Maintenance of Certification clinical management series

Series editors: James T. Li, MD, PhD

Common variable immunodeficiency

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Activity Objectives

1. To identify the most frequent clinical presentations of common variable immunodeficiency (CVID).
2. To use immunoglobulin measurement and specific antibody testing in the diagnosis of CVID.
3. To understand considerations for determining proper dosage of immunoglobulin replacement.
4. To appreciate the effect of immunoglobulin replacement on infection susceptibility and the development of chronic complications of CVID.

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Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: J. T. Li has consulted for Abbott. The rest of the authors declare that they have no relevant conflicts of interest.

CLINICAL VIGNETTE

A 50-year-old woman with a history of recurrent infections since her early 20s presents for immunologic evaluation. After a medically uneventful childhood and teenage years, she began to experience recurrent sinus infections in her early 20s treated with antibiotics and finally sinus surgery in 1990, which was successful in reducing symptoms. In the next decade, she began to note excessive fatigue and then bruising with a petechial rash. In 2000, she was given a diagnosis of immune thrombocytopenic purpura (ITP) with a platelet count of 2000. After 6 months of unsuccessful therapy with prednisone, her ITP went into remission with a course of intravenous immunoglobulin (IVIG) only to recur in 2002. At that time, she underwent splenectomy, which did not increase her platelet count. She was again treated with prednisone and IVIG, finally achieving resolution of thrombocytopenia. However, over the next 5 years, she required multiple courses of steroids to control both recurring sinusitis and the re-emergence of ITP. When oral steroids could no longer relieve sinus disease, she had formal allergy testing in 2007 that was unrevealing for environmental hypersensitivity. In the fall of 2010, she had shingles, and her chronic fatigue worsened, which she attributed to an increasingly demanding work schedule. However, she was subsequently referred for an immunologic evaluation because of her steadily worsening clinical condition.

At the time of evaluation, her complete blood count showed a white blood cell count of 11,900 μL, a hemoglobin value of 12.9 g/dL, a platelet count of 556,000 μL, a neutrophil count of

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Received for publication February 2, 2012; revised March 20, 2012; accepted for publication March 22, 2012.

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0091-6749/$36.00

doi:10.1016/j.jaci.2012.03.025

7770/μL, a lymphocyte count of 2650/μL, a monocyte count of 1230/μL, and an eosinophil count of 150/μL. Results of routine chemistry, liver, and renal function blood testing were all within normal limits. A computed tomographic scan of the chest and abdomen revealed hepatic and pulmonary nodules of unclear cause. Quantitative immunoglobulin measurement revealed an IgG level of 295 mg/dL (reference range, 694-1618 mg/dL), an IgA level of 7 mg/dL (reference range, 81-463 mg/dL), and an IgM level of 44 mg/dL (reference range, 48-271 mg/dL). Urinalysis did not demonstrate proteinuria. Specific antibody testing revealed that antibody titers did not reach protective levels for diphtheria, tetanus, or any of the 14 pneumococcal serotypes examined after vaccination. Thus the patient met the formal diagnosis of CVID.

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DISCUSSION

Overview

CVID is the most common symptomatic primary immunodeficiency, affecting an estimated 1 in 25,000 to 75,000 subjects, depending on the population examined.[E1] Such values might be an underestimate because heightened physician awareness of the diagnosis and increased participation in primary immunodeficiency registries could reveal a greater incidence. Of note, although IgA deficiency is actually the most common primary immunodeficiency at an estimated frequency of 1:223 to 1:3000 in the United States, most patients are asymptomatic.[E2] CVID differs from many other primary immunodeficiencies in that it is most frequently diagnosed in adults aged 20 to 40 years. However, about 20% of subjects are given a diagnosis before the age of 21 years; although the clinical phenotype is similar for children with significant B-cell defects, other immune defects, such as X-linked agammaglobulinemia or hyper-IgM syndromes, must be considered. Although more than 2000 articles on the subject can be retrieved from PubMed, clinical appreciation of CVID remains limited, commonly leading to a 6- to 8-year delay in making this diagnosis. Lack of diagnosis delays the initiation of the most proved medical intervention, immunoglobulin replacement therapy, a treatment that reduces bacterial infections and limits hospitalizations, as well as organ damage.[E3,E4]

In addition to infections, patients with CVID also have a propensity to having a number of chronic complications, including autoimmunity, chronic lung disease, inflammatory bowel disease, systemic granulomatous disease, lymphoid hyperplasia, and malignancy.[E1,E5] Prevention of these complications remains a major goal for immunologists treating patients with CVID, and management remains a major challenge. The clinical case exemplifies the common constellation of symptoms found in such patients, including the history of ITP in this case leading to splenectomy, shingles, and unusual radiologic findings. It also illustrates the theme of numerous referrals to disparate specialties and the diagnostic delay commonly experienced.

