Common Variable Immunodeficiency: Test Indications and Interpretations

Catherine R. Weiler, MD, PhD, and Jennifer L. Bankers-Fulbright, PhD

Common variable immunodeficiency (CVID) is one of the most common primary immunodeficiencies diagnosed in humans and the most commonly diagnosed in adults. Common variable immunodeficiency has multiple phenotypes, and patients with CVID usually report onset of symptoms in the second or third decade of life; there is no sex preference. Similar to other immunodeficiencies, symptoms include recurrent infections and/or infections that are difficult to treat. The hallmark of CVID is an IgG level at or greater than 2 SDs below the mean (≤500 mg/dL in adults), usually accompanied by deficiencies in IgA and/or IgM. However, hypogammaglobulinemia is a laboratory finding that is associated with a number of clinical conditions, including several hematologic and acquired disorders (Table 1) as well as primary combined immunodeficiencies (Table 2). Most importantly, other primary humoral immunodeficiencies can mimic CVID (Table 3). Thus, in the absence of a definitive test for this disease, CVID remains a diagnosis of exclusion that requires eliminating other explanations for hypogammaglobulinemia. We summarize information on the etiology of hypogammaglobulinemia and specifically address the diagnosis and treatment of CVID.

Primary immunodeficiencies, if not immediately severe and life threatening, are usually not diagnosed until at least 10 to 20 years after onset of symptoms. This delay between onset of symptoms and initiation of treatment often results in unnecessary suffering of patients whose condition is undiagnosed or misdiagnosed, as well as increased health care costs due to repeated infections that can lead to permanent tissue damage. In the first national immunodeficiency disease survey conducted in the United States, the most common diagnoses before the diagnosis of immunodeficiency were as follows (in order of frequency): sinusitis (67%), bronchitis (55%), pneumonia and ear infections (51% for each), diarrhea (30%), malabsorption (9%), sepsis (5%), meningitis (4%), hepatitis (3%), and cancer (2%). Of the patients with immunodeficiency, 76% had no family history, and the diagnosis was made in 41% of the patients between the age of 18 and 64 years.

From the Department of Internal Medicine and Division of Allergic Diseases, Mayo Clinic College of Medicine, Rochester, Minn.

Address correspondence to Jennifer L. Bankers-Fulbright, PhD, Allergic Diseases Research Laboratory, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (e-mail: bankers.jennifer@mayo.edu). Individual reprints of this article and the entire series on Genetics in Clinical Practice will be available for purchase from our Web site www.mayoclinicproceedings.com. © 2005 Mayo Foundation for Medical Education and Research
Figure 1. Algorithm of clinical observations that should result in an immune system work-up of patients suspected of having a primary immunodeficiency. HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; IV = intravenous.

B-CELL BIOLOGY AND THE GENETIC ETIOLOGY OF HYPOGAMMAGLOBULINEMIA

Any abnormality in the development, activation, or differentiation of B lymphocytes can result in clinical hypogammaglobulinemia. To appreciate how distinct deficiencies cause different patterns of clinical disease, one must understand B-cell development, the genetic makeup of immunoglobulins, and the interactions between T and B cells.

Because of the unlimited number of potential antigens, the immune system needs to be extremely diverse while concurrently being extremely selective. To facilitate this, each B lymphocyte bears a unique antigen receptor on its surface—the B-cell receptor—consisting of an immunoglobulin molecule along with Igα and Igβ signaling proteins. During B-cell development, immunoglobulin gene cassettes coding for the variable region of the antibody chains are randomly rearranged (and modified via non-germline changes to the coding sequence) to code for a
functional immunoglobulin molecule. (Figure 3, top).167 The immunoglobulin heavy chain has multiple different constant region isotypes that are connected to the variable domain of the heavy chain during transcription. The constant germline regions, in order of their arrangement on the Ig heavy chain locus on chromosome 14 are μ (IgM), δ (IgD), γ3 (IgG3), γ1 (IgG1), α1 (IgA1), γ2 (IgG2), γ4 (IgG4), ε (IgE), and α2 (IgA2).168 Each stage of B-cell development is characterized by the expression of various forms of the B-cell receptor complex, and a block at any developmental stage causes a lack of mature, circulating B cells and a characteristic cell surface phenotype (Figure 3, bottom).

