ORIGINAL ARTICLE

TJG
The Turkish Journal of Gastroenterology

The diagnosis and outcomes of persistent diarrhea in infants aged 0-24 months - A Turkish cohort study

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Background/aims: *Infantile persistent diarrhea series are not well documented in the literature. Evaluating the literature, the aim of this study was to document persistent diarrhea cases followed in our center and to constitute a practical diagnostic algorithm for the pediatrician by means of surveying methods.* ***Methods:*** *Diarrheas lasting more than 14 days were accepted as persistent diarrhea. Forty-one persistent diarrhea cases aged 0-24 months were investigated in this study. The cases were evaluated for the presence of mucus and/or leukocytes in stool and were thus divided into two major groups as colitis or enteropathies. For the differential diagnosis of the persistent colitis group, stool cultures, dietary restrictions, complete blood count, acute phase reactants, pathergy test, gene analysis for familial Mediterranean fever and Behçet's disease, colonoscopy, and biopsies were performed. In the persistent enteropathy group, differential diagnosis was made with the following tests: serum and stool electrolytes, arterial blood gases, serum albumin, total protein, lipid profile, stool alpha-1 antitrypsin level, stool pH, presence of stool fat and reducing substance, endoscopy, and biopsies.* ***Results:*** *The 27 persistent enteropathy cases included 7 celiac disease, 5 intestinal lymphangiectasia, 2 microvillus inclusion disease, 2 abetalipoproteinemia, and 11 cow's milk allergy. The 13 cases of the infantile colitis group included 1 Behçet's disease, 1 colitis ulcerosa and 11 cow's milk allergy. Two cases presenting as pancreatic insufficiency were diagnosed as cystic fibrosis. One case was diagnosed as cystic fibrosis plus cow's milk allergy.* ***Conclusions:*** *Reviewing the literature, these cases represent the largest non-infectious infantile group of persistent diarrheas. A practical diagnostic algorithm for persistent diarrheas has been constituted.*

Key words: Persistent diarrhea, infant, intractable diarrhea

İnfantil (0-24 ay) persistan ishallerde tanı ve takip: Türk kohort çalışması

Amaç: *İnfantil persistan ishal, literatürde çok iyi dökümante edilmemiştir. Bu çalışmanın amacı; kliniğimizde izlenen infant dönemde ortaya çıkan persistan ishalli olguların, literatür bilgileri eşliğinde gözden geçirilerek, pediatrik gastroenterologlar için pratik bir algoritma oluşturmaktır.* ***Yöntem:*** *Ondört günden daha uzun süren ishal olguları persistan ishal olarak kabul edilmiştir. Yaşları 0-24 ay arası olan 41 persistan ishal olgusu çalışmaya dâhil edilmiştir. Hastalar, gaitalarında mukus ve/veya kan bulunup bulunmamasına göre kolitler ve enteropatiler olmak üzere iki ana gruba bölünmüştür. Kolit grubunda ayırıcı tanı amacıyla; gaita kültürleri, diyet kısıtlamaları, tam kan sayımı, akut faz reaktantları, Paterji testi, Ailevi Akdeniz ateşi ve Behçet hastalığı için gen analizleri, kolonoskopi ve biyopsileri yapılmıştır. Enteropati grubunda ise ayırıcı tanı amacıyla serum ve gaita elektrolitleri, arterieyel kan gazları, serum albümin seviyesi, lipit profilleri, gaita alfa-1 antitripsin seviyeleri, gaita pH'ları, gaitada yağ ve redüktan madde varlığına bakılmış, endoskopi ve biyopsileri yapılmıştır.* ***Bulgular:*** *Toplam 41 persistan ishalli olgu içerisinde; 7 çölyak hastalığı, 5 intestinal lenfanjiektazi, 2 mikrovillus inklüzyon cisimciği hastalığı, 2 abetalipoproteinemi vakası ve 11 inek sütü protein alerjisi, 27 vakalık enteropati grubunu oluşturmuştur. Toplam 13 hastadan oluşan kolit grubunda ise; 1 Behçet hastalığı, 1 kolitis ülseroza ve 11 inek sütü protein alerjisi olgusu mevcuttu. Pankreatik yetmezlik olarak kendini gösteren 2 hasta kistik fibrozis tanısı aldılar. Bir hastada ise, kistik fibrozis ve inek sütü protein alerjisi mevcuttu.* ***Sonuç:*** *Literatür incelendiğinde, bu olgu serisi enfeksiyon kaynaklı olmayan en geniş persistan ishal grubunu oluşturmaktadır.*

