

The Many Gaps in Our Knowledge of the Etiology, Pathogenesis, Complications, and Prognosis of Hypogammaglobulinemia and Common Variable Immune Deficiency



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Most adult referrals to clinical immunology clinics involve patients with a history of persistent sinopulmonary infections refractory to aggressive antibiotic therapy. The mainstay for clinical diagnosis of antibody deficiency has been measurement of serum immunoglobulin levels.^{1,2} Although some of these patients suffer from hereditary agammaglobulinemia (eg, X-linked agammaglobulinemia), a secondary antibody deficiency due to malignancy (eg, chronic lymphocytic leukemia), chemotherapy, or immune-suppressive therapy (eg, Rituxan), systemic losses (eg, gastrointestinal), or antigen-specific antibody deficiencies (eg, specific polysaccharide antibody deficiency), the precise mechanisms underlying immune deficiency in most antibody-deficient patients are poorly understood.

The range of antibody deficiency is vast and includes those with selective IgM, selective IgA, and selective IgG deficiency, including selective IgG subclass deficiencies and combinations thereof.^{1,2} By definition, all individuals with an IgG serum level that is less than 2 SDs below the mean for their age can be considered hypogammaglobulinemic. Unfortunately, again by definition, this would identify at least 2.3% of the population as being antibody deficient and thus potential candidates for immunoglobulin therapy. Thus, additional criteria to define “clinically relevant” hypogammaglobulinemia have been sought.

The simplest additional criterion is a history of recurrent sinopulmonary infection refractory to antibiotic therapy. Unfortunately, sinusitis and bronchitis are also very common complaints with their own spectrum of risk and severity.³ This spectrum includes patients who suffer sinusitis or bronchitis seasonally and have normal lung and immune function, patients who suffer recurrent subclinical infections that lie under the clinical radar until the patient develops frank bronchiectasis, and patients who suffer occasional minor infections only to develop acute life-threatening pneumonia. In addition, antibody-

deficient patients are paradoxically at greater risk for a range of inflammatory antibody-mediated autoimmune disorders, including systemic lupus erythematosus, myasthenia gravis, pernicious anemia, thyroid disease and others, as well as for a range of lymphoid malignancies.⁴ Each of these manifestations implies that rather than the core disease being a simple disorder of antibody production with an attendant susceptibility to infection, it is a complex disorder affecting lymphocyte development and self-/nonself discrimination as well.

To achieve greater precision in diagnosis, better guidance in therapy, and a framework for research into etiology and pathogenesis, a specific subset of patients has been carved out of the larger pool of IgG deficiency. The threshold for a low IgG level can be reduced, commonly to 500 mg/dL, and evidence of a more general difficulty in antibody production sought, most commonly deficiency in either IgA or IgM as well. This subset is termed common variable immune deficiency, or CVID.^{1,2} Attempts to further refine diagnostic criteria have relied on the application of new technologies and include the use of ELISA to assess specific levels of antibodies against antigen, typically vaccine, challenge; the use of flow cytometry to quantitate total B-cell and T-cell numbers, and then total B-cell subset numbers; MHC haplotype; and, more recently, first candidate, then exome, and finally complete genome sequencing.^{1,2,5}

In this issue of the journal, Filion et al⁶ have revisited the issue of the significance to prognosis and therapy of the diagnosis of CVID versus hypogammaglobulinemia. In a retrospective electronic chart analysis covering a 4-year period, they extracted clinical and laboratory data from the medical records of patients assigned *International Classification of Disease* codes for CVID (*International Classification of Diseases, Ninth Revision* code 279.06; *International Classification of Diseases, Tenth Revision* code D83.0) or IgG deficiency (*International Classification of Diseases, Ninth Revision* code 279.03; *International Classification of Diseases, Tenth Revision* code D80.3) at their institution. They tabulated histories of sinopulmonary infection, including bronchiectasis; measures of vaccine response; B-cell and T-cell numbers; and B-cell subset numbers. They also tabulated the occurrence of autoimmune and inflammatory diseases. The results of the comparisons were revealing in some cases, and paradoxical in others.

Unsurprisingly, because by definition CVID includes patients with more severe serum immunoglobulin deficits, they found that IgG levels were lower in CVID. In correlation with these findings, patients with CVID had lower percentages and numbers of IgM and class switched memory B cells, reduced responsiveness to T-independent antigen vaccines, and lower CD4 T-cell numbers.

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In addition, they found that patients with CVID exhibited a higher prevalence of autoimmune and inflammatory disorders. This is in keeping with the concept that the greater dysregulation and disruption in B-cell development and antibody production, the more abnormal the immune response.

Conversely, they found that patients with CVID and IgG-deficient patients exhibited the same rates of sinusitis and pneumonia, although patients with CVID were more likely to carry the diagnosis of bronchiectasis. At first glance, the similarity in the prevalence of infection would suggest that CVID and IgG deficiency both require intervention to protect against infection. Intervention would include intermittent vaccination boosting, use of prophylactic antibiotics, and/or immunoglobulin replacement therapy. At second glance, however, the issue of a bias in ascertainment must be addressed, because patients were identified by the use of *International Classification of Diseases* codes that require measurement of serum immunoglobulin levels, which is not a standard test in primary care. However, the alternative explanation that IgG deficiency in these patients was a statistical anomaly reflecting association but not causation is argued against by the observation that a significant minority of these less IgG-deficient patients fell within the same range of poor vaccine responses, diminished lymphocyte numbers, infectious complications, lung impairment, and noninfectious manifestations as did those with CVID.

These findings call attention to the multiple gaps in our knowledge of primary antibody deficiency. The etiology of the condition, or range of conditions, often remains unclear. A number of genetic polymorphisms have been identified as causal in the development of CVID,^{1,2} with many of these involved in late-stage B-cell homeostasis and follicular T-cell-B-cell interactions. However, in most cases, many individuals carrying these polymorphisms, including first-degree relatives or even identical twins, do not suffer from clinically apparent disease; thus, the genetics appears complex. Furthermore, this is typically an adult-onset disease and the question of whether there can be an inciting event remains unanswered, although anecdotally patients may pinpoint an episode of intense inflammation as the starting point of their clinical complaints.

The pathogenesis also often remains unclear. The noninfectious complications tend to reflect enhanced immune responses either by promoting inflammation or breaking tolerance and inducing an immune response against self. Whether this reflects the consequences of diminished B-cell numbers and thus homeostatic increases in B-cell growth factors that could lower the threshold for inflammation or autoimmunity remains a possibility, as does the possibility that individual gene polymorphisms adjust the threshold for immune disruption.

Issues with regard to diagnosis, therapy, and prognosis are also unanswered. Evaluation of immune responses by commercial laboratories can be inconsistent.⁷ Moreover, these studies measure the total quantity of binding antibodies, rather than the functional activity of neutralizing antibodies.⁸ Opsonization assays may help pinpoint IgG-deficient patients who would be more likely to benefit from immunoglobulin replacement.

Finally, many genetic polymorphisms associated with CVID are linked to the major histocompatibility complex and to killer-cell immunoglobulin-like receptor (KIR).^{5,9} The association between these genes/haplotypes and the risk of noninfectious polymorphisms remains undefined, but it is striking that MHC haplotypes associated with CVID are also associated with the same autoimmune phenomena.

The work of Filion et al⁶ serves as a reminder to the large gaps in our knowledge of the most common manifestation of immune dysfunction in adult patients cared for by clinical immunologists. Given the effects of this disease complex on the health of our patients and the costs of immunoglobulin replacement therapy, the questions they have raised need to be addressed for the benefit of our society.

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