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Gastrointestinal Manifestations in Children with Primary Immunodeficiencies: Single Center: 12 Years Experience

Bilge S. Akkelle[a] Engin Tutar[a] Burcu Volkan[a] Ozlem K. Sengul[a] Ahmet Ozen[b] Cigdem A. Celikel[c] Deniz Ertem[a]

[a]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Marmara University School of Medicine, Istanbul, Turkey; [b]Division of Pediatric Allergy and Immunology, Marmara University School of Medicine, Istanbul, Turkey; [c]Department of Pathology, Marmara University School of Medicine, Istanbul, Turkey

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Abstract
Background: It has been reported that 5–50% of patients with primary immune deficiencies (PID) may present with or develop gastrointestinal (GI) manifestations. ***Objective:*** This study was aimed at analyzing GI and related endoscopic, histopathological findings in children with PID. ***Methods:*** Children with PID who were evaluated by endoscopy between 2005 and 2016 were enrolled in this study. Demographic data, growth parameters, signs and symptoms at diagnosis were obtained. ***Results:*** Of 425 children with PID, 195 had GI manifestations. Forty-seven of 195 children required endoscopic investigation, 30 (63.8%) were male, and the mean age was 7.7 ± 5 years. The rate of consanguinity was 61.7%, and the most common symptom was chronic diarrhea (57.4%). Seventy-two percent of the patients were malnourished. Giardia intestinalis was detected in 4, and *Helicobacter pylori* was confirmed in 8/45 (17.7%) patients. Non-celiac villous flatting was discovered in 15.5% of patients. Twelve patients were diagnosed as having immunodeficiency associated inflammatory bowel disease (IBD)-like colitis. ***Conclusions:*** PID may present with GI manifestations or develop during the course of the disease. Investigating immunodeficiency in patients with atypical GI symptoms can provide an appropriate therapeutic option, and an improved quality of life, particularly in populations with a high rate of consanguinity.

Introduction

Primary immunodeficiencies (PID) are a group of disorders that result from intrinsic impairments of the immune system [1]. Gut-associated lymphoid tissue is a barrier for immune system and plays an important role in maintaining the balance between active immunity and tolerance in the gut [2, 3]. Also, secretory IgA controls the

E-Mail karger@karger.com
www.karger.com/ddi

Prof. Dr. Deniz Ertem
Chief, Division of Pediatric Gastroenterology
Marmara University School of Medicine, Başıbüyük Campus
Maltepe Başıbüyük Yolu Sok. Number 9/1, TR–34854 Istanbul (Turkey)
E-Mail denizertem@marmara.edu.tr

mucosal immune system and facilitates growth of normal gastrointestinal (GI) microbiota [2, 4, 5]. Dysregulation and defects in either humoral, cellular immunity or complement system may lead to an uncontrolled inflammatory process, and subsequently mucosal damage. Therefore, lymphoid tissue-rich GI tract is frequently affected in PID [4].

More than 150 genetically heterogeneous entities have come to be known as PID disorders [1, 2, 6]. These conditions usually manifest clinically as increased susceptibility to infections. However, clinical manifestations may be more subtle and surreptitious, and can present later in life, even during adulthood. Children with PID are prone to developing infectious, inflammatory, autoimmune diseases, and malignancies [7–11]. GI manifestations have been reported in approximately 5–50% of patients with PID [2, 12, 13]. GI manifestations in patients with PID may mimic other GI diseases, such as inflammatory bowel disease (IBD) and celiac disease; however, they differ in pathogenesis and response to the conventional treatment [4]. Thus, early recognition of GI manifestations of PIDs might alter the treatment strategy.

GI manifestations of childhood-onset PID are scarcely published in pediatric gastroenterology literature. The aim of this study was to analyze endoscopic, histopathological, and clinical findings among pediatric PID patients who had been evaluated for GI manifestations.