Anahtar kelimeler: Persistan ishal, infant, inatçı ishal

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Manuscript received: 02.05.2010 **Accepted:** 22.11.2010

Turk J Gastroenterol 2011; 22 (3): 260-269
doi: 10.4318/tjg.2011.0211

INTRODUCTION

Diarrheal disease is a major cause of childhood morbidity and mortality worldwide. Major advances in the understanding of the pathophysiology in infantile persistent and intractable diarrheas allow a new conceptual view of this heterogeneous group of disorders. Several enteral feeding products may be required. If enteral therapy fails, parenteral nutrition becomes necessary. Sometimes, none of these is sufficient for this heterogeneous and difficult group. Diarrheas lasting more than two weeks must be investigated for diagnosis and therapy. Chronic diarrhea etiology may differ due to epidemiologic and risk factors between developed and developing countries. Risk factors for developing countries may be listed as: protein energy malnutrition, vitamin A deficiency, zinc (Zn) deficiency, inadequate mother-fed babies, and acquired immune deficiencies. Exploring the English and Turkish literature, we found no data about infantile chronic diarrhea in Turkey. This work is not a multicenter study and may not reflect a view on Turkey; however, as being the first published data, we believe it is worthy. The aim of this study was to constitute an easily applicable, and in addition, developable diagnostic guideline throughout the laboratory tests and results phase (1-3).

MATERIALS AND METHODS

Gazi University School of Medicine Pediatric Gastroenterology Clinic in Ankara is a major center in Turkey with an average of 5000 outpatients and 1200 endoscopies per year. This Pediatric Gastroenterology Clinic is a referral center especially in chronic diarrhea and celiac disease (CD). None of the chronic diarrhea cases detailed below included any infectious-originated states. We believe persistent and chronic diarrheas of infectious origin are treated generally in primary and secondary centers without referral. Diarrheas lasting more than 14 days were accepted as persistent diarrhea. Forty-eight patients aged 0-24 months who admitted to our clinic with persistent diarrhea between 2003 and 2007 were analyzed retrospectively. Seven patients were excluded as they were seen once as an outpatient and did not comply with follow-ups. Diarrheal symptoms were recorded as time of onset, frequency and presence of mucus or blood in stool. Weight and height measurements, degree of dehydration and presence of edema were also noted. The primary step is evaluating the cases with macroscopic (mucus and/or blood) plus microscopic stool examination, and the cases are grouped into either the enteropathy or colitis group. This step facilitates further specific diagnosis. Laboratory tests to be performed for specific diagnosis were as follows: complete blood count, serum electrolytes, liver function tests, lipid profile, apolipoprotein B, total protein, albumin, acute phase reactants, arterial blood gases, immunoglobulins, skin prick test for food allergy, celiac antibodies, ferritin, vitamin B12, folic acid, sweat test, and cystic fibrosis (CF) and familial Mediterranean fever (FMF) disease gene analysis. Stool samples were examined for microscopy and culture, pH, presence of fat and reducing substance, occult blood, alpha-1 antitrypsin level, and electrolytes. Abdominal ultrasonography (USG) and small and large bowel radiographs were performed. Endoscopic and/or colonoscopic examinations were done, and endoscopic biopsies were taken. Endoscopic biopsies were performed with an Olympus GIF P230 videogastroscope (Olympus Optical Corporation, Tokyo, Japan), and at least two samples were obtained under direct visualization. Biopsy specimens were evaluated in light microscopy (LM) and/or electron microscopy (EM). Patients were initially classified as enteropathy including protein-losing diarrhea, colitis and pancreatic insufficiency based on history, physical examination and laboratory tests. Twenty-seven patients (65.8%) were diagnosed as enteropathy [7 CD, 5 primary intestinal lymphangiectasia (PIL), 2 microvillus inclusion disease (MID), 2 abetalipoproteinemia (ABL), 11 cow's milk protein allergy, enteropathy type]. The colitis group (31.7%) was composed of 11 cow's milk allergy, 1 infantile colitis and 1 Behçet's disease patients. Two patients (4.8%) were diagnosed as CF. One case was diagnosed as cow's milk protein allergy plus CF. Twenty-seven patients (65.8%) were outpatients. Fourteen patients (34.1%) were hospitalized. The diagnosis and treatment, complications and follow-up of cases are as follows.

