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Sprue-Like and Other Intestinal Diseases in the Common Variable Immunodeficiency (Cvid) Spectrum

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Abstract Many forms of immunodeficiency have been described. There may be about 150 different types, some with inherited or genetic causes, some with recognized specific molecular defects. Most can be classified as affecting the humoral or cellular, sometimes both, immune systems. In adults, the most common symptomatic form, albeit rare, is common variable immunodeficiency, or CVID. In recent years, it has also been suggested that rather than a single disease, CVID represents a heterogeneous group marked by panhypogammaglobulinemia and variable clinical features. In most, intestinal symptoms predominate, including, but not limited to sprue-like intestinal disease, a disorder that fails to respond to a gluten-free diet. Also, several types of colonic disease may occur similar to ulcerative colitis, Crohn's disease and, most recently reported, collagenous colitis. Treatment of these disorders remains largely empirical and based on disease seen in the absence of CVID. Added molecular genetic studies are needed to more fully characterize the immune defects in CVID and, ultimately, to provide more evidence-based treatments.

Keywords: *immunodeficiency, common variable immune deficiency, celiac disease, sprue-like intestinal disease*

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1. Introduction

The primary immunodeficiency syndromes refer to an increasingly large and heterogeneous group of disorders that now number more than 150, many being inherited or genetically-based, some due to specific intrinsic defects in the immune system [1,2,3,4,5,6]. In recent decades, much added information has appeared with most immunodeficiency syndromes being popularly classified as largely humoral (B cell), some cellular (T cell), or both. The most common *symptomatic* form of primary immunodeficiency disease identified in adults, although still very rare, is common variable immunodeficiency (CVID), or, alternatively labeled, late-onset immunodeficiency. Rather than a single disease, some have characterized CVID as a "collection of hypogammaglobulinemic syndromes resulting from various molecular (genetic) defects" and "variable" because of its numerous heterogeneous clinical manifestations. However, in most, respiratory and/or intestinal symptoms predominate. Indeed, since the intestinal mucosa contains more immunological cells than any other organ system, it may be anticipated that significant intestinal changes would occur during its long-term natural history, especially in the presence of an immunodeficiency disorder.

2. Prevalence and Clinical Features

Estimates for prevalence of CVID have ranged from 1 in 25,000 to 1 in 50,000 [2,3]. Although it has been suggested that genetic factors play a role, the pathogenesis of CVID remains unclear despite decades of research investigation and definition of a number of specific gene mutations in development of B-cells [1]. Interestingly, CVID patients commonly have a first-degree family member with an immunodeficiency syndrome, such as IgA deficiency (i.e., about 20%) so inherited factors are likely candidates in performing a critical role in onset and progression of the disease [3].

Most of these patients present clinically with repeated upper and lower bacterial respiratory tract infections, sometimes leading to bronchiectasis along with a high frequency of gastrointestinal infections. Other major clinical features include autoimmune diseases, particularly immune thrombocytopenic purpura or autoimmune hemolytic anemia. Granulomatous and lymphoid infiltrative disorders may also occur along with an enhanced risk of malignancy [4].

3. Diagnosis and IgG Infusions

Diagnosis of CVID is generally based on quantified reductions in serum immune globulin (IgG, IgA and/or IgM) levels along with reduced, even absent, antibody responses to vaccines made with tetanus or diphtheria toxoid, Hemophilus influenza type b conjugate along with measles, mumps, rubella and pneumococcal polysaccharide vaccines. Others [7] have historically included lymphocyte transformation *in vitro* having markedly reduced responses to phytohemagglutinin, conconavalin A and pokeweed mitogen [8,9]. In addition, skin testing for delayed hypersensitivity may be impaired to purified protein derivatives, mumps, streptokinase-streptodornase and Candida. Finally, sensitivity to dinitrochlorobenzene may be impaired despite repeated applications [10] along with reduced formation of T-cell rosettes [11]. Together, these findings implicate a defective B-cell response (and also T-cell) in the pathogenesis of its immunological reaction to most infections. Interestingly, patients fail to also

produce antibodies to transglutaminase, endomysium or gliadin [12]. Most patients are initially diagnosed in the third to fifth decades, sometimes later, but, in retrospect, even after diagnosis, most have had previous recurrent symptoms, often over many years. Treatment with IgG infusions were historically used and may have been helpful, however, limited numbers with CVID make definitive recommendations difficult, particularly for such a heterogeneous disorder and further evaluation in future seems warranted.