Materials and Methods

A total of 195 out of 425 children with an established diagnosis of PID after meticulous immunological and genetic investigations were presented to the division of the Pediatric Gastroenterology between 2005 and 2016. These children with PID, who had unremitting GI symptoms severe enough to require upper GI endoscopy and/or colonoscopy, were retrospectively analyzed. Patients were divided according to the updated classification for PID, established by the International Union of Immunological Societies Expert Committee [14].

Forty-seven patients with PID, and a total of 68 endoscopic examinations (45 upper GI tract endoscopy and 23 colonoscopy) were reviewed for this study. Histopathological samples from the GI tract were available in all patients for histopathological examination and a rapid urease test for *Helicobacter pylori* infection. Duodenal aspirate had also been collected for microscopic examination of giardia trophozoites in patients with growth failure. The same pathologist reinvestigated the endoscopic biopsy samples for this study. Demographic data, GI signs and symptoms, and growth parameters, assessed by using weight for height, height for age, and body mass index Z scores at diagnosis were noted. The study was approved by the local Ethics Committee of Marmara University School of Medicine. Informed written consents were obtained from parents or guardians of patients. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a prior approval by the institution's human research committee.

Results

Of the 47 patients, 30 (63.8%) were male, and the mean age of patients was 7.7 ± 5 years when they were consulted. The primary diagnosis of the patients are outlined in Table 1. The mean proportion of consanguineous marriages was 61.7% in the study group.

Both acute and chronic malnutrition were remarkable in the study group. Chronic malnutrition was found in 34/47 (72%) patients. Additionally, more than 60% (29/47) of the patients with PID had acute malnutrition, of which 20% (6/29) was severe.

Patients included in this study had variable GI symptoms such as chronic diarrhea with/without blood (57.4%) and abdominal pain (53%). GI manifestations were the presenting symptom in 24 of 47 patients (51%), and evaluated mainly by a pediatrician or pediatric gastroenterologist at admission. Of the 24 patients, 13 (54%) were referred during infancy (Table 2).

Endoscopic examination of the esophagus was normal in 57.4% of the patients. Congestion (49%) and antral nodularity (16%) were the most common endoscopic findings in the stomach. Duodenal ulcer was identified in 2 patients. *H. pylori* infection was confirmed with both rapid urease test and histopathological examination in 8 out of 45 (17.7%) patients. *Giardia intestinalis* was detected in 4 patients by direct microscopic visualization of the parasite in the duodenal aspirates. Mucosal ulcer and hyperemia were commonly detected colonoscopic pathologies that were found in 43.4 and 30% of the patients, respectively.

Most of the patients (44.6%) in the study group had predominant antibody deficiencies, specific diagnostic data of which are depicted in Table 1. Chronic diarrhea and growth retardation were the most common complaints. All patients in this group underwent gastroscopy, and villous atrophy was found in 6. Two of them had nonceliac villous atrophy and the remaining 4 who had IgA deficiency were diagnosed as celiac disease. Colonoscopy was carried out in 10 of 21 patients with antibody deficiencies; and 50% of them had histopathological evidence of colitis (Table 3). Three of these patients demonstrated clinical and histopathological features of colitis mimicking IBD (Table 4).

Nine patients had combined immune deficiency with syndromic features (Table 1). The most common GI

Table 1. Specific diagnoses of patients with primary immune deficiency

Group of immunodeficiency	Type of immunodeficiency	Patients, *n*
Predominantly antibody deficiencies (*n* = 21)	CVID	7
	Selective IgA deficiency	8
	IgG subclasses deficiency	1
	Hypogammaglobulinemia	1
	Agammaglobulinemia	2
	PIK3CD mutation	2
Combined immune deficiency with associated or syndromic features (*n* = 9)	Ataxia telangiectasia	2
	Nijmegen breakage syndrome	1
	Bloom syndrome	2
	HIES	2
	ICF syndrome	1
	THE syndrome	1
Immunodeficiency affecting cellular and humoral immunity (*n* = 5)	SCID	2
	CSR defect	1
	LRBA deficiency	2
Congenital defects of phagocyte number and/or function (*n* = 5)	Congenital neutropenia	4
	CGD	1
Diseases of the immune dysregulation (*n* = 3)	IL10RB deficiency	1
	IPEX	2
Complement deficiencies (*n* = 3)	Deficiency of complement decay-accelerating factor (CD55)	3
Undetermined (*n* = 1)	CD4 lymphopenia	1

