Review article

Gastrointestinal manifestations in children with primary immunodeficiency diseases

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Introduction
Primary immunodeficiency (PID) diseases are a heterogeneous group of rare genetic disorders that affect the development and function of immune cells. To date, more than 150 defects have been identified and the number is growing. These disorders are broadly classified into defects affecting the humoral (B cell) immunity, defects of the cellular (T cell) immunity or both T cell and B cell, neutrophil and macrophage defects, and defects in the innate immunity. The hallmark clinical feature is recurrent and/or severe infections. However, some type of immune defect may present with autoimmune manifestations, and increased risk of malignancy in association with their underlying immunodeficiency.

In PID diseases, the gastrointestinal (GI) tract is the second target organ affected after the respiratory tract. In fact, the GI is largest lymphoid organ in the body with a unique function to handle the process of regulation and suppression of foreign antigens including viruses, bacteria, parasites, and food. Therefore, in PID the dysfunction of the regulatory mechanisms that maintain the balance between active immunity and tolerance in the gut may lead to mucosal damage and chronic GI diseases.

The GI manifestations in PIDs can be categorized into five different forms: (1) Infection throughout the GI tract or hepatobiliary system such as giardiasis in humoral immunodeficiency; cytomegalovirus colitis and hepatitis in severe T cell dysfunction as well as hepatic abscess in phagocytic defect. (2) Autoimmune phenomena such as autoimmune hepatitis and enteropathy that are associated with some PIDs and may mimic classic forms of diseases such as celiac disease (CD), inflammatory bowel disease (IBD), and pernicious anemia, but differ in pathogenesis and are often unresponsive to conventional therapies. (3) Unregulated inflammatory conditions such as granulomatous colitis in common variable immunodeficiency (CVID) and chronic granulomatous disease (CGD). (4) Malignancies involving the GI tract and hepatobiliary system. (5) GI and hepatic complications secondary to therapeutic intervention such as liver or gut graff-versus-host-disease and veno-occlusive disease post hematopoietic stem cell transplantation in certain PID diseases.

This review focuses on the characteristic chronic GI manifestations that are commonly encountered in some PID diseases (Table 1).

Severe Combined Immunodeficiency (SCID)
SCID is a heterogeneous group of molecular defects in both T- and B-cell number and function. According to the presence or absence of T cells, B cells and natural killer (NK) cells, this group is broadly classified as T-B+NK+, T-B+NK−, T-B-NK+, and T-B-NK−. To date, more than 15 genetic mutations result in the SCID phenotype. The mode of inheritance of these mutations is autosomal recessive (AR) except the defect in the common gamma chain which is X-linked and is considered the most common form reported so far. SCID is estimated to be in 1 of 50,000 to 500,000 live births; however, it is believed that the incidence of SCID is much higher than these figures since many affected infants die of infection before diagnosis. The onset of clinical manifestations is usually during early infancy. Affected infants usually present with severe recurrent bacterial, fungal or viral infections, erythroderma, failure to thrive, fulminant sepsis or complications following the administration of live vaccines such as Bacillus–Calmette Guerin (BCG). The diagnosis of SCID is established when the absolute lymphocyte count is less than 2500 cells/mm³, T cells make up less than 20% of the total lymphocytes, and the response to mitogens is less than 10% of the control. Serum levels of immunoglobulins are usually very low, and specific antibody responses are impaired. GI disorders are common in SCID patients. Affected infants develop severe persistent oral and perianal candidiasis, chronic watery diarrhea and malabsorption. Chronic infection with rotavirus has been reported in patients who have received the live vaccination. GI biopsy specimens show hypocellular lamina propria, absent plasma cells and lymphocytes. Villous atrophy may occur in some infants owing to damage in the intestinal mucosa after viral or bacterial infec-
Cytomegalovirus and adenovirus infections also have been identified in GI biopsy specimen. Patients with SCID who receive blood transfusions or hematopoietic stem cell transplantation are susceptible to graft versus host disease (GVHD) and a GVHD-like process affecting the colon and small intestine.