I- ENTEROPATHY GROUP

IA- Celiac Disease

Seven cases under the age of 2 were diagnosed as CD during the period 2003-2007 in our clinic. Seven patients admitted with typical symptoms of CD like diarrhea and abdominal distention. Stools were watery and shapeless. Biopsy specimens were classified according to Marsh classification. No-

ne of the cases had IgA deficiency. The delay between onset of symptoms and diagnosis was an approximate average period of 6.3 months. The sociocultural status, being a rural population, and difficulties in reaching a specialist or an urban hospital partly explain this diagnostic delay. Demographic and clinical features of CD patients are shown in Table 1. Once the diagnosis was made, other family members were also screened for CD. Cases were evaluated for iron (Fe), Zn, folic acid levels, and bone mineral densitometry. Symptoms, serologies, weight and height measurements, and clinical follow-ups were scheduled at 3-month intervals.

IB- Primary Intestinal Lymphangiectasia

Intestinal lymphangiectasia (IL) was observed in 5 of 41 cases (12.2%). These cases were followed as chronic diarrhea during the infantile period. All patients presented with hypoalbuminemia and edema, except Case 3, who had consanguineous parents. Hepatic and renal functions and urine protein of the cases were all in normal ranges. Secondary IL was excluded with echocardiography and abdominal USG evaluation. Cases 3 and 5 were considered as having ascites formation by abdominal ultrasound. Ascites fluids were in chylous state and triglycerides were 156 and 144 mg/dl in these cases, respectively. The demographic and laboratory characteristics of the 5 cases are summarized in Table 2. Follow-up periods of IL cases were a minimum of 6 months and maximum of 6 years (average: 33 months). None of the cases was controlled with a high-protein diet and usage of medium-chain triglycerides (MCT) alone; all of them required octreotide treatment. The youngest patient (Case 5) received a single octreotide dose of 25 µg/day and symptoms were controlled with this dose. In Case 3, 25 µg/day octreotide dosages were started after diagnosis of IL. During the hospital follow-up, diarrhea continued and serum albumin levels were further reduced to 1.8 g/dl. Albumin was replaced and octreotide dosage was elevated during the follow-up according to the degree of edema and albumin requirement periods. In the last year, octreotide dosage was a total of 125 µg/day and albumin requirement period was 4 months in each. Case 1 and Case 4 are today 7 and 8 years old, respectively, with no symptoms, and we managed to cut-off octreotide treatment in

Table 1. Demographic and clinical features of celiac disease patients

Age of diagnosis (Months)	Onset of symptoms (Months)	Sex	Clinical features		Serology				Endoscopic visualization	Marsh classification
			Abdominal distention	Diarrhea	tT IgA	tT IgG	AGA IgA	AGA IgG		
23	12	F	+	-	+	+	+	+	Mucosal Cracks	Type 3c
18	12	M	+	+	+	+	-	-	Normal	Type 3a
22	15	M	+	+	+	-	+	+	Normal	Type 3c
22	20	F	+	+	+	-	+	+	Mucosal cracks	Type 3c
21	12	M	+	+	+	+	+	+	Mucosal cracks	Type 3c
23	18	M	+	-	+	+	-	-	Mucosal cracks	Type 3a
14	10	M	+	+	+	+	+	+	Mucosal cracks	Type 3c

Table 2. Demographic and laboratory characteristics of intestinal lymphangiectasia patients