4. Sprue-like Intestinal Disease

The high frequency (i.e., up to 60% or more) of intestinal changes in CVID, especially in those with chronic or persistent diarrhea, were noted from the outset, even dating back to its earliest recognition and description [3,4,5,6].

A commonly reported finding in mucosal biopsy material, particularly from the small intestine, has been the distinctive absence or a remarkable reduction in

mucosal (lamina propria) plasma cells [13]. However, this needs more critical evaluation since some have normal plasma cell numbers. These changes may also be reported in biopsies from stomach, colon or rectum. In the small bowel, biopsy changes may have a superficially similar appearance to celiac disease with villous flattening as in so-called “sprue-like intestinal disease”. An improved histopathological response to a strict gluten-free diet fails to occur as reflected in careful histopathological studies with repeated and sequential biopsies [7]. In some with CVID, however, crypt epithelial mitotic figures may be reduced in numbers (i.e., hypoplastic crypts) in contrast to the hyperplastic crypt epithelium of celiac disease. As well, the mucosal lesion is often associated with diminished serum IgG, IgA and IgM levels. In addition, trophozoites (and cysts) of Giardia lamblia may be commonly detected in biopsies along with other bacterial and viral agents (eg., cytomegalovirus) [7]. These infectious agents may, in part, also contribute to the some of the histopathologic changes observed. Often, the resultant diarrhea, malabsorption and/or steatorrhea associated with giardiasis may be responsive to treatment courses of metronidazole, but sometimes repeated courses of the antibiotic may be required to eradicate organisms as demonstrated in follow-up biopsy material. In addition to mucosal architectural changes, some patients may develop extensive, benign-appearing lymphoid nodular hyperplasia. This may occur throughout the intestinal tract, particularly in small intestine, but in some, also diffusely in stomach and large intestine.

Massive involvement may sometimes result in intestinal intussusception and obstruction. Others have suggested that definitive evidence for presentation with lymphoma or, specifically, progression to lymphoma is still required [4,14].

5. Inflammatory Bowel Diseases

Another reported presentation of CVID is the development of inflammatory bowel disease, superficially resembling Crohn’s disease or ulcerative colitis. In some, presentation with diarrhea and/or weight loss may occur similar those presenting with small bowel mucosal changes. Biopsy specimens from the large bowel mucosa have also been reported to show an absence or paucity of lamina propria plasma cells [12], an increase in intra-epithelial lymphocytes, altered crypt architecture with occasional sporadic mucosal granulomas and giant cells. In addition, histopathological appearances of graft-versus-host disease may occur [12].

For most patients, immunoglobulin infusions may limit infections but the colitis persists [12]. Most have been treated with similar pharmacological and biological agents compared to types of colitis (without immunodeficiency) but evidence to support their use is limited, largely in case reports. Moreover, in those with significant T-cell defects treated with steroids, immunosuppressant drugs or biological agents (eg., infliximab), there may be a high risk for other opportunistic infections.

In recent years, CVID has also been associated with rare reports of collagenous infiltration in the mucosa [14,15,16,17,18], extending the usual list of enumerated gastrointestinal mucosal histopathological changes described in most reports. In one recent clinical series [18], a paucity of plasma cells was not evident in most patients. Of interest, most patients with CVID and collagenous colitis were usually under age 50 years, much different from the typical older age spectrum of patients with collagenous colitis, but without CVID. It is conceivable that this simply reflects a form of early mortality bias with CVID so collagenous colitis would not have sufficient time to appear and be recognized.

6. Summary

In summary, CVID is a rare immunological disorder of unknown cause, usually presenting with recurrent respiratory and intestinal infections in middle-aged and more senior adults. Perhaps, 20% have a family history of IgA deficiency. In small bowel, changes of sprue-like intestinal disease may be present with histologic features reminiscent of celiac disease but no response occurs with a strict gluten-free diet. In colon, a variety of different

patterns of inflammatory bowel disease have been reported, including ulcerative colitis-like disease, Crohn's-like disease and, most recently, collagenous colitis. Most often, the prescribed treatments have been similar to disease in the absence of CVID along with gamma-globulin infusions. Further studies are needed to more optimally describe and classify the different forms of CVID, their specific clinical manifestations and their treatment.

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