**Table 1. Primary Immunodeficiency Diseases with Gastrointestinal Manifestations.**

<table>
<thead>
<tr>
<th>Primary Immunodeficiency</th>
<th>Main GI Characteristics</th>
<th>Laboratory Evaluation</th>
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<td><strong>Combined Immunodeficiencies</strong></td>
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<tr>
<td>Severe combined immunodeficiency</td>
<td>Colitis and hepatitis (CMV), candidiasis, chronic diarrhea, GVHD</td>
<td>Marked decrease in lymphocyte count, Low serum lgs, diminished/absent T cell, B cell, and NK cell numbers, decreased response to mitogens PHA, ConA, PWM, eosinophilia and high IgE in Omenn syndrome.</td>
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<tr>
<td>SCID</td>
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<td>Omenn syndrome</td>
<td>Diarrhea, hepatosplenomegaly, eosinophilic enteropathy</td>
<td>Decreased CD4 cells, normal or decreased serum lgs, absent MHC II expression on lymphocytes</td>
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<td>ADA deficiency</td>
<td>Hepatitis (autoimmune), chronic diarrhea</td>
<td>Low IgG and IgA, normal or increased IgM, normal or increased B cell numbers, impaired specific antibody response, decreased T cell responses in CD40L/Cd40 deficiency</td>
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<td>MHC-II deficiency</td>
<td>Chronic diarrhea (Cryptosporidium), progressive liver disease</td>
<td>Serum IgA absent or near absent (&lt; 10 mg/dL), normal IgG and IgM levels, IgG2 subclass deficiency may be present</td>
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<td>(Bare lymphocyte syndrome)</td>
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<td>Hyper IgM syndrome</td>
<td>Oral ulcers, diarrhea (Cryptosporidium), progressive liver disease, sclerosing cholangitis</td>
<td>Absent IgM, IgG, and IgA, B cells &lt; 1 % of lymphocytes, absent specific antibody response</td>
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<td>Predominantly AB deficiencies</td>
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<td>Selective IgA deficiency</td>
<td>Chronic diarrhea (Giardia), celiac disease, nodular lymphoid hyperplasia</td>
<td>Low IgG and IgA, absent specific antibody response, normal or decreased B cell numbers, decreased T cell responses</td>
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<td>Agammaglobulinemia (XL, AR)</td>
<td>Chronic diarrhea, malabsorption</td>
<td>Serum IgA absent or near absent (&lt; 10 mg/dL), normal IgG and IgM levels, IgG2 subclass deficiency may be present</td>
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<td>Common variable immunodeficiency (CVID)</td>
<td>Chronic diarrhea, malabsorption, nodular lymphoid hyperplasia, flat villous lesions, IBD-like disease, atrophic gastritis, pernicious anemia</td>
<td>Absent IgM, IgG, and IgA, B cells &lt; 1 % of lymphocytes, absent specific antibody response</td>
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<td><strong>Phagocytic Disorder</strong></td>
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<td>Chronic granulomatous disease (CGD)</td>
<td>Granulomatous colitis, perianal fistulae, hepatic abscess, gastric outlet obstruction, small-bowel obstruction, granulomatous stomatitis, oral ulcers, esophageal dysmotility</td>
<td>Defective oxidative burst in neutrophils by DHR or NBT tests</td>
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<td>Shwachman–Diamond syndrome</td>
<td>Pancratic enzyme insufficiency, diarrhea, malabsorption</td>
<td>Pancytopenia, defective chemotaxis</td>
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<td><strong>Other well-defined IDs</strong></td>
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<td>Wiskott–Aldrich syndrome</td>
<td>Colitis, bloody diarrhea, eosinophilic enteropathy, lymphoma</td>
<td>Decreased platelet number and size, low IgM; normal or low IgG, increased IgA and IgE, decrease Ab response to polysaccharides, normal B-cell numbers, progressive decrease in T-cell numbers with abnormal lymphocyte response to anti-CD3</td>
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<td>Hyper-IgE syndrome</td>
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<td>Elevated serum IgE, decreased specific antibody production</td>
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<td>IPEX and IPEX-related disorders</td>
<td>Severe enteropathy, diarrhea, malabsorption</td>
<td>High IgA and IgE; normal B-cell numbers; lack of CD4+CD25+ FOXP3 regulatory T cells; eosinophilia</td>
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<tr>
<td><strong>Diseases of immune dysregulation</strong></td>
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<td><strong>Defects in innate immunity</strong></td>
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<td>IFN-γ and IL-12 circuit defect (MSMD)</td>
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ADA; adenosine deaminase, AR; autosomal recessive, DHR; dihydrorhodamine, FOXP3; forkhead box3, GVHD= Graft versus host disease, IBD; Inflammatory bowel disease, IFN-γ; interferon-γ, lgs; immunoglobulins, IL-12; interleukin-12, IPEX; Immune dysregulation polyendocrinopathy enteropathy X-linked, MHC-II; major histocompatibility complex-II, MSMD; Mendelian susceptibility to mycobacterial disease, NBT; nitroblue tetrazolium PHA; phytohemagglutinin, PWM; pokeweeds mitogen, STAT3; signal transducer and activator of transcription-3, TNF-α; tumor necrosis factor-α.
Hyper IgM (HIGM) syndrome

This rare PID disease is caused by defective immunoglobulin class switch recombination (CSR) leading to normal or high immunoglobulin (Ig) M along with low or undetectable IgG, IgA and IgE11. A variety of molecular defects result in different HIGM genotypes and phenotypes. The X-linked form is due to defects of CD40 ligand (CD40L) and the AR forms are due to defects in CD40, nuclear factor-κ B essential modulator (NEMO), activation-induced cytidine deaminase and uracil-DNA glycosylase3,12.