	Age (Months) Sex	Onset of symptoms	Physical Examination		Immunoglobulin levels (mg/dl)			Albumin (gr/dl)	Fecal alpha 1 antitrypsin levels	Endoscopic findings	Dilated lymphatic ducts in LM
			Ascites	Edema symmetric	IgA	IgG	IgM				
Case 1	23, F	Since birth	-	+	60	**300***	55	2,5	300 mg/dl (N:147-245)	Multiple whitish spots	+
Case 2	20, M	19 months	-	+	45	**345***	125	2,6	350 mg/dl (N: 147-245)	Multiple whitish spots	+
Case 3	4, F	Since birth	+ (Chylous)	+	18	**180***	100	2,5	-	Multiple whitish spots	-
Case 4	18, M	15 months	-	+	25	**389***	67	2,5	-	Multiple whitish spots	+
Case 5	2, F	Since birth	+ (Chylous)	+	10	**125***	76	2,0	-	Multiple whitish spots	+

*Immunoglobulin levels indicated as bold characters are low according to age group

both cases. Headache was the only side effect presented in Case 4 and it disappeared with discontinuation of octreotide. Case 2 has had no complaints for the last year and attained a normal growth pattern, so octreotide dosage was reduced. Diuretics were administered to the patient with ascites.

IC- Microvillus Inclusion Disease

Two male patients aged 45 and 56 days were diagnosed with MID. Onset symptoms were watery diarrhea without any blood or mucus beginning from 3 and 15 days of life, respectively. Diarrhea resulted in serious weight loss and dehydration. Both cases were admitted to our clinic with critical dehydration and acidotic state. Consanguineous parents, polyhydramnios and admittance weight below birth weight were the common features of the two cases. Mucosal findings in the endoscopic evaluation of both cases after general health condition improvement were considered as normal. Villous atrophy was noted in LM examination in both cases. EM examination of Case 1 showed normal finding at the first examination. The patient was hospitalized for 156 days, and in the 12th month, endoscopic evaluation was repeated during a wellness period. After one year, in the second EM examination, typical intracytoplasmic inclusion bodies were present, and the diagnosis of MID was made. Case 1 died from nosocomial sepsis. In Case 2, diagnosis became definite due to the first EM examination (Figure 1) that showed a typical intracytoplasmic inclusion bodies pattern concordant with MID. Case 2 also died from a nosocomial sepsis after a 68-day hospitalization period.

ID- Abetalipoproteinemia

Two ABL cases under the age of 2 years were diagnosed and followed. Cases were 15 and 10 months old, both had consanguineous parents, and they were admitted with diarrhea since birth. Stool examination and cultures were normal except positivity for fat. Serum total protein and albumin levels as well as immunoglobulin levels of the two cases were within normal limits. Triglycerides and total cholesterol levels were low in both patients according to their age group (triglycerides: 5-8 mg/dl, total cholesterol: 80-70 mg/dl, respectively). Chylomicron bands were not seen by lipid electrophoresis, and diffuse white granular pattern was noted in endoscopic evaluation of the duodenum in both cases (Figure 2). Lipid vacuoles were seen as widespread in LM analysis examination of enterocytes (Figure 3). The patients are be-

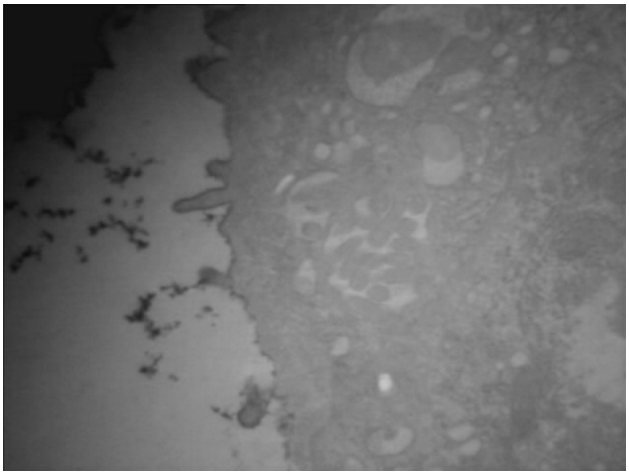


Figure 1. Electron microscopic examination of microvillus inclusion disease (Case 2)

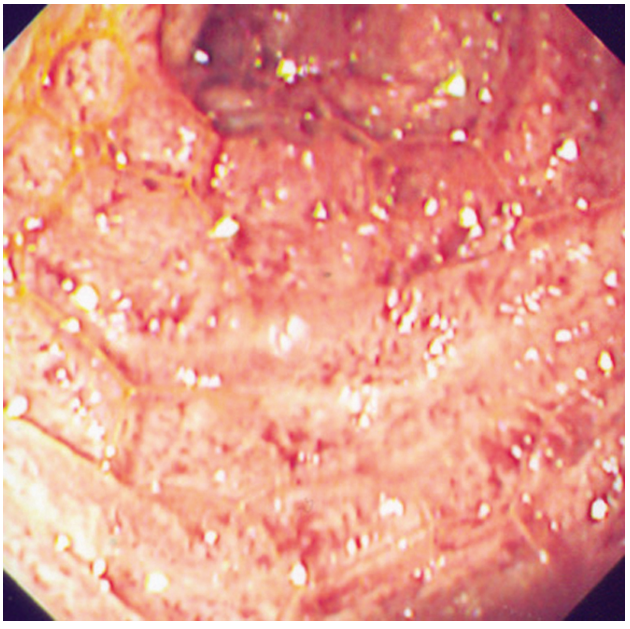


Figure 2. Diffuse white granuler pattern in duodenum in a patient with abetalipoproteinemia

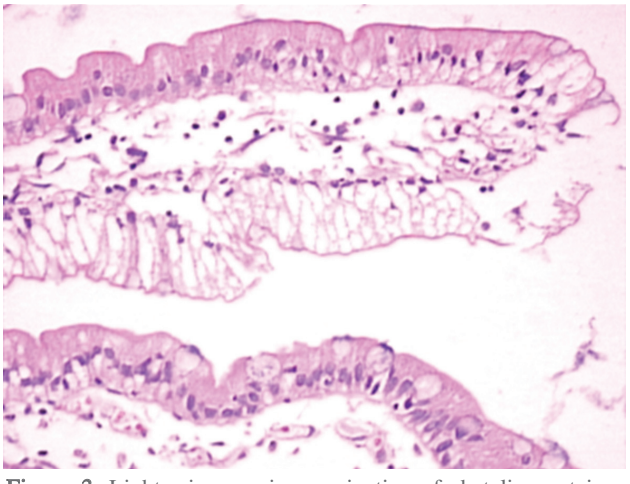


Figure 3. Light microscopic examination of abetalipoproteinemia cases

ing followed at 3-month intervals and supported with a diet rich with MCT and fat-soluble vitamins. Ophthalmic and neurologic consultations are done periodically.

IE- Pancreatic Insufficiency (Cystic Fibrosis)

Two cases representing pancreatic insufficiency and chronic diarrhea were followed between 2003 and 2007. Case 1 was 54 days old and admitted with vomiting and diarrhea since birth. Growth retardation was present due to excessive diarrhea without mucus or blood. In physical examination, lower extremity and eyelid edema was significant. Stool fat was positive, pH: 5, and reducing substance was negative. Biochemistry values were as follows: total protein: 4.2 g/dl, albumin: 2.0 g/dl, kidney functions: normal, aspartate aminotransferase (AST): 58 U/L, alanine aminotransferase (ALT): 82 U/L, and gamma glutamyl transpeptidase (GGT): 170 U/L. Sweat test result was performed twice with a result of 100 mEq/L, so the patient was accepted as CF. Genetic analysis showed N1303K/N1303K homozygote mutation. Case 2 was a 4-month-old girl that had been followed as cow's milk protein allergy disease (enteropathy type), and increasing diarrheal symptoms led to reevaluation of the patient. There was no adaptation problem of the mother to the given dietary recommendations and the patient was only breastfed. Stool microscopy was clear and cultures were negative for pathogens. Stool pH was 5, fat was positive and reducing substance was negative. Sweat test resulted in 90 mEq/L twice and genetical analysis for CF revealed class 2 mutation. The patient was diagnosed as cow's milk protein allergy and CF. The 2 patients are under treatment with pancreatic enzymes.