CVID, common variable immunodeficiency; PIK3CD, phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta; HIES, hyper IgE syndrome; ICF, immunodeficiency with centromeric instability and facial anomalies; THE, trichohepatoenteric syndrome; SCID, severe combined immunodeficiency; CSR, class switch recombination defect; LRBA, lipopolysaccharide responsive beige-like anchor deficiency; CGD, chronic granulomatous disease; IPEX, immunodysregulation, polyendocrinopathy, enteropthy-X linked.

Table 2. The distribution of patients manifested with GI symptoms

Type of immunodeficiency	Number of patients presented with GI symptoms	Number of patients presented at infancy
LRBA deficiency (*n* = 2)	2	1
Bloom syndrome (*n* = 2)	1	0
HIES (*n* = 2)	2	1
CVID (*n* = 7), *n* (%)	4 (57)	3
Selective IgA deficiency (*n* = 8), *n* (%)	6 (75)	2
IL10RB def. (*n* = 1)	1	1
CD55 def. (*n* = 3)	3	1
Hypogammaglobulinemia (*n* = 1)	1	0
Agammaglobulinemia (*n* = 2)	1	1
CD4 lymphopenia (*n* = 1)	1	1
THE syndrome (*n* = 1)	1	1
IPEX (*n* = 2)	1	1

LRBA, lipopolysaccharide responsive beige-like anchor deficiency; HIES, hyper IgE syndrome; CVID, common variable immunodeficiency; THE, trichohepatoenteric syndrome; IPEX, immunodysregulation, polyendocrinopathy, enteropthy-X linked.

Table 3. Histopathological findings of endoscopic biopsies in PID patients with antibody deficiencies

	Histopathological findings	Selective IgA deficiency	CVID	IgG subclass deficiency	Hypogammaglobulinemia	Agammaglobulinemia	PIK3CD
Esophagus	Esophagitis	4/8	4/7	–	–	–	1/2
Stomach	*H. pylori* (–) gastritis	2/8	2/7	1/1	1/1	1/2	1/2
	H. pylori (+) gastritis	2/8	–	–	–	–	–
	Atrophic gastritis	1/8	–	–	–	1/2	1/2
	Focally enhanced gastritis	–	1/7	–	–	–	1/2
	İntestinal metaplasia	–	–	–	–	–	–
Duodenum	Duodenitis	–	1/7	–	1/1	2/2	–
	Villous atrophy	4/8	1/7	–	–	–	1/2
	İncreased İEL	4/8	2/7	–	–	–	1/2
	Apoptosis	–	–	–	–	–	1/7
	Lymphoid hyperplasia	–	2/7	–	–	–	1/7
İleum	İleitis	–	1/7	–	–	–	–
	Villous flattening	–	1/7	–	–	–	–
	Lymphoid hyperplasia	–	–	–	–	1/2	1/2
Colon	Colitis	–	3/7	–	–	1/2	1/2
	Apoptosis	–	–	–	1/1	–	–
	Drop-out necrosis	–	–	–	–	1/2	–
	Lymphoid hiperplasia	–	–	–	–	–	1/7