Pulmonary infections are the most common clinical feature in HIGM syndrome, commonly caused by Pneumocystis jiroveci pneumonia (PJP)13,14. More than 50% of patients suffer from GI manifestations in the form of chronic diarrhea due to Cryptosporidium, Giardia lamblia, Salmonella or Entamoeba histolytica infection13. In some patients, inflammatory bowel disease and intestinal hyperplasia may cause chronic diarrhea with subsequent failure to thrive. The liver is often affected and the common lesion is sclerosing cholangitis (SC) due to Cryptosporidium infection, which may require liver transplantation14. In HIGM syndrome, there is high risk of neoplasm, especially lymphoma, carcinomas affecting the liver, the biliary tract as well as the pancreas14,15. The exact underlying mechanism for the susceptibility of HIGM patients to biliary tract carcinoma is still unclear. It is hypothesized that chronic cryptosporidium infection may lead to bile duct dysplasia14. Hepatitis B, C, and cytomegalovirus (CMV) infections were also documented along with autoimmune hepatitis, to possibly progress to hepatocellular carcinoma in adulthood. SC and malignant tumors of the liver, biliary tree and pancreas are predictors of poor outcome in HIGM13,15.

Treatment for hyper-IgM includes monthly immunoglobulin replacement therapy and antibiotics for specific infectious complications. Careful monitoring is especially essential in those with Cryptosporidium infection, given the complications described earlier, it is recommended that patients boil drinking water or filter it through a professionally fitted filter with less than a 1-μm pore size1,14,15. The administration of granulocyte colony-stimulating factor may be indicated to treat neutropenia. Hematopoietic stem cell transplantation should be performed early in such patients13.

Agammaglobulinemia

Agammaglobulinemia is characterized by absence of circulating B cells (less than 2% of circulating lymphocytes) with severe reduction in serum level of all classes of immunoglobulins. Both the X-linked agammaglobulinemia (XLA) and the AR forms present during early infancy with recurrent severe bacterial infections. The incidence of the disease varies from 1: 100,000 to 1: 200,000 depending on the ethnicity and specific genetic defects involved14. Infections of the GI tract are more frequent in XLA patients leading to manifestations of chronic diarrhea and malabsorption. Giardia lamblia frequently isolated from stool samples from these patients and is often difficult to eradicate despite adequate treatment with immunoglobulin replacement therapy16-19.

Patients with XLA are susceptible to Campylobacter jejuni20 and enteroviral infections with subsequent devastating neurologic complications21. Rare cases of gastric adenocarcinoma and CD-like disease occurring in the small bowel in XLA patients have also been reported22.

Common variable immunodeficiency (CVID)

The diagnosis of CVID is based on reduced levels of two serum immunoglobulins, IgG and IgA and/or IgM, at least 2 standard deviations below the age-specific mean values, in addition to impaired specific antibody production in response to recent infection or vaccination1,4. CVID disease commonly presents at late childhood and adolescence with recurrent sinopulmonary infections such as bronchitis, pneumonia, and sinusitis. The spectrum of GI disorders in CVID includes chronic diarrhea with steatorrhea and/or giardiasis, achlorhydria, abnormal Schilling test, pernicious anemia, malabsorption and morphological abnormalities on small intestinal biopsy. GI manifestations are more common in CVID than XLA and IgA deficiency, suggesting that T cell dysfunction contributes to the pathogenesis of intestinal disease3,10. The reported incidence of GI disorders in CVID ranges from 20%–60% of patients23,24.

