

Intractable Diarrhea of Infancy: 10 Years of Experience

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ABSTRACT

Objectives: Intractable diarrhea of infancy (IDI), a group of prolonged diarrheal disorders, is difficult to diagnose and manage. We documented general features of patients and the causes of IDI.

Methods: The present retrospective study included 60 hospitalized patients with IDI ages 0 to 24 months during January 2000 to December 2010. Detailed history, laboratory and endoscopic findings, diagnoses, and clinical courses were reviewed. Descriptive analyses were used for statistical evaluation.

Results: The male/female ratio was 1.4. The median age at onset of diarrhea was 12 days. A total of 70% and 11% of patients were severely and moderately malnourished, respectively. Carbohydrate malabsorption (CM) and food allergies (n=11, 18% for both) were the most frequent causes. A total of 16 of the patients (27%) did not have a specific diagnosis. The other diagnoses were infections (n=5), immune-mediated disorders (IMD) (n=6), congenital enterocyte defects (CED) (n=3, 5%), short bowel syndrome (n=2), cystic fibrosis (n=2), intestinal pseudoobstruction (n=1), congenital disorder of glycosylation (n=1), abetalipoproteinemia (n=1), and proprotein convertase (PC) 1 deficiency (n=1). Stool calprotectin level was high in 10 of 19 patients with Crohn disease (n=3, mean 1116 ± 851 mg/L), food allergy (n=4, mean 516 ± 288 mg/L), and undefined etiology (n=3, mean 616 ± 780 mg/L). The mean duration of hospitalization was 76 days.

Conclusions: IDI is a heterogeneous group of diarrheal disorders. The most frequent causes were CM and food allergies in our study. Because high levels of calprotectin support inflammation, calprotectin levels may help to discriminate CED and inflammatory causes of IDI.

Key Words: calprotectin, chronic diarrhea, nutrition

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Intractable diarrhea of infancy (IDI) was first described in 1968 by Avery as prolonged diarrhea of infants younger than 3 months old that persists longer than 2 weeks with negative stool cultures (1,2). This definition has undergone a few alterations to define duration and clinical course better. Some authors offered to use the term “severe and protracted diarrhea” instead of IDI, and they also emphasized that identified specific etiologies including infections

that can persist longer than expected should be included in this description (3); however, IDI was also described as “prolonged diarrhea that emerges within the first 2 years of life, lasts for longer than 2 weeks, and usually leads to dependence on parenteral nutrition (PN)” (1,3,4). Infections, disaccharidase deficiencies, and food allergies were the most frequent causes of IDI. Over the years, longer survival of children by means of PN, and the availability of novel diagnostic tools have provided opportunities to identify new causes of IDI. Hereby, congenital enterocyte defects (CED) and immune enteropathies have been brought into prominence. Despite advances in both diagnostic techniques and treatment modalities, IDI is troublesome in follow-up and treatment by pediatricians and pediatric gastroenterologists. Management of IDI requires a multidisciplinary approach and follow-up in experienced centers.

The aim of the present study was to review the demographic and clinical findings, diagnoses of IDI, laboratory results, endoscopic findings, and follow-up results of 60 children with IDI. As researchers at one of the most experienced centers in Turkey, we studied to define the profiles of our patients with IDI to shed light on general features of infants with chronic diarrhea.

METHODS

A total of 60 hospitalized patients ages 0 to 24 months with IDI during January 2000 to December 2010 were included in the present study. A patient with prolonged diarrhea that emerges within the first 2 years of life, lasts for longer than 2 weeks, and usually leads to dependence on PN was diagnosed as having IDI. Demographic, clinical, laboratory, and endoscopic findings; diagnosis; therapeutic approach; and clinical courses were analyzed retrospectively.