The genetic cause of CVID is most commonly unknown and most frequently the result of a sporadic emergence in individual patients. However, the identification of CVID familial cohorts and the progression of some IgA-deficient patients to CVID indicate a strong contribution of genetics.[E6] Polymorphisms in the costimulatory molecules CD18, CD19, CD20, CD21, inducible costimulator, transmembrane activator and calcium-modulating and cyclophilin ligand interactor (TACI), and B cell–activating factor of the TNF family have all been linked to CVID.[E7] This correlation is not surprising because B cells from patients with CVID are inhibited in their ability to develop into class-switched memory and plasma cells, a maturation process that requires adequate costimulation. Genetic studies, including linkage analysis of familial cohorts, as well as genome-wide polymorphism associations, continue to enhance our understanding of the complex molecular mechanisms underlying CVID.[E8]

Diagnosis and evaluation

The diagnosis of CVID is based on reduced levels of total IgG, IgA, and/or IgM and a demonstrated deficiency in specific antibody production.[E1,E9] The IgG level is generally less than 400 mg/dL. Deficiency of antibody production can be demonstrated by the lack of protective titers to several protein-based vaccines and after immunization with pneumococcal vaccine. Because the diagnosis of CVID is a lifelong diagnosis, we usually test antibody titers to tetanus and diphtheria toxoids, *Haemophilus influenzae*, measles, mumps, rubella, varicella, and pneumococcus to validate fully the immune defect. Additionally, titers to hepatitis A or B after vaccination can also be considered, as can titers to influenza virus or isohemagglutinins, if available, and the blood type is known. If the quantitative serum IgG level is less than 200 mg/dL, we would strongly consider initiating immunoglobulin replacement, even in an absence of functional antibody defect given the increased pneumonia risk in our experience.[E3] In addition, for very low serum IgG levels, one can debate the value of incurring the expenses of obtaining multiple antibody titers when the medical decision to start immunoglobulin replacement therapy has been made. Part of the diagnostic criteria of CVID includes excluding other diagnoses that might lead to hypogammaglobulinemia. This comprises other genetic diseases, immunoglobulin loss in urine or stool, use of medications, and malignancy.

Chronic oral corticosteroid use can lead to reduced IgG levels[E10]; in the case outlined here, the patient had not received such therapy for some months. The mechanism of IgG suppression is unclear but might be due at least in part to corticosteroid-induced catabolism of IgG, suppression of leukocyte responses that promote IgG secretion, or both. Interestingly, the effect appears to be most potent for IgG, and IgE levels do not seem to be similarly suppressed in studies of allergic patients taking chronic oral corticosteroids. Conventional low doses (5 mg) of oral corticosteroids do not typically decrease IgG levels, although there is a reported case of hypogammaglobulinemia in a patient who was receiving low-dose corticosteroid therapy for 36 years.[E11] Hypogammaglobulinemia associated with extended courses of high-dose steroids has been reversed by corticosteroid abstinence in our experience.

Other medications linked to suppression of antibody responses include antirheumatic agents, such as azathioprine, cyclophosphamide D-penicillamine, gold, and sulfasalazine.[E12] Additionally, anticonvulsants, such as carbamazepine, levetiracetam, oxcarbazepine, and phenytoin, have all been associated with selective isotype deficiency or losses among all isotypes.[E13-E16] The exact mechanism by which anticonvulsants inhibit IgG responses is unknown and can require months to years of medication avoidance to return to normalized immunoglobulin levels.[E14,E15] The most common medications associated with hypogammaglobulinemia are listed in Table E1,[E12-E16] along with relevant citations.