There is a high prevalence of inflammatory and infectious GI disorders in patients with CVID23. Mild, watery diarrhea is common and occurs periodically in about 20% of patients, with 10% having a more severe enteropathy resulting in malabsorption and weight loss26. In these patients, GI pathology includes nodular lymphoid hyperplasia, inflammatory bowel disease (ulcerative colitis, ulcerative proctitis, or Crohn’s disease), CD-like disease with flat villi, giardiasis and
nonspecific malabsorption. Defects in cellular immunity, rather than antibody deficiency alone, appear to predispose patients to such symptoms. Helicobacter pylori is an important pathogen in CVID resulting in chronic active gastritis involving both antrum and corpus. Approximately 10% of CVID patients have significant liver dysfunction, with hepatitis B and C virus infection, primary biliary cirrhosis, and granulomatous disease in the liver. Moreover, approximately 20–25% of patients with CVID have, at the time of diagnosis or later, developed one or more autoimmune conditions such as autoimmune hemolytic anemia, thrombocytopenia, rheumatoid arthritis, or pernicious anemia. The mechanism underlying the increased susceptibility to autoimmunity in CVID patients is not clearly understood. Most CVID patients with idiopathic thrombocytopenia purpura (ITP) or autoimmune hemolytic anemia have been successfully treated with infusions of high doses of IVIG, coupled with a short course of corticosteroids and other immunosuppressive drugs. However, due to a higher incidence of medical complications associated with use of immunosuppressive in patients with CVID, this type of therapy should be used with caution. Individuals with CVID are susceptible to malignancy, particularly lymphoma. The incidence of malignancy is increased during the fifth and sixth decades of life. The majority of these malignancies involve the GI tract and the lymphoid tissues.

Chronic granulomatous disease (CGD)
This disease is caused by a group of genetic defects in the NADPH oxidase, the enzyme complex responsible for the phagocyte respiratory burst which leads to the generation of superoxide and other reactive oxygen species (ROS) in phagocytic cells. Five genetic mutations involving the phagocytic oxidase system have been identified so far. The most common is an X-linked recessive defect in gp91phox. The other four autosomal recessive (AR) defects include P22phox, P47phox, P67phox and P40phox. CGD is clinically characterized by recurrent superficial and deep abscesses involving various organs such as the lungs, GI and the liver. Affected patients may present with granulomatous lesions throughout the GI tract from the oral cavity to the colon causing dysphagia, dysmotility, bowel wall thickening, or obstruction. These manifestations may present either at the time of diagnosis or later. In addition, up to 50% of patients may develop GI complications including non-caseating granulomatous colitis, protein losing enteropathy, and inflammatory disease mimicking CD. The rate of gut involvement has been reported to be higher in the X-linked gp91phox deficiency compared to the AR forms of the disease. Endoscopic studies reveal findings similar to idiopathic IBD, with colonic narrowing, a cobblestone pattern, thickened bowel wall, multiple fistulae, colitis, patchy friability, pseudopolyps, and hemorrhage. Microscopically there are large granulomas usually in the muscularis, submucosal edema, crypt abscesses, and lipid-laden histiocytes. Hepatic abscess is also common in CGD and may be recurrent and prolonged. Staphylococcus aureus and Pseudomonas aeruginosa are the main organisms identified in patients with hepatic abscess; patients present with fever, abdominal colic, fatigue, weight loss, and night sweats. These abscesses require aggressive surgical drainage and antimicrobial therapy based on culture. Meanwhile, steroids and interferon gamma have been reported to be effective in controlling the GI granulomatous inflammation.

IPEX syndrome
Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) is a rare X-linked recessive disorder of immune regulation. The genetic basis of IPEX is mutations in the gene (FOXP3), a gene encoding putative deoxyribonucleic acid (DNA)-binding protein of the forkhead family, which acts as transcriptional repressor and key modulator of regulatory T cell function. The disease usually manifests within the first year of life with severe diarrhea and failure to thrive, early-onset diabetes mellitus, thyroid disease, autoimmune cytopenia and variable skin lesions. The most prominent GI features occur as an early onset severe watery or mucoid-bloody diarrhea typically starting in early infancy and leading to failure to thrive. GI manifestations are usually associated with villous atrophy and lymphocytic infiltrates in the small bowel mucosa. The most common pathogens include enterococcus, staphylococcus, cytomegalovirus and candida. Hypofunctional mutations of FOXP3 can lead to milder phenotypes and a later disease onset. Apart from the typical presentation (severe bowel disease, diabetes and eczema in infancy), any male patient presenting with features of several autoimmune diseases, in particular of the gut and endocrine organs, should therefore raise the suspicion of IPEX.
Conclusion
Since patients with PID diseases are more susceptible to infection, it is expected that these patients manifest with GI problems, which sometimes could be the initial presentation. Therefore, proper evaluation for a possible underlying PID should be carried out to any patient presenting with typical or atypical GI diseases that may resemble classic forms of IBD or CD and fail to respond to conventional therapy. The workup should be in a multidisciplinary fashion including gastroenterologists, immunologists and pathologists aiming at initiating a proper intervention that definitely offers a better quality of life and prevents long-term complications.

REFERENCES