Demographic data, referral or admission age, age at onset and duration of diarrheal symptoms, frequency of stool and presence of mucus or blood in stool, type of diarrhea (whether osmotic or secretory), antibiotic usage before admission, and feeding type were recorded. Presence of parental consanguinity, similar symptoms in the family, or mortality of siblings because of diarrheal disorders was ascertained. On physical examination, anthropometric measurements and edema were recorded. *z* scores for weight-for-age were calculated to evaluate patients' nutritional status. *z* scores <-3 standard deviations (SD), between -2 SD and -3 SD, between -2 SD and -1 SD, and above 2 SD were accepted as severe, moderate, mild malnutrition, and obesity, respectively (5,6). *z* scores were calculated according to the World Health Organization Global Database on Child Growth and Malnutrition, version 3.2.3 (January 2011).

From laboratory tests, complete blood count, serum electrolytes, blood gases, albumin, total protein, erythrocyte sedimentation rate (normal range 0–20 mm/h), C-reactive protein (0–0.8 mg/dL), immunoglobulin (Ig) levels (IgA, IgG, IgM, IgE), celiac antibodies, sweat chloride test, and cytomegalovirus (CMV) serology were recorded. Specific IgEs for cow's milk and skin prick test were also noted to define IgE-mediated food allergy. Stool samples were examined for pH, presence of reducing substances, and steatocrit.

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Reducing substance (sugar) type was identified by chromatography. Stool microscopy, culture, and occult blood were also noted. Stool calprotectin level was studied with micro-enzyme-linked immunosorbent assay method (normal <25 mg/L) in 19 patients. Osmotic diarrhea was defined as diarrhea that did not improve after stopping oral feeding or stool sodium <70 mEq/L, chloride <35 mEq/L, and osmolality >135 mOsm/kg; secretory diarrhea was defined as diarrhea that did not improve with hunger or stool sodium >70 mEq/L, chloride >40 mEq/L, and osmolality <50 mOsm/kg (7).

Upper endoscopy (UE) and colonoscopy were performed in patients whose diarrhea etiology could not be clarified by previous investigations. A total of 23 patients underwent both UE and colonoscopy, 5 had only UE, and 1 had only colonoscopy. Olympus Q260 videoendoscope and colonoscope (Olympus, Tokyo, Japan), and, for underweight infants, Olympus XP260N videoendoscope were used in the procedures. Biopsy samples were obtained from all endoscopic procedures. Enteral feeding (standard formula, gluten-free diet, enteral formulas) was applied for 56 patients, and 24 of these patients also received PN.

Patients who were admitted to the hospital 10 days after discharge of their first admission were recorded as rehospitalization (2 patients). Duration of hospitalization, final clinical status of patients, mortality rate, and mortality causes were mentioned. Patients who were able to be discharged and tolerated enteral feeding were accepted as "recovered."

Statistical analyses were performed using the SPSS software package (version 17.0, SPSS Statistics, Armonk, NY). Descriptive analyses were used for statistical evaluation. The study was approved by the Hacettepe University noninvasive clinical research ethics board and performed according to the Declaration of Helsinki.

RESULTS

General Features of 60 Patients With IDI

Baseline characteristics of patients are shown in Table 1. A total of 36 (60%) patients had diarrhea in the first month of life, and 83.3% (n = 30) of them were symptomatic in the first 10 days. Two patients with diarrhea after 12 months of life had CMV colitis and giardiasis. Number of stools per day was >10 in 60% of patients. Stools of 25 (41.6%) patients had mucus, and 7 (11.7%) patients had bloody diarrhea. Stool electrolytes were obtained from 33 patients. Seventy-six percent had osmotic diarrhea, and 24% had secretory diarrhea.

Nutrition

Feeding types before diarrhea are summarized in Table 1. Before referral to our hospital, breast-feeding or standard formula

was replaced by another type of formula in 22 patients for treatment. PN was started in 5 (8.3%) patients before referral.

Family History

Parental consanguinity was recorded in 40 (66.7%) patients. In the undefined etiology group, 11 (68.6%) patients had consanguinity. A total of 14 (23.3%) patients had relatives with a history of chronic diarrhea, and 13 of them had a history of sibling death because of protracted diarrhea. There was no information of ethnic origin in medical records.

Physical Examination

Anthropometric measurements are listed in Table 2. Because there were no data about lengths of 5 newborns, 55 patients were evaluated for length/height. Weight on admission of 25 patients was less than the birth weight. The only obese child had CMV colitis. Pretibial edema was stated in 2 patients with the diagnoses of giardiasis and cystic fibrosis.