complaint was abdominal pain in this group. Upper GI endoscopy revealed esophageal varices in 3 patients with hyper-IgE syndrome, Bloom and ICF (Immunodeficiency with Centromeric instability and Facial anomalies) syndrome along with portal hypertension. One of the patients with Bloom syndrome, already diagnosed and treated for Wilm's tumor, was consulted for unrelenting abdominal pain and chronic diarrhea. Duodenal biopsies showed focal destruction of intestinal villi, increased intraepithelial T lymphocytes, and apoptosis. Lymphoid hyperplasia and cryptitis were the histopathologies observed in the colonic biopsies. The second patient with Bloom syndrome who was admitted to the hospital with severe obstructive symptoms underwent an abdominal surgery, and diffuse B cell lymphoma was diagnosed after histopathological examination of the jejunal specimen. Another patient with syndromic features was consulted with complaints of growth retardation and intractable diarrhea at 9 months of age. Multiple ulcerations were observed at sigmoid colon, and histopathological examination demonstrated vacuolar changes in epithelial cells and inflammation with increased eosinophils, suggesting colitis, mimicking IBD (Table 4). Subsequent genetic investigation revealed mutations in the SKIV2L gene and the diagnosis was TricoHepatoEnteric Syndrome.

Table 4. Primary immunodeficiencies presenting IBD-like phenotype and age at presentation

Diagnosis of PID (number of patients)	Age at presentation
CD55 ($n = 3$)	3, 5, and 16 years
G6PC3 ($n = 2$)	10 and 16 years
CVID ($n = 1$)	11 years
RAG2 deficiency (SCID; $n = 1$)	9 years
Agammaglobulinemia ($n = 1$)	15 years
PIK3CD ($n = 1$)	7 years
IL10RB deficiency ($n = 1$)	11 months
CD4 lymphopenia ($n = 1$)	1 year
SKIV2L mutation (THE; $n = 1$)	9 months

G6PC3, glucose-6-phosphatase catalytic subunit 3 deficiency; CVID, common variable immunodeficiency; RAG2, recombination activating gene 2; SCID, severe combined immunodeficiency; PIK-3CD, phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta; SKIV3L, superkiller viralicidic activity 2-like; THE, trichohepatoenteric syndrome.

In the study group, there were 5 patients with immunodeficiency affecting both cellular and humoral immunity (Table 1), and chronic diarrhea was the most common (80%) manifestation. The histopathological findings of both upper GI tract and ileocolonic biopsies are listed in Table 5. Two of the 5 patients who had already been

Table 5. Histopathological findings in patients with combined immunodeficiency

	Increased intraepithelial T lymphocytes	Villous atrophy	Apoptosis	Lymphoid hyperplasia
SCID (patient number 1: RAG 2 deficiency)				
Upper GI tract endoscopy	+	+	+	–
Colonoscopy	+	–	+	–
SCID (patient number 2: RAG 2 deficiency)				
Upper GI tract endoscopy	+	–	–	–
CSR defect (patient number 3)				
Upper GI tract endoscopy	+	–	+	–
LRBA deficiency (patient number 4)				
Upper GI tract endoscopy	+	+	–	–
Colonoscopy	+	–	–	–
LRBA deficiency (patient number 5)				
Upper GI tract endoscopy	+	–	–	+

SCID, severe combined immunodeficiency; RAG 2, recombination activating gene 2; CSR, class switch recombination defect; LRBA, lipopolysaccharide responsive beige-like anchor.