Abnormal radiologic findings of nodules in the liver and lung, such as seen in our example patient, are indicative of granulomatous disease that is found in 8% to 22% of patients with CVID.[E17] Such findings often lead to diagnostic delay, such as can happen when pulmonary nodules are attributed to sarcoidosis rather than unappreciated CVID. Moreover, the presence of granulomatous disease might indicate the necessity for immunosuppressant treatment.[E18] Of note, a history of shingles is not uncommon in patients with CVID and might be due to reported deficiencies in T-cell responsiveness in at least subsets of these patients.[E19]

Management

The standard of treatment for CVID is 400 to 600 mg/kg of immunoglobulin replacement therapy administered either intravenously, generally every 3 to 4 weeks, or as subcutaneous immunoglobulin, most commonly every 1 to 2 weeks. The route of immunoglobulin replacement therapy is best determined by patient preference, as well as clinical considerations of the patient. Commercially available immunoglobulin preparations

vary in composition, each having an additive, such as an amino acid, sorbitol, salt, or sugar, to prevent protein aggregations. These can influence the selection of a preparation for an individual patient. Although there is one product very low in IgA that has been used in subjects with anti-IgA antibodies, testing for anti-IgA antibodies is not generally done before starting immunoglobulin replacement because of the rarity of clinically important antibodies of this kind.

The dosage of immunoglobulin for intravenous use is evaluated by measuring trough IgG levels drawn before administration. Although an earlier goal of immunoglobulin replacement was considered to be a trough serum value of around 600 mg/mL,[E20] a number of recent studies suggest that higher, even individualized, dosages might be beneficial.[E21] For subcutaneous delivery, a sample drawn just before a treatment can provide this value. Although trough levels of 1000 mg/dL correlated with a 5-fold decrease in pneumonia when compared with patients at 500 mg/dL in one meta-analysis,[E21] comprehensive reduction in the incidence of multiple infections is not always associated with higher trough values.[E22] Contributing to the inherent complexity of dosing IgG replacement are the physiologic differences among patients relating to immunoglobulin production and metabolism, making the extrapolation of a single goal IgG trough for all patients inappropriate. Goal IgG troughs are dictated by the baseline serum IgG level, as well as the extent of functional antibody responses.[E5] Accordingly, a goal trough IgG level should be determined based on the preintervention baseline: a patient with profoundly compromised IgG levels might see noted clinical benefit from a goal trough of 600 mg/dL of IgG, whereas a patient with slightly below-normal IgG levels yet profoundly compromised specific antibody responses might need a significantly higher trough level to achieve clinical benefit. In other words, immunoglobulin replacement should be individualized, with dose adjustment considered based on clinical course. Moreover, physiologic determinants, such as neonatal Fc receptor expression, might affect the half-life of immunoglobulin, consequently requiring higher doses to achieve clinical response in certain patients.[E23] The neonatal Fc receptor is a broadly expressed MHC class I–like molecule that functions to increase IgG half-life through protection from catabolism.[E24] Once established on immunoglobulin replacement therapy, IgG trough levels are measured every 6 to 12 months to ensure adequate dosing and administration.

THE CASE REVISITED

Finally, a consulting hematologist who saw this patient in 2011 decided to refer her for immune deficiency evaluation based on her history of recurrent sinusitis, shingles, hepatic and pulmonary nodules, and ITP. The serum immunoglobulins were examined, and antibody defects were documented. On the basis of the diagnosis of CVID, she was started on 400 mg/kg IVIG once a month. The primary goal of this therapy will be to reduce the incidence of sinus infections and reduced use of antibiotics and corticosteroids. Although episodes of ITP are reduced in patients with CVID who have had recurrent bouts of thrombocytopenia,[E25] pulmonary nodules are not likely to be altered by this therapy, as for most of the other noninfectious complications of CVID.[E1,E26]

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TABLE E1. Medications associated with hypogammaglobulinemia

Medication	Reference
Azathioprine	Lee et al[E12]
Cyclosporine	Lee et al[E12]
D-penicillamine	Lee et al[E12]
Gold	Lee et al[E12]
Sulfasalazine	Lee et al[E12]
Carbamazepine	Hayman and Bansal[E13]
Levetiracetam	Azar and Ballas[E14]
Oxcarbazepine	Knight and Cunningham-Rundles[E15]
Phenytoin	Pereira and Sanchez[E16]