Diagnoses

The most frequent causes of IDI in our study were carbohydrate malabsorption (CM) and food allergies (n = 11, 18.3% for both). A total of 16 (26.7%) patients could not obtain a specific diagnosis. The classification of patients according to diagnoses and the mean ages at onset of diarrhea in each group are shown in Table 3.

The prominent diagnosis in the CM group was glucose-galactose malabsorption (6/11, 54.5%). Two patients in the CM group were named as unclassified CM because diarrhea could be controlled only by feeding with carbohydrate-free formula and gradual addition of fructose was possible.

In the food allergy group, cow's-milk protein allergy (CMPA) was the most frequent cause (9/11, 81.8%). Patients were presented in 2 clinical courses: cow's-milk-sensitive enteropathy (n = 7) and IgE-related CMPA (n = 2).

CED was detected in 3 patients. Partial duodenal villous atrophy without crypt hyperplasia, positive staining of apical membrane by periodic acid-Schiff, and polyclonal carcinoembryonic antigen were the diagnostic data of microvillus inclusion disease (MID) in light microscope (n = 2). The light microscopic findings of a 60-day-old boy with tufting enteropathy showed partial villous atrophy and minimal inflammation in lamina propria of duodenum and diagnostic "epithelial tufts."

There were 4 patients (girls:boys 3/1) with Crohn disease. The mean ages at onset of diarrhea and diagnosis were 1.8 ± 1 and

TABLE 1. Baseline characteristics of 60 patients

Female/male sex, n (%)	25 (42)/35 (58)
Mean $\pm$ SD/median (range), days	
Age at admission	156 $\pm$ 144/105 (6–525)
Age at onset of diarrhea	60 $\pm$ 102/12 (0–465)
Duration of diarrhea before admission	96 $\pm$ 108/54 (3–450)
Antibiotic usage before referral, n (%)	45 (75)
Nutrition before onset of diarrhea, n (%)	
Breast-feeding	33 (55)
Standard formula	15 (25)
Breast-feeding + standard formula	5 (8)
Weaning period	7 (12)
Parental consanguinity, n (%)	40 (67)

SD = standard deviation.

TABLE 2. Anthropometric features of patients

Weight <3p, n (%)	47 (78)
Length or height <3p, n (%)	26/55 (47)
z score, WFA (n = 60)	
Mean/median z score	−3.7 $\pm$ 2.0/−3.2
Range of z score	Between −8.12 and +2.48
Classification of patients for WFA, n = 60 (%)	
Severe malnutrition	42 (70)
Moderate malnutrition	7 (11)
Mild malnutrition	6 (10)
No malnutrition	4 (7)
Obesity	1 (2)

WFA = weight-for-age.

TABLE 3. Classification of patients according to diagnosis and age at onset of diarrhea

Causes of IDI	No. patients (%)	Age at onset of diarrhea (mean), days
CM	11 (18)	
Glucose-galactose malabsorption	6 (10)	5.6
Lactose intolerance	3 (5)	56.3
Unclassified CM	2 (3.3)	15.5
Food allergy	11 (18)	
Cow's-milk protein allergy	9 (15)	39.2
Gluten allergy	1 (2)	70
Multiple food allergy	1	3
Other IMDs	6 (10)	
Crohn disease	4 (7)	47.8
Celiac disease	1	270
AIE	1	270
Infections	5 (8)	
CMV gastroenteritis	1	45
CMV colitis	1	465
Postenteritis syndrome	1	50
Giardiasis	1	435
Amebiasis	1	35
CED	3 (5)	
Microvillus inclusion disease	2 (3)	2.5
"Tufting" enteropathy	1	10
Short bowel syndrome	2 (3)	48.5
Motility disorders	1 (2)	
Chronic intestinal pseudoobstruction	1	3
Other diagnoses	5 (8)	
Cystic fibrosis	2 (3)	52.5
Congenital disorder of glycosylation, type IIh	1	75
Abetalipoproteinemia	1	60
PC 1 deficiency	1	7
Undefined etiology	16 (27)	58.7

AIE = autoimmune enteropathy; CED = congenital enterocyte defects; CM = carbohydrate malabsorption; CMV = cytomegalovirus; IDI = intractable diarrhea of infancy; IMD = immune-mediated disorders; PC 1 = proprotein convertase 1.

