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REVIEW

Diagnosis and treatment of primary immunodeficiency disease in patients with gastrointestinal symptoms

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Abstract An estimated 250,000 individuals in the Unites States have been diagnosed with a primary immunodeficiency disease (PIDD). Early diagnosis and treatment of PIDD are critical to minimizing morbidity and improving quality of life. Patients with certain subtypes of PIDD may present with gastrointestinal complaints such as chronic or acute diarrhea, malabsorption, gastrointestinal pain, and inflammatory bowel diseases. Therefore, gastroenterologists are well positioned to help identify patients with PIDD. The hallmarks of PIDD include recurrent or persistent infections, infections due to microorganisms that rarely cause significant disease in immunocompetent people, unusually severe or life-threatening infections, and either low or persistently high white blood cell counts. An assessment for PIDD involves detailed patient and family histories, a physical examination, and diagnostic screening tests. Immunoglobulin replacement therapy is the cornerstone of treatment for most subtypes of PIDD.
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1. Introduction

Primary immunodeficiency disease (PIDD) comprises more than 150 genetically heterogeneous disorders involving intrinsic impairments of the immune system [1]. Results of a 2005 survey sponsored by the Immune Deficiency Foundation (IDF) indicated that approximately 250,000 individuals in the United States (or 1 in 1200) have been diagnosed with a PIDD [2]. The actual number of affected individuals may very well be higher because many patients are undiagnosed [2].

The broad categories of PIDD include antibody production defects (B-cell defects), cellular or combined defects (T-cell defects or B-cell and T-cell defects), phagocytic cell (neutrophil) defects, and complement defects [3]. The most frequently seen subtypes of PIDD are common variable immunodeficiency (CVID), immunoglobulin A (IgA) deficiency, X-linked agammaglobulinemia (XLA, also called Bruton's agammaglobulinemia), IgG subclass deficiency, chronic granulomatous disease (CGD), and severe combined immunodeficiency (SCID) [2,4].

Primary immunodeficiency diseases predispose affected individuals to an increased risk of infection [3]. Early diagnosis of PIDD is important because delays in diagnosis and treatment may result in severe, life-threatening infections and chronic organ damage [5–9]. Infections resulting from a delay in the diagnosis and treatment of PIDD may also result in unnecessary exposure to the adverse events of unneeded treatments such as antibiotics [8].

The gastrointestinal (GI) tract is the largest organ of the immune system [10,11]. Because it is constantly exposed to ingested foreign antigens, the gut is in a state of physiologic inflammation [11,12]. As the barrier for the systemic immune system, gut-associated lymphoid tissue (GALT) plays a critical role in the balance between inflammation and immune tolerance [13]. Peyer's patches, which are specialized lymphoid follicles in the wall of the small intestine, contain follicular dendritic cells, T-cell rich areas, and naïve B cells [13]. T lymphocytes are a major component of cell-mediated immunity and typically regulate immune responses to viruses, proteins, and intracellular bacteria and parasites [10]. T-cells become activated in an antigen-specific manner and are involved in cytokine production, among other functions [11]. B lymphocytes mediate humoral immunity by secreting immunoglobulins (Ig) [10].

The most common Ig in the immune system is IgA. Over the past decade, the role of IgA in protecting against pathogens and preserving the microbial milieu within the gut has been further elucidated. With small amounts of IgM, IgA blocks binding of luminal antigens to the intestinal epithelium by forming complexes that target bacterial and viral epithelial cell attachment sites [10]. For example, IgA dimers secreted by intestinal B cells bind to the polymeric Ig receptor (pIgR) and subsequently translocate to the surface of epithelial cells to generate secretory IgA (sIgA) complexes [14]. Secretory IgA enhances immune exclusion by trapping dietary antigens and microorganisms in the mucus. Additional roles of sIgA include decreasing the expression of proinflammatory bacterial epitope commensal bacteria; helping maintain appropriate bacterial communities in specific segments of the intestine; blocking microbial components participating in epithelial attachment; and mediating intraepithelial neutralization of pathogens and microbial inflammatory products. Secretory IgA also adheres selectively to microfold cells in intestinal Peyer's patches, transports antigens across the intestinal epithelium to dendritic cells in the subepithelial dome region, and promotes antigen sampling [14]. This interaction occurs under noninflammatory conditions and prevents overreaction of the immune system while maintaining productive immunity [15]. In addition, sIgA may benefit normal gut flora by facilitating biofilm formation, which may contribute to immune exclusion and facilitate growth of normal flora [16]. When microorganisms breach the epithelial barrier, IgA dimers locally released by plasma cells remove these microorganisms by returning them to the lumen through the pIgR and by facilitating their clearance via the IgA Fc receptor [14].

Depending on the subtype of PIDD, the prevalence of GI disorders in patients with PIDD ranges from 5% to 50% [8,10]. Although most patients present with infections of the lungs and paranasal sinuses, GI disorders (especially diarrhea and malabsorption) may be the most prominent or only complaints in some patients [10]. Gastroenterologists are therefore in a position to aid in the identification and diagnosis of patients with PIDD.

This article reviews the recognition and assessment of patients with PIDD presenting with GI complaints and explores treatment options, including Ig replacement therapy, which typically does not treat the GI manifestations.

2. Recognition of PIDD presenting as a GI complaint

Significant GI symptoms may occur in defects in B-cell function (e.g., XLA, selective IgA deficiency), B- and T-

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