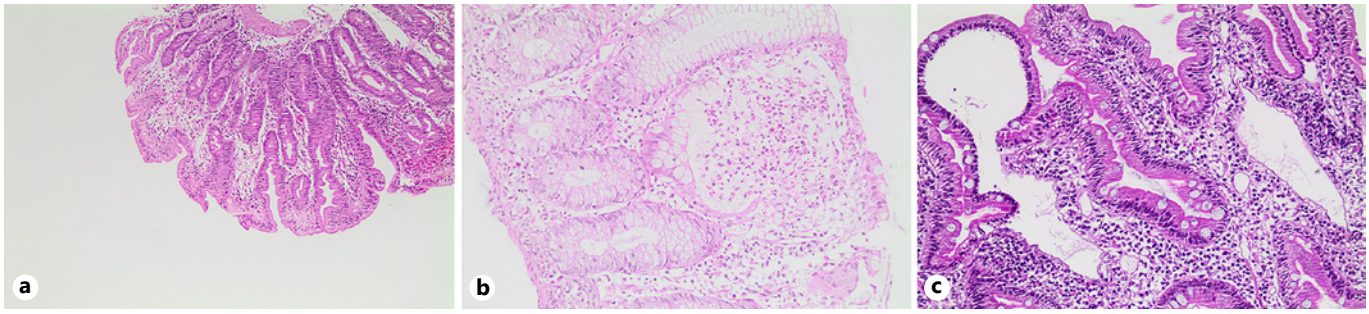

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Fig. 1. Histopathological findings of endoscopic biopsies (H&E staining). **a** Duodenal biopsy with villous blunting and increased apoptosis in crypts. **b** Colonic biopsy with crypt abscess and apoptosis at the basal crypts. **c** Duodenal biopsy with partial villous blunting and mucosal lacteal dilatation.

diagnosed with celiac disease were referred because of persistent diarrhea despite a gluten-free diet. Refractory villous atrophy, in association with scattered apoptotic cells in the duodenum and colon (Fig. 1a), prompted further immunological investigation. Ultimate diagnosis was achieved in these 2 patients after detecting mutations in RAG2 and LRBA genes.

In congenital defects of phagocyte number and/or function group, there were 4 patients with congenital neutropenia, and 3 patients with mutations in the G6PC3 gene (glucose-6-phosphatase catalytic subunit), resulting in G6PC3 deficiency associated with severe congenital neutropenia (Table 1). One of them presented with recurrent bouts of subtotal intestinal obstruction, and colonoscopy revealed severely inflamed stricture in the hepatic flexura. Eventually, the patient underwent hemicolectomy, which disclosed transmural inflammation consistent with IBD (Table 4). Another patient with G6PC3 deficiency was referred for evaluation of the intractable diarrhea associated with failure to thrive. Multiple erosions and ulcerations were observed in all colonic segments, which revealed apoptosis, increased lymphocytes, and plasma cells in the lamina propria, consistent with IBD-like colitis.

One patient, who was evaluated on account of intractable diarrhea, and recurrent perianal abscesses starting within the first months of life, underwent a colonoscopy. Colonic biopsies showed inflammatory cell infiltration with a preponderance of eosinophils, cryptitis, cryptic abscesses, and drop out necrosis, which were consistent

with immunodeficiency-associated colitis (Fig. 1b). Subsequently, IL10R gene sequencing in this patient revealed a mutation, resulting in the deficiency of IL10RB that is characterized with immune dysregulation (Table 1). The patient received hematopoietic stem cell transplantation by the age of 14 months after which GI complaints resolved significantly.

Three of our patients who complained of chronic diarrhea, peripheral edema, and hypoalbuminemia were investigated by colonoscopy. Colonic biopsies showed scarce apoptotic bodies, reduced goblet cells, and moderate degree of inflammation, particularly increased lymphocytes and plasma cells, suggesting IBD. However, none of the patients responded to conventional immunosuppressive treatment, and one of them underwent surgery because of recurrent bouts of intestinal obstruction. The histopathological examination of transmural jejunal biopsies of the patient revealed the presence of lymphangiectasia (Fig. 1c). As a consequence, 3 patients were referred to the pediatric immunology for further immunological investigation because of immunosuppressive-resistant protein losing enteropathy. The genetic investigations disclosed deficiency of complement decay-accelerating factor (CD55), namely the CHAPLE syndrome (Table 1).

Discussion

PID are a heterogeneous group of inherited disorders, characterized by variable genetic immune defects. Since GI tract is the largest organ of the immune system, and is constantly exposed to antigens, GI symptoms may be the most prominent or sole manifestation of PID.