8.8 ± 5.7 months old, respectively. The mean duration of follow-up was 32 ± 27 months (range 6–70 months). Two of these patients presented with enterocutaneous and rectovesical/rectovaginal fistulas. All of the patients were tested for Ig levels, and only 1 patient had a mild decreased level of IgG. Nitroblue tetrazolium test was performed in 3 patients, and results in all of the patients were negative. One patient was evaluated for IL-10 receptor mutation, and no mutation was detected. Granuloma was detected in 1 patient's biopsy samples.

There were 2 patients with cystic fibrosis. The mean duration of diarrhea before admission was 3.3 months. Patients who presented with pseudo-Bartter syndrome were severely malnourished and dehydrated.

Congenital disorder of glycosylation was diagnosed in 1 patient by confirmation of mutation in oligomeric Golgi complex (COG8) gene. A 5-month-old patient with abetalipoproteinemia had low levels of plasma lipids, prebetalipoprotein, and betalipoprotein. The patient had homozygous 2-nucleotide deletion in exon 4 (c.398-399delAA) of microsomal triglyceride transfer protein gene (8).

A girl who had diarrhea from the 28th day of life had central hypothyroidism beginning with the 15th month of hospitalization. Later on, a high level of proinsulin was detected. The patient had neither hypocortisolemia nor hypoglycemia. A novel mutation in the PCSK1 gene causing stop codon R517X(c.1551 C>T) verified proprotein convertase 1 (PC 1) deficiency. Soon after, diabetes insipidus, polyphagia, and obesity were added to the clinical course.

Laboratory Findings

Anemia was determined in 27 (45%) patients. Three of 4 patients with Crohn disease and 5 of 11 patients with food allergy were anemic. Acidosis was ascertained in 24 (40%) patients. Alkalosis was presented in 15% (n = 9) of patients. The highest blood pH (7.74) was determined in cystic fibrosis. A total of 17 (28.3%) patients, 5 of whom had food allergy, were hypoalbuminemic. At admission, 11 of 29 (37.9%) patients who were tested for both C-reactive protein and erythrocyte sedimentation rate showed elevation of these markers. Only 3 of them had Crohn disease.

Stool calprotectin level was high in 10 (52.6%) of 19 patients, with a mean level of 726 ± 631 mg/L. The Crohn disease group had the highest mean level of calprotectin (Table 4).

Endoscopic Findings

The most frequent macroscopic abnormal finding in UE was duodenal ulcer (n = 3; giardiasis, CMV gastroenteritis, and Crohn disease), whereas 82% of patients had a normal mucosal appearance. Normal colonic mucosa was determined in 14 of 24 (58.3%) patients, and hyperemia was the most frequently detected abnormality in colonoscopy (16.7%). The presence of inflammatory cells in lamina propria was the most frequent finding in both UE and colonoscopic biopsies (39.9% and 50%, respectively). A total of 12 patients received their definite diagnoses by biopsy findings

TABLE 4. Distribution of stool calprotectin levels according to diagnoses

Patients	Stool calprotectin levels, mg/L (mean/median/range)
Total (n = 19)	726 ± 631/625/50–2100
Diagnoses	
Crohn disease (n = 3)	1116 ± 851/625/625–2100
Undefined etiology (n = 3)	616 ± 780/292/50–1506
Food allergy (n = 4)	516 ± 288/627/89–723

(Crohn disease [n = 4], MID [n = 2], CMV colitis [n = 1], tufting enteropathy [n = 1], autoimmune enteropathy [AIE] [n = 1], celiac disease [n = 1], giardiasis [n = 1], and amebiasis [n = 1]).