IF- Cow's Milk Protein Allergy (Enteropathy Type)

During the period 2003-2007, a total of 35 cases were diagnosed as enteropathy type cow's milk protein allergy. Eleven of them had diarrhea lasting more than 14 days without mucus or blood. Stool counts were increased and stools were watery and shapeless. No leukocytes or erythrocytes were seen in microscopic evaluation. Fat and reducing substance were negative and pH was normal. Demographic features are summarized in Table 3. Fully hydrolyzed cow's milk formula and additional foods were started. All of the patients except one benefitted from the diet. Diarrhea persisted despite dietary regulations and this patient showed hypoalbuminemia during breastfeeding. Suspected diagnosis was CF, sweat test was positive twice, and Class 2 mutation was detected. This case was followed as cow's milk protein allergy plus CF. The CF-associated patient had exacerbation in symptoms during restart of cow's milk, and despite reaching 2 years of age is still under dietary restrictions.

II- COLITIS GROUP

IIA- Cow's Milk Protein Allergy

Between 2003 and 2007, 38 patients were diagnosed as colitis type cow's milk protein allergy disease in our clinic. Eleven of them had diarrhea lasting more than 14 days with mucus or blood. Their characteristics are summarized in Table 3. None of them had malnutrition or perianal fissure and all patients seemed to be healthy. All patients with mucoid diarrhea had leukocytes in microscopic examination. Stool cultures were negative for all patients. Vomiting was the additional symptom of 3 patients, 2 of them with gastroesophageal reflux disease. Cow's milk protein allergy is a non-IgE-associated state, and allergic screening was not performed in most of the patients as seen in our follow-up scale. After the diagnosis phase, cow's milk elimination was started and prohibition of milk products was implemented to mothers of mother-fed babies. The earliest response to dietary restrictions was noted at the end of the first week and the late response was in 3 weeks. Dietary restrictions were gradually reduced in follow-ups after 1 year of age.

IIB- Behçet's Disease

A single infant case with colitic manifestations was diagnosed as Behçet's disease. The case admitted at the age of 10 months. The onset of the disease was at the age of 45 days with episodic abdominal pain and fever followed by rectal bleeding and mucoid diarrhea. History revealed recurrent perianal, oral aphthous lesions and complicated afebrile convulsion. Two male siblings had died in the infantile period due to afebrile convulsion, rectal bleeding and mucoid diarrhea. The parents were consanguineous. None of the family members had Behçet's disease diagnosis. Before referral to our clinic, afebrile convulsion investigation resulted in normal neurologic and ophthalmic examination. Electroencephalogram, cranial magnetic resonance imaging (MRI), computerized tomography

Table 3. Clinical and laboratory characteristics of cow's milk protein allergy disease patients

	Age (months)	Onset of symptoms	Sex	Vomiting	Diarrhea	Blood in stool	Atopy in family	RAST	Prick test	Feeding
Case 1	45	1,5 months	F	-	-	+	-	ND	ND	Only BF
Case 2	20	40 day	F	-	+	+	+*	+	ND	4 months BF
Case 3	2,5	Since birth	M	-	+**	+	-	ND	ND	Only BF
Case 4	6,5	3 month	M	-	+**	+	-	+	-	1 month BF
Case 5	5	3 month	M	-	+**	+	-	ND	ND	Only BF
Case 6	11	4 month	M	-	+	-	-	ND	ND	4 months BF
Case 7	6	3 months	M	-	-	+	-	ND	ND	3 months BF
Case 8	6	15 day	M	-	+**	+	-	ND	ND	BF & formula
Case 9	33 day	Since birth	M	-	+	-	-	ND	ND	BF & formula
Case 10	4	1,5 month	F	-	-	+	-	ND	ND	Only BF