The activation of mature, naive B cells usually requires T-cell “help” to mount a functional response to antigen (the notable exception being antibody responses to polysaccharide antigens). This B-cell/T-cell interaction, often referred to as the immunological synapse, is usually required for production of antibody classes other than IgD and IgM (class or isotype switch), somatic hypermutation, and the generation of memory B cells (Figure 4).169 Three primary connections between T and B cells comprise the core of the immunological synapse. First, the presentation of processed protein antigen by class II major histocompatibility complex (MHC) on the B cell to the T-cell receptor (TCR) initiates the interaction. Second, CD28 on the T cell binds to CD80/CD86 on the B cell, resulting in up-regulation of CD40 ligand (CD154) on the T-cell surface.170 Third, the newly up-regulated CD40 ligand on the T-cell binds to CD40 on the B cell, triggering cytokine secretion by the T cell. Once these 3 primary bridges (MHC:TCR, CD80/CD86:CD28, CD40:CD40 ligand) are made between the B and T cells, immunoglobulin class switch, B-cell prolifera-

FIGURE 2. Algorithm for determining which tests are required to assess the immune response and determine a diagnosis, as well as indications for when a patient suspected of having a primary immunodeficiency should be referred to an immunologist. CBC = complete blood cell count.
tion, and differentiation into plasma cells and memory B cells can occur.

Depending on the cytokines secreted by the T cell, the B cell will be instructed to undergo a class switch to different

### COMMON VARIABLE IMMUNODEFICIENCY

A consensus statement from the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiencies that defines the minimum requirements for a probable and possible diagnosis of CVID has been published. Both probable and possible CVID diagnostic criteria include (1) immunodeficiency developing after a person is 2 years old, (2) poor antibody response to polysaccharide and protein antigens, and (3) exclusion of other causes of hypogammaglobulinemia (Tables 1 through 3). A probable diagnosis of CVID requires serum IgG and IgA levels at least 2 SDs below the mean for the patient’s age; a possible diagnosis of CVID requires that only 1 of the major antibody isotypes (IgG, IgA, or IgM) is more than 2 SDs below the mean for the patient’s age. In most patients with CVID, the diagnosis is made in the second, third, or fourth decade of life, and a bimodal distribution of the age at onset has been reported, with peaks at 1 to 5 years and 16 to 20 years. Patients typically present with repeated respiratory infections, often caused by *Haemophilus influenzae, Moraxella catarrhalis,* and *Streptococcus pneumoniae.*

All patients who present with the symptoms summarized in Figure 1 should undergo an immunodeficiency work-up (Figure 2). Prediagnostic screening for a patient suspected of having an immunodeficiency starts with a

---

**TABLE 1. Secondary Etiologies Associated With Hypogammaglobulinemia**

<table>
<thead>
<tr>
<th>Hematologic disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Primary amyloidosis</td>
<td></td>
</tr>
<tr>
<td>Acquired disorders</td>
<td></td>
</tr>
<tr>
<td>Drug induced</td>
<td></td>
</tr>
<tr>
<td>Protein-losing enteropathy/intestinal lymphangiectasia</td>
<td></td>
</tr>
<tr>
<td>Chronic intestinal pseudo-obstruction</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td>Transplantation</td>
<td></td>
</tr>
<tr>
<td>Primary chylious disorders</td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td></td>
</tr>
</tbody>
</table>

*ADA = adenosine deaminase; GH = growth hormone; IL = interleukin; X-linked syndrome; IPEX = immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PNP = purine nucleotide phosphorylase; SCID = severe combined immunodeficiency; WHIM = warts, hypogammaglobulinemia, infections, and myelokathexis.

†Genetic defect(s) in parentheses.