Enteral Nutrition

Oral feeding was stopped because of worsening of diarrhea in 4 patients (MID, tufting enteropathy, short bowel syndrome, and undefined etiology), but other patients with secretory diarrhea were given minimal enteral feeding. The most preferred formulas were amino acid–based (n = 18, 30%) and extensively hydrolyzed (n = 13, 21.7%) formulas. The others were fructose-based (n = 6), lactose-free (n = 4), carbohydrate-free (n = 2), and fat-free (n = 1) formulas. A total of 10 patients received standard formula or complementary food; 2 received a gluten-free diet.

Parenteral Nutrition

A total of 28 (46.7%) patients received PN. Mean and median duration of PN was 102 ± 124 and 42 days, respectively (range 2–386 days).

Medications

The patient with AIE was given a gluten-free diet combined with steroid for induction and azathioprine for remission. Two patients with Crohn disease were given steroid plus mesalazine therapy, and they were lost to follow-up. The other 2 patients who had fistulas were receiving steroid or cyclosporine for induction, azathioprine, and, after some time, infliximab therapy for remission. One of them was unresponsive to infliximab and referred to surgery, and the other was lost to follow-up on infliximab therapy.

Resin binders were given to 2 patients in the undefined etiology group, and they were unresponsive to therapy. Two other patients in this group given loperamide were also unresponsive.

Outcome of Patients

The mean duration of hospitalization was 76 ± 119 days (median 30 days, range 4–631 days). The patient with PC 1 deficiency had the longest hospitalization duration. After exclusion of 15 patients who were lost to follow-up, the remaining 38 patients recovered (84.4%) and 7 (15.6%) patients died. The diagnoses of the deceased patients were MID, congenital disorder of glycosylation, abetalipoproteinemia, short bowel syndrome (n = 1 for each), and undefined etiology (n = 3). The causes of death were sepsis-related acute respiratory distress syndrome (n = 1) or thrombocytopenia-associated multiorgan failure (n = 4). Two patients died at home.

DISCUSSION

IDI is a spectrum of heterogeneous diarrheal disorders that have become the center of attention during the last 2 decades because of an understanding of pathophysiology and mucosal alterations of enteropathies (4); however, there are disagreements about the definition and terminology. Larcher et al used the terminology of “protracted or persistent diarrhea” that refers only to duration of diarrhea (9). In 1995 Guarino et al indicated that regardless of etiology and age, patients with severe diarrhea who usually need PN should be grouped under “severe and protracted diarrhea” (3). After 2000, authors focused on enteropathies because of primary enterocyte abnormalities and immune-mediated disorders (IMD), but some of them decided to investigate anomalous presentations of common etiologies first (10,11). The age at onset of diarrhea of patients varied in studies of children up to 1 or 2 years old (3,4,9). In the present study, “IDI” was used for patients with diarrhea longer than 2 weeks in the first 2 years of life and who may require PN.

Our reference hospital in Turkey retrospectively analyzed 60 patients with IDI to present our experiences. The present study has the largest number of patients with IDI; however, inadequacies of diagnostic tools and medical records are the limitations of the study.

The distribution of age at the onset of diarrhea was in a wide spectrum. In our study, the median and mean age at onset was 12 and 60 days, respectively. In the previous studies, median ages at onset of diarrhea were 60 to 180 days (3,4,12). The mean age on admission was as long as 156 days, reflecting late referral to our hospital. Before the onset of diarrhea, most of the patients were breast-fed and/or fed by standard formula. Before referral to our clinic, breast-feeding or standard formulas had been replaced with lactose-free or amino acid–based formula in 37% of patients to rule out the most common causes, that is, lactose intolerance and food allergy. The parental consanguinity rate was 66.7%. The sibling history rate was higher than that reported in the literature (2,4) as a consequence of a high frequency of autosomal recessive diarrheal disorders in our study and a high prevalence (21%) of consanguineous marriages in our country (13). In the undefined etiology group, 11 (68.6%) of 16 patients had consanguinity. This finding may support probable undetected inborn errors in this group despite metabolic investigations.