Growth retardation is an important consequence of all chronic diseases, which may affect both the prognosis of the disease and the quality of life. The rate of acute and chronic malnutrition in our study group was 60 and 75%, respectively.

In the Eastern Europe, it has been reported that the incidence of *H. pylori* infection among children who underwent upper GI endoscopy was 40–45% [15, 16]. The overall rate of *H. pylori* infection was 17.7% in this cohort, and the infection was detected in 28% of the children with CVID. This rather lower rate of *H. pylori* infection among PID patients compared to the rate observed in immune-competent children might be explained by the frequent use of antibiotics. This figure is similar to the previously published incidence in adult and pediatric CVID patients [17, 18].

Giardia is a common infectious cause of chronic diarrhea along with villous atrophy in PID, particularly in patients with IgA deficiency. Giardia trophozoites were detected in 4 patients with PID (agammaglobulinemia, hyper IgE syndrome, and 2 patients with IgA deficiency). Therefore, microscopic examination of the duodenal fluid aspirate for giardia trophocytes might be a simple and complementing test in patients who underwent a gastroscopy.

Patients with selective immunoglobulin A deficiency have a 10- to 20-fold increased risk of developing celiac disease. The prevalence of celiac disease in IgA-deficient people has been reported to be between 10 and 30% [7]. Since IgG-based serological tests are not sufficiently reliable, and IgA-based tests are usually negative in these patients, serologic screening of celiac disease would be misleading in patients with PID. In this study, examination of duodenal biopsies revealed celiac disease in half of the patients with IgA deficiency. Flattening of the intestinal villi, resembling classical celiac disease is a common histopathological finding in PID [17, 19]. Previously, intraepithelial lymphocytosis with villous atrophy had been demonstrated in 31–60% of patients with CVID [7, 17]. However, celiac disease-specific IgA and IgG antibodies are usually absent in those patients [20]. In this cohort, 11 patients (24.4%) had villous atrophy in the duodenal mucosa, and 4 of them were diagnosed with celiac disease. Hence, the rate of non-celiac villous atrophy was 15.5% in this study group. Two of the patients with non-celiac villous flattening, who had not responded to a gluten-free diet during follow-up, was diagnosed with RAG 2 and LRBA deficiency after genetic analysis.

IBD is a chronic inflammatory disease caused by a dysregulated immune response to host intestinal microbiota [21]. Patients with PID have a higher risk of developing intestinal inflammation compared to the immune-competent individuals. In our cohort, colitis was found in 42.8% of the patients with CVID, and 1 out of 7 patients with CVID presented with Crohn-like clinical and histopathological features except for the absence of plasma cells in the lamina propria of the colon biopsies. IBD-like manifestations have been reported in nearly 4–6% of patients with CVID [7, 22, 23]. In our study population, 12 patients with different PID had presented with clinical features of enteropathy and/or colitis, and histopathological findings of the colonic and/or intestinal biopsies were similar to the patients with IBD as well.

Although IBD is a polygenic disorder, there is a diverse spectrum of rare genetic disorders, which mimic clinical and endoscopic features of IBD [24–29]. The rate of

monogenic disorders presenting with IBD-like manifestations correlates inversely with the age at disease onset [24, 30, 31]. In our study group, 8 of 12 patients with IBD-like colitis were diagnosed with PID, with a defined genetic defect. Moreover, symptoms manifested before 10 years of age in 6 of them corresponded to the definition of early onset IBD.

In conclusion, GI manifestations due to PID are common, often associated with high morbidity. Usually, they do not respond to conventional treatments. Therefore, pediatric gastroenterologists are in a position to assist in recognition and diagnosis of patients with PID. In countries with a high percentage of consanguineous marriages such as ours, PID should be suspected in every child with unrelenting GI symptoms, particularly starting at early ages. In recent years, advancement and availability of genetic investigations have enabled the discovery of newly recognized PID, and allowed the early initiation of more specific therapies that may improve the quality of life.

Disclosure Statement

The authors declare that there is no conflict of interest.

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