Common Variable Immunodeficiency

Diagnosis, Management, and Treatment

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KEYWORDS

- Common variable immunodeficiency • CVID • Antibody deficiency
- Primary immune deficiency • Immune activation • Autoimmunity
- Lymphoproliferation

KEY POINTS

- Common variable immunodeficiency (CVID) is a grouping of heterogeneous diseases with the common finding of impaired antibody production.
- Morbidity is not limited to infection; in fact, noninfectious complications can be the most threatening and difficult to treat.
- Proper care of patients with CVID includes both replacement of immunoglobulin G and monitoring for CVID-associated disease on a regular basis.

INTRODUCTION

Common variable immunodeficiency (CVID) refers to a grouping of antibody deficiencies that lack a more specific genetic or phenotypic classification. It is the immunodeficiency classification with the greatest number of constituents, likely because of the numerous ways in which antibody production can be impaired and the frequency in which antibody production becomes impaired in human beings. CVID comprises a heterogeneous group of rare diseases. Consequently, CVID presents a significant challenge for researchers and clinicians. Despite these difficulties, both our understanding of and ability to manage this grouping of complex immune diseases has advanced significantly over the past 60 years.

Disclaimers: none.
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Immunol Allergy Clin N Am 35 (2015) 637–658
http://dx.doi.org/10.1016/j.iac.2015.07.009 **immunology.theclinics.com**
0889-8561/15/$ – see front matter

DIAGNOSIS

Initial Evaluation

Historically, the definition of common variable immunodeficiency (CVID) focused on the predominant finding of antibody deficiency, but more recent definitions have focused on the associated clinical features frequently seen. The most cited definition of CVID was presented by the European Society for Immunodeficiency (ESID) and the Pan American Group for Immunodeficiency in 1999, and the following criteria for probable CVID were proposed: greater than 2 years of age, immunoglobulin G (IgG) and immunoglobulin A (IgA) less than 2 standard deviations from the mean for age, either absent isohemagglutinin or absent vaccine responses, and no other defined causes of hypogammaglobulinemia.[1] Recently, there has been a growing concern that the application of these criteria to the clinical setting has resulted in the inappropriate administration of immunoglobulin replacement in a substantial number of patients that were unlikely to benefit from this therapy but still met the CVID criteria.[2] As a result, alternative diagnostic criteria have been proposed to include the following additional features: symptoms directly attributable to failure of antibody production, additional supportive laboratory findings, and pathologic confirmation of diseases frequently seen in CVID.[3] The latest combined ESID working criteria for classification of primary immune deficiency incorporated these concerns and also made efforts to remove diseases in which hypogammaglobulinemia likely results from a profound deficiency of T cells (**Table 1**).[1,4]

Differential Diagnosis

Secondary causes of decreased serum immunoglobulin levels must be ruled out in any patient that meets the diagnostic criteria for CVID because these causes can have dramatically different treatment implications. Infection, protein losing enteropathy, renal protein loss, genetic syndromes, immunosuppressive medications, other medications, and malignancy can all induce hypogammaglobulinemia.[2,5] Malignancy in particular can present with profound immune system derangement, and some advocate that all initial CVID diagnoses should remain provisional for a brief period of time to allow for emergence of malignancy.[3,6] Secondary causes of hypogammaglobulinemia are numerous, and the process of exclusion is often tedious; however, diligent consideration of these processes is essential to achieve an accurate diagnosis.

Pitfalls

The antibody response to polysaccharide pneumococcus vaccine, PNEUMOVAX23, is frequently measured to fulfill the antibody response criterion of the CVID diagnostic criteria; however, the validity of this type of testing is uncertain. In the United States, response to pneumococcal vaccination is assessed with laboratory-developed tests that demonstrate significant variability when the same sera are evaluated in different laboratories.[7] Additionally, what constitutes a normal response to vaccination lacks consensus; the chosen thresholds for measuring responsiveness dramatically influence the outcome.[8] Functional assays that measure opsonophagocytosis or antibody affinity promise to more accurately assess whether a vaccine response is protective, but they are not available to the practicing clinician in the United States. As a result, the abnormal antibody response to Pneumovax23 is likely the largest contributor to the misdiagnosis of CVID and inappropriate use of immunoglobulin replacement.[2] The authors advise that responsiveness to Pneumovax23 should be interpreted with great caution when considering a diagnosis of CVID.