Malnutrition and diarrhea have a reciprocal cause-and-effect relation (14). Increased permeability resulting from mucosal injury can cause malabsorption, and malnutrition induces permeability disorder (15). In the literature, malnutrition was established in 56% to 66% of patients with persistent diarrhea (12,16). Weight-for-age <70% was accepted as a risk factor for prolongation of diarrhea (17). Also, severe malnutrition is known to increase the relative risk of death by 17 times in persistent diarrhea (18). In our study, 70% of patients were recorded as being severely malnourished. Late referral and worsening of diarrhea because of insistence on oral nutrition may be 2 factors aggravating malnutrition.

There are several reasons for chronic diarrhea in infancy. Therefore, a diagnostic algorithm is required to identify the main cause of diarrhea and to achieve perfect management. The chronic diarrhea algorithm of our department is basically designed according to stool features of the diarrhea (Fig. 1). Various physical and endoscopic/histological findings are also important in the flow of the diagram.

In our study 73% of patients were given a specific diagnosis, whereas in the previous studies the ratio is 84% to 92% (3,4,9,12). The most frequent causes in our study were CM and food allergies. According to the literature, different diagnoses come into prominence in different studies. In the study by Guarino et al, enteric infection (47%) was the first reason and food intolerance (21%) was

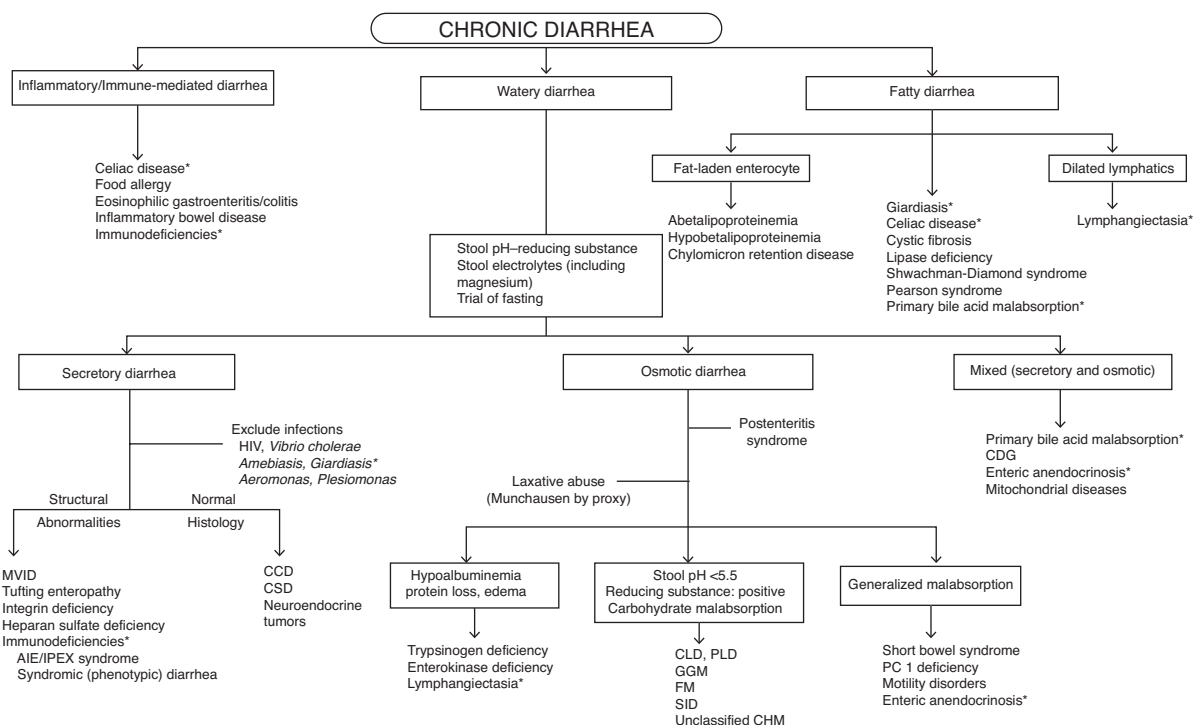


FIGURE 1. A diagnostic algorithm for intractable diarrhea of infancy. *These diseases are located in different columns of the diagram because of the various features of diarrhea. AIE = autoimmune enteropathy; CCD = congenital chloride diarrhea; CDG = congenital disorder of glycosylation; CHM = carbohydrate malabsorption; CLD = congenital lactase deficiency; CSD = congenital sodium diarrhea; FM = fructose malabsorption; GGM = glucose galactose malabsorption; HIV = human immunodeficiency virus; IPEX = immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; MVID = microvillus inclusion disease; PC 1 deficiency = proprotein convertase 1 deficiency; PLD = primary lactase deficiency; SID = sucrase-isomaltase deficiency.

the second (3). Studies after 1995 revealed that CED and IMD have taken the first position because of advanced techniques. A study from Italy pointed out that AIE (25%) and CED (22%) were the most frequent reasons (2). Beck et al reported that 48% of patients were in the immune enteropathy group, whereas 24% and 20% of patients had lymphangiectasia and CED, respectively (4). The ratio of infections, food allergies, and CM decreases in tertiary hospitals. Early diagnosis and treatment of these diseases in local hospitals may reduce the referral; thus, the ratio of CED, AIE, or even unknown etiology may seem to be relatively high. In a study from Turkey, 22 of 41 (54%) patients with persistent diarrhea had CMPA as the most frequent cause (19).

In the CM group, there were 2 patients with a diagnosis of unclassified CM who had excessive fecal sugar loss. They tolerated the addition of fructose gradually to carbohydrate-free formula, supporting the idea of maturation of intestinal absorptive function. The rate of fructose transport is affected by fructose concentration and maturity. Hence, facilitated transport of fructose and an increase in expression of GLUT5 according to concentration of fructose in the lumen (20,21) support the gradual addition of fructose to the carbohydrate-free diet.

CED that was recorded as 5% in our study is characterized by villous atrophy with normoplastic crypts. MID is the prominent cause of CED, and studies after 1995 show that the prevalence of MID differs between 5% and 22% (1–4).

Early-onset obesity, hypoglycemia, hypocortisolemia, excessive proinsulin levels, hypothyroidism, hypogonadism, and growth hormone deficiency are characteristic features of PC 1 deficiency. Dysmaturation of propeptides in enteroendocrine cells that express PC 1 is the main cause of intestinal dysfunction (22,23).

In our study, the patient had hypothyroidism and diabetes insipidus but no hypoglycemia.

The etiology of IDI could not be defined in 27% of our patients. Keating reported that diagnosis cannot be determined in 10% to 25% of patients (24), whereas Guarino et al noted that it can vary from 0% to 100% according to enrollment criteria and diagnostic techniques (3). Because of rare causes of diarrheal disorders, DNA samples of the patient and the parents should be stored for further analysis, especially in consanguineous marriages. It must be noted that human immunodeficiency virus infection should be taken into consideration in the case of secretory diarrhea. Munchausen by proxy should be suspected when the complaints are inconsistent with physical examination findings.

Calprotectin, a protein in neutrophils, is a reliable marker of gastrointestinal inflammation (25,26). It is reported as an available tool to differentiate between CED and IMD. Despite increased permeability in CED, calprotectin stays in normal ranges in CED, whereas it rises in IMD (25). A total of 10 of 19 patients in our study had high levels of calprotectin. The Crohn disease group had the highest level of calprotectin, and the undefined etiology group had a moderate increase. Patients with moderately high levels of calprotectin should be evaluated in terms of IMD existing with inflammation.

Enteral nutrition is an important step for diarrhea management. After identifying the patients with osmotic diarrhea, enteral formula for probable CM was chosen according to fecal sugar chromatography, and follow-up was designed using this test. In the course of inadequate energy intake or cessation of oral feeding, PN was given. Besides nutritional support, PN is known as a tool for promoting mucosal healing in CED (27). In our study, 28 (47%)

patients received PN with a mean duration of 102 days (median 42 and range 2–386). In previous studies, PN was given for 29 to 63 days (median) (3,4). A study from Italy drew attention to a long period of PN for a mean time of 40 months (2).

In conclusion, IDI is a complicated group of disorders for pediatricians and pediatric gastroenterologists to manage. A high rate of parental consanguinity is a risk factor for novel causes of IDI to occur. We have highlighted the definition criteria of IDI and algorithm of management of variable causes of IDI.

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