---

**TABLE 2. Combined Immunodeficiency States Associated With Hypogammaglobulinemia and Genetic Defect**

<table>
<thead>
<tr>
<th>X-linked</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked SCID</td>
<td></td>
</tr>
<tr>
<td>WASP, Xq11.22</td>
<td></td>
</tr>
<tr>
<td>IPEX</td>
<td></td>
</tr>
<tr>
<td>FOXP3, Xq11.23</td>
<td></td>
</tr>
<tr>
<td>Agammaglobulinemia and GH deficiency</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Autosomal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2Ra deficiency</td>
<td></td>
</tr>
<tr>
<td>IL-7Ra deficiency</td>
<td></td>
</tr>
<tr>
<td>JAK3 deficiency</td>
<td></td>
</tr>
<tr>
<td>ADA deficiency</td>
<td></td>
</tr>
<tr>
<td>PNP deficiency</td>
<td></td>
</tr>
<tr>
<td>MHC class II deficiency</td>
<td></td>
</tr>
<tr>
<td>MHC class I deficiency</td>
<td></td>
</tr>
<tr>
<td>CD3 deficiency</td>
<td></td>
</tr>
<tr>
<td>ZAP-70 deficiency</td>
<td></td>
</tr>
<tr>
<td>Omenn syndrome</td>
<td></td>
</tr>
<tr>
<td>Artemis deficiency</td>
<td></td>
</tr>
<tr>
<td>CD45 deficiency</td>
<td></td>
</tr>
<tr>
<td>WHIM syndrome</td>
<td></td>
</tr>
<tr>
<td>Griscelli syndrome</td>
<td></td>
</tr>
<tr>
<td>Chédiak-Higashi syndrome</td>
<td></td>
</tr>
<tr>
<td>Severe congenital neutropenia</td>
<td></td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td></td>
</tr>
<tr>
<td>Chronic mucocutaneous candidiasis</td>
<td></td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td></td>
</tr>
<tr>
<td>Dystrophic myotonia types I and II</td>
<td></td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
<td></td>
</tr>
<tr>
<td>Autoimmune lymphoproliferative syndrome</td>
<td></td>
</tr>
<tr>
<td>Cornel-Netherton syndrome</td>
<td></td>
</tr>
</tbody>
</table>

*ADA = adenosine deaminase; GH = growth hormone; IL = interleukin; IPEX = immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; JAK = Janus kinase; MHC = major histocompatibility complex; PNP = purine nucleotide phosphorylase; SCID = severe combined immunodeficiency; WHIM = warts, hypogammaglobulinemia, infections, and myelokathexis.

†Genetic defect(s) in parentheses.
Igα/β deficiency, Ig heavy chain deficiency, Ig light chain deficiency, BLNK deficiency, ICOS deficiency, BLA deficiency, HIGM1 deficiency, HIGM3 deficiency, HIGM4-NEMO deficiency, HIGM4-NEMO variant, HIGM4-NEMO variant, XLP 163-166 SH2D1A (SAP) – –/+++ – –/++ +(++) ++(+) XL

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Known genetic mutation</th>
<th>Expected laboratory results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Igα/β deficiency</td>
<td>Loss of Igα or Igβ</td>
<td>IgM IgG IgA Specific Ig B cells T cells Inheritance</td>
</tr>
<tr>
<td>(B) Ig heavy chain deficiency</td>
<td>≥1 Ig heavy chains</td>
<td>+ + + – –/+++ +/+++ +++ AR</td>
</tr>
<tr>
<td>(C) Ig light chain deficiency</td>
<td>≥1 Ig light chains</td>
<td>–/+++ –/++ –/+++ –/+++ –/+++ +++ AR</td>
</tr>
<tr>
<td>(D) BLNK deficiency</td>
<td>BLNK</td>
<td>– – – – –/+++ +/+++ AR</td>
</tr>
<tr>
<td>(E) ICOS deficiency</td>
<td>ICOS</td>
<td>+ + + – –/+++ +/+++ AR</td>
</tr>
<tr>
<td>(F) BLA deficiency</td>
<td>Bruton tyrosine kinase</td>
<td>– – – –+++ XL</td>
</tr>
<tr>
<td>(G) HIGM1 deficiency</td>
<td>CD40 ligand</td>
<td>+++(+) ++ + – +++(+) +++ XL</td>
</tr>
<tr>
<td>(H) HIGM3 deficiency</td>
<td>CD40</td>
<td>+++(+) ++ + – +++ +++ AR</td>
</tr>
<tr>
<td>(I) HIGM2 deficiency</td>
<td>AID</td>
<td>+++(+) –/+ –/+ – –+++ +++ AR</td>
</tr>
<tr>
<td>(J) HIGM4-NEMO deficiency</td>
<td>IKBK (exon 9)</td>
<td>+++(+) + + – +++(+) +++ XL</td>
</tr>
<tr>
<td>(K) HIGM4-NEMO variant</td>
<td>IKBK (exon 9)</td>
<td>+++(+) IgG3 – ++ – +++(+) +++ XL</td>
</tr>
<tr>
<td>(L) HIGM2-UNG deficiency</td>
<td>UNG</td>
<td>+++(+) –/++ –/+ – +++ +/+++ AR</td>
</tr>
<tr>
<td>(M) HIGM4-NEMO variant</td>
<td>SHZD1A (SAP)</td>
<td>– –/+++ – –/+ +/+++ +++ XL</td>
</tr>
</tbody>
</table>

*AID = activation-induced cytidine deaminase; AR = autosomal recessive; BLNK = B-cell linker protein; HGIM = hyper-IgM syndrome; ICOS = inducible costimulator; NEMO = nuclear factor-kB essential modulator; SAP = signaling lymphocyte activation molecule (SLAM)-associated protein; UNG = uracil-DNA glycosylase; XL = X-linked; XLA = X-linked agammaglobulinemia; XLP = X-linked lymphoproliferative syndrome; +++ = normal; ++ = low; + = very low; – = absent; ? = unknown; –/+ = phenotype varies from absent to very low; –/++ = phenotype varies from absent to low; –/+++ = phenotype varies from absent to normal; +(++) = phenotype varies from very low to low; ++(+) = phenotype varies from low to normal; +++(+) = phenotype varies from normal to high.

**Table 3. Expected Laboratory Findings for Known Primary Humoral Immunodeficiencies**

The first order of testing should include a complete blood cell count with differential, total complement levels, total IgG, IgA, and IgM levels including IgG subclasses, and analysis of functional in vivo immunity (Figure 2). Complete blood cell count values and total complement levels are typically within normal limits in patients with CVID, unless the patient has an acute infection at the time of testing. Nephelometry is used to quantify serum levels of IgM, IgA, and IgG (including IgG subclasses). In vivo function of the immune response is most commonly evaluated by quantitating serum immunoglobulin specific for both T-cell dependent (eg, tetanus or diphtheria) and T-cell independent (eg, isohemagglutinins or pneumococcal vaccine) antigens. Ideally, prevaccination and postvaccination immunoglobulin levels should be analyzed (eg, for tetanus/diphtheria and pneumococcal vaccine). Antigen-specific antibodies are quantified by an enzyme-linked immunosorbent assay or other similar technique. Absence of antigen-specific immunoglobulin in response to both polysaccharide and protein-based antigenic stimulation is consistent with a diagnosis of CVID but is not definitive. Additionally, in vivo T-cell function, examined by delayed type hypersensitivity skin testing, is deficient in more than 50% of patients with CVID.**

**Second Level of Testing**

The second level of testing of patients suspected of having CVID focuses on ruling out all other known primary or secondary causes of hypogammaglobulinemia and identifying subtypes of CVID. In the absence of a clear secondary cause of hypogammaglobulinemia (Table 1), a genetic etiology should be suspected. Several other primary immunodeficiency conditions with known genetic aberrations in which the patients present with hypogammaglobulinemia need to be identified because they could be erroneously diagnosed as CVID (Tables 2 and 3). It is critical to identify patients with these conditions for genetic counseling because there have been reports of “mild” forms of X-linked agammaglobulinemia (XLA), X-linked lymphoproliferative syndrome, Wiskott-Aldrich syndrome, and adenosine deaminase deficiency being misdiagnosed as CVID. Of note, exclusion of all other forms of hypogammaglobulinemia is labor intensive, and tests are not generally available; thus, ideally, patients should be referred to an immunologist for an appropriate diagnostic evaluation.
FIGURE 3. B-lymphocyte development and immunoglobulin production. B cells develop in a defined series of steps, during which time DNA coding for the heavy and light chains of the immunoglobulin is rearranging. Top, Schematic showing the final structure of the immunoglobulin protein as secreted by a plasma cell. Note how light and heavy chains are located such that they together create the antigen binding site (F-ab) on each arm of the antibody. Only the heavy chains of the immunoglobulin bind to Fc receptors on cells (Fc-portion). J, D, V = joining, diversity, and variable regions. Bottom, B-cell development occurs in discrete stages defined by unique patterns of surface molecule expression. The stage at which B-cell development is blocked by a given primary immunodeficiency is shown on the right; superscripted letters refer to the more complete descriptions of the deficiencies listed in Table 3. BCR = B-cell receptor; BLNK = B-cell linker protein; HIGM = hyperimmunoglobulin M; ICOS = inducible costimulator; XLA = X-linked agammaglobulinemia; XLP = X-linked lymphoproliferative syndrome.
COMMON VARIABLE IMMUNODEFICIENCY

double negative) cells is also done at this point, and up to 50% of patients with CVID have a decreased CD4/CD8 ratio. B-cell phenotyping to identify the presence of pre-B cells (CD19+, CD10+, CD21+, IgM+), immature B cells (CD19+, CD10+, CD21+, IgM+) and mature B cells (CD19+, CD10+, CD21+, IgM+) will distinguish between patients with XLA and other early B-cell defects from patients with later or mature B-cell defects. In patients who have pre-B cells in the absence of immature or mature B cells, the diagnosis of XLA is strongly suggested. The exception would be the 5% to 10% of patients with CVID who have B cells that comprise less than 1% of the total peripheral blood lymphocyte population; they likely have early B-cell defects. Additionally, tests for other surface markers such as CD40 or CD40 ligand (hyperimmunoglobulinemia M syndrome 1) or mutant intracellular proteins such as Bruton tyrosine kinase (XLA) are available by flow cytometric analysis and can be used to rule out other primary immunodeficiencies.

Recently, flow cytometric determination of CVID subclasses using B-cell markers was correlated with clinical outcomes. As mentioned previously, a decrease in memory (CD27+) B cells is generally observed in patients

**FIGURE 4.** B-lymphocyte activation and differentiation (the “immunological synapse”). This diagram depicts the critical and relevant cell surface interactions that occur during T-cell (blue portion) mediated activation of a B cell (green portion). Selected receptors, ligands, and signaling proteins are identified. Superscripted letters indicate that the protein (or lack thereof) is associated with hypogammaglobulinemia as described in Table 3. AID = activation-induced cytidine deaminase; Ag = antigen; BAFF = B-cell activation factor of the tumor necrosis factor family; BAFF-R = BAFF receptor; ICOS = inducible costimulator; MHC = major histocompatibility complex; NEMO = nuclear factor kB essential modulator; SAP = signaling lymphocyte activation molecule (SLAM)-associated protein; TACI = transmembrane activator and CAML (calcium modulator and cyclophilin ligand) interactor; TCR = T-cell receptor; UNG = uracil-DNA glycosylase.
with CVID. By further characterizing the CD27+ B-cell compartment in patients with CVID, Warrnatz et al. defined 2 main subgroups, collectively referred to as the Freiburg classifications: group I patients have a decreased (<0.4% total lymphocytes) isotype switched memory B-cell compartment (CD19+, IgD−, CD27+), whereas group II patients have normal levels of these cells. Additionally, group I is subdivided into patients who have more than 20% non-mature (CD21−) peripheral B cells (group Ia) and those who have normal levels of CD21+ B cells (group Ib). Patients in group Ia have an increased incidence of splenomegaly or autoimmune disease.

Similarly, Piqueras et al. classified patients with CVID into 3 groups, MB0, MB1, or MB2, collectively referred to as the Paris classifications, based on flow cytometric analysis of the same B-cell surface markers, regardless of CD21+ detection or peripheral B-cell number. Patients in the MB0 group have decreased levels of peripheral memory B cells (<11% of total B cells), both switched (CD19+, IgD−, CD27+) and nonswitched (CD19+, IgD+, CD27−); MB1 patients have reduced (<8% of total B cells) switched memory B cells only, and MB2 patients have normal levels of memory B cells. Autoimmunity complications were increased in patients in the MB0 and MB1 groups compared to those in the MB2 group, and granulomatous disease and splenomegaly were found more often in the patients in the MB0 group. Additionally, patients with CVID who lack nonswitched memory B cells have an increased incidence of bacterial pneumonia and structural lung damage. Although not precisely overlapping, MB2 patients are most similar to group II patients, and MB0/MB1 patients most closely match the group I designation. Most relevant for routine clinical testing, flow cytometric classification of these B-cell populations was recently shown to be feasible for whole blood samples.

In Vitro Immune System Evaluation. In addition to the Freiburg and Paris CVID classifications, another classification of CVID is based exclusively on in vitro B-cell function. Although all patients examined had clinical hypogammaglobulinemia, when B cells were cultured in vitro with anti-IgM and interleukin 2, they responded in 1 of 3 ways which defined a “group.” Group A patients had B cells that did not secrete IgM or IgG in vitro; B cells from group B patients secreted only IgM in response to stimulation, and B cells from group C patients secreted both IgM and IgG in vitro. Groups A and B are generally similar to Freiburg group I and Paris MB0/MB1, whereas group C is similar to Freiburg group II and Paris MB2; however, these correlations are not robust.

Genetic Testing. In the past 2 years, 4 genes have been identified in which mutations can lead to a CVID phenotype. The first gene mutation to be described was in the ICOS gene, and 9 patients have been described worldwide since 2003. Mutations in the remaining 3 genes lead to defective expression of the corresponding protein—CD19, BAFF-R (B-cell activation factor of the tumor necrosis family receptor), and TACI (transmembrane activator, calcium modulator, and cyclophilin ligand interactor)—which have been documented in 4, 3, and 24 patients, respectively. In particular, TACI mutations are proposed to account for 10% of all cases of CVID. Although these mutations have been associated with CVID in several patients, it is likely there are several other genetic defects yet to be discovered that can also result in CVID; thus, the failure to detect any of these 4 mutations does not rule out a diagnosis of CVID.

Identifying the specific genetic defect (ICOS, BAFF-R, CD19, or TACI) associated with a CVID phenotype in an individual requires confirmatory flow cytometric and molecular analysis. The absence of ICOS can be determined by intracellular staining on activated T cells, whereas the absence or down-regulation of CD19 or BAFF-R is detected on the surface of B cells. Expression of TACI can be examined on B cells and a subset of T cells. Once flow cytometry reveals the absence or reduced expression of a given protein, extensive molecular analysis, including sequencing of the gene, can be undertaken to identify the specific mutation.

Interestingly, several other molecular abnormalities have been documented in B and/or T cells from patients with CVID, although in most cases the underlying genetic defects and clinical correlations of these phenotypes remain elusive. One example is the recently identified abnormal interaction between TCR CD3ζ and ZAP-70. Additionally, several other proteins have been shown to be dysregulated in at least some patients with CVID, including Pax5, CCR7, CD45RA, CD86, CD95, the immunoglobulin surrogate light chain λ 5/14.1, and MHC class II and III. However, determination of expression levels of these proteins is not currently useful for the clinical diagnosis of CVID. Finally, genetic testing, especially genomic sequencing, allows physicians to identify any molecular defect leading to a clinical presentation of immunodeficiency, even those that would be missed by flow cytometric analysis because of mutations that block the function, but not the expression, of a protein.

The above combination of hematologic, molecular, and genetic testing has excluded all other forms of hypogammaglobulinemia, the most appropriate diagnosis is CVID. The standard treatment of CVID is immunoglobulin replace-
ment therapy. Although immunoglobulin therapy clearly reduces the frequency of infections in patients with CVID, antibiotic prophylaxis should be initiated in those who have recurrent infections despite immunoglobulin replacement. Immunoglobulin therapy also has been reported to have other immune-modulating effects, resulting in improvement of CVID-associated autoimmune disease. Because patients with CVID have variable levels of the different immunoglobulin isotypes, IgG levels should be monitored closely while they receive immunoglobulin replacement therapy and adjusted when needed for better long-term outcomes.

Immunoglobulin therapy is usually administered intravenously in the United States at an initial dosage of 400 to 600 mg/kg body weight every 2 to 4 weeks. Patients who are very ill and severely hypogammaglobulinemic will benefit from an increase in the frequency of infusions to every 5 days for 5 infusions, at which point steady-state IgG levels are achieved. The goal for a trough IgG level in patients with CVID is 850 mg/dL or higher, which has been shown to be associated with less end-organ damage, especially to the lungs. If the total IgG trough level is not within the therapeutic range after 5 infusions, the frequency needs to be adjusted to every 1 to 3 weeks to achieve this trough. The most common adverse effects of intravenous immunoglobulin treatment are local swelling, redness, and pruritus, which resolve within a day. Additional adverse effects to intravenous immunoglobulin, such as anaphylaxis, septic meningitis, loss of venous access, severe incapacitating headaches, generalized aches and pains, serum sickness, history of pulmonary embolism, risk for thrombosis, and angioedema (C.R.W., unpublished data). Multiple studies have shown that the 2 techniques are equally efficacious for treating hypogammaglobulinemia. The dosage of subcutaneous immunoglobulin is 100 mg/kg body weight once a week, the rate of the infusion is between 15 mL and 40 mL per hour, and the limit per infusion site is 22 mL.

In addition to immunoglobulin replacement therapy, aggressive treatment with antibiotics should be used for breakthrough bacterial infections. Patients with CVID should not receive live vaccinations; at least some patients with CVID benefit from killed vaccines even in the absence of B-cell memory. Individual patient lymphocyte profiles should be taken into account during therapy. For example, Pneumocystis carinii pneumonia prophylaxis may be considered when a patient’s CD4 count is less than 200 cells/mm³. Other therapeutic modalities, such as interleukin 2 treatment (to enhance T-cell function in patients whose T cells produce low interleukin 2 in vitro), have shown some promise, but further studies are needed.

Patients with CVID should be monitored regularly for autoimmune disorders and malignancy because of their increased risk of developing both. Approximately one third of patients with CVID will develop some sort of autoimmune disease, including but not limited to hemolytic anemia, purpura, autoimmune hepatitis, idiopathic thrombocytopenia, autoimmune neutropenia, rheumatoid arthritis, systemic lupus erythematosus, vitiligo, primary biliary cirrhosis, thyroiditis, dermato myositis, and Graves disease. Additionally, granulomas, particularly of the lungs, liver, spleen, or conjunctivae, may occur. In terms of malignancies, patients with CVID have been reported to have up to a 300-fold increased risk for lymphoma and a 50-fold increased risk for gastric cancer. Moreover, liver disease (10% of patients) and gastrointestinal disorders, such as inflammatory bowel disease, giardiasis, and nonspecific malabsorption, develop in patients with CVID. Importantly, pulmonary function tests should be performed regularly (twice a year), and computed tomographic imaging of the chest should be performed if symptoms increase or if a decrease in lung function is noted.

Genetic counseling should be offered to patients and their families, especially if a particular mutation has been identified, a situation that will become more common during the next few years. Although the inheritance pattern of CVID is not simple (at times “skipping” a generation), 10% to 20% of patients with CVID have more than 1 family member with either CVID or selective IgA deficiency. Thus, genetic counseling will inform the family members, including offspring, and expedite early detection and treatment of any affected children or adults in future generations. The prognosis of patients with CVID depends on early intervention to prevent tissue damage from recurrent infections and whether complications such as autoimmunity or cancer develop (as mentioned previously).

CONCLUSION

Common variable immunodeficiency continues to be an immunodeficiency “diagnosis of exclusion.” In the past, many patients have certainly received a misdiagnosis of CVID because of a lack of adequate understanding of the disease and testing. With the development of routine flow cytometric and genetic-based tests, the diagnosis of CVID is evolving into a more clearly defined set of immunodeficiency.
ciencies. Continued identification of the molecular and genetic causes of CVID will facilitate optimal treatment of patients with different forms of this disease.

We thank Roshini S. Abraham, PhD, and Danir Matesic, MD, for critical review of the manuscript.

REFERENCES


COMMON VARIABLE IMMUNODEFICIENCY


