of 400–600 mg/kg of gammaglobulin per month.^{2,70} This dose can be divided every 3–4 weeks for i.v. administration or every 1–2 weeks for subcutaneous administration. Both i.v. and subcutaneous methods have been shown to be safe and effective for replacement.^{12,70–73}

Subsequent dosing should not be based on IgG immunoglobulin level, but rather on preventing infection. Although trough IgG levels should be drawn before initial administration and may be used to help guide therapy, recent studies have shown that individualized dose adjustments based on clinical course may be preferable to blanket goal IgG trough levels.^{74,75} Furthermore, higher doses are required for patients with significant pulmonary disease (*i.e.*, bronchiectasis), sinus disease, GLILD, or splenomegaly.⁷⁵ Once patients are established on immunoglobulin replacement therapy, IgG trough levels are measured every 6–12 months to ensure adequate dosing with a minimum trough level of 500 mg/gL.

There is no convincing evidence that one brand of gammaglobulin is better than others in reducing infections. However, products do differ in their preparation, and when choosing a product one must consider osmolality, pH, sodium, sugar, and IgA content. A full

in-depth comparison of gammaglobulin formulations is beyond the scope of this discussion, but a summary of available brands of immunoglobulin and their characteristic can be found at the Immune Deficiency Foundation website.⁷⁶

Additives in the preparations used to prevent protein aggregations⁷⁷—such as amino acids, sorbitol, salt, or sucrose—may lead to adverse effects in certain clinical settings. For example, sugar content should be considered in a patient with diabetes or prediabetes. Furthermore, sucrose content has been associated with renal failure or insufficiency.^{78,79} Because of the large protein load, patients with renal dysfunction might want to avoid intravenous immunoglobulin (IVIg) entirely, using subcutaneous immunoglobulin instead. The major contributors to osmolality in IVIg are sodium and sugar content. Reconstitution of lyophilized preparations can also result in hyperosmolar solutions. Osmolality is an important concern because hyperosmotic states have been implicated in thrombotic complications.⁸⁰

Although the mortality of CVID caused by common infectious pathogens has declined with the increased use of high-dose immunoglobulin replacement,⁸¹ patients may continue to develop obstructive, restrictive, or bronchiectatic changes.⁷ In fact, GLILD is refractory to gammaglobulin replacement therapy and bronchiectasis may develop despite antibody replacement therapy.^{29–35}

For the most part, many of the complications of CVID may be treated in the same manner as immunocompetent patients with similar diseases. Oral corticosteroids, immunomodulatory dosages of IVIg (2 g/kg per month), and rituximab have been used to treat autoimmune hemolytic anemia or autoimmune thrombocytopenia in patients with CVID.^{19,45,82–84} Splenectomy is to be avoided, because severe infections have occurred.^{8,85} Treatment of bronchiectasis in patients with CVID is similar to the therapy of idiopathic bronchiectasis. Mobilization of pulmonary secretions through the use of medications such as β 2-agonists along with chest physiotherapy is frequently used, although there are few trials that show the effectiveness of pulmonary hygiene.^{86,87}

The optimal treatment for GLILD in CVID is unknown, but these patients appear to have a high mortality rate if left untreated. GLILD is resistant to corticosteroid therapy so alternative treatment regimens should be considered. Steroid sparing agents such as azathioprine, 6-mercaptopurine, cyclosporine A, mycophenolate mofetil, or methotrexate have been tried with inconsistent results.⁵⁰ TNF inhibitors have also been tried and some success has been reported.^{88,89} However, the low prevalence of this complication in CVID patients makes controlled or open trials difficult. Recent data from a retrospective analysis of seven CVID patients with biopsy-proven GLILD aged 18–43 years suggests that combination chemotherapy with rituximab and azathioprine may be beneficial in this select patient population.⁶⁸ Patients showed statistically significant improvement in HRCT score ($p < 0.011$) and pulmonary function testing (forced expiratory volume in 1 second, $p < 0.04$ and forced vital capacity, $p < 0.036$). These findings are encouraging but highlight the urgent need for similar prospective studies to ascertain the most effective medications, optimal timing, duration of therapy, and effect on long-term morbidity and mortality.

CONCLUSION

CVID is a complex, multifocal disease with a large array of clinical manifestations and complications. Treatment with gammaglobulin and improved antibiotic coverage have vastly improved the outlook for patients; however, as infections and infectious complications become less prominent, morbidities from disordered inflammation or immune dysregulation have become greater areas of concern. Continued studies are needed to illuminate the many causes of this disease and possibly therapeutic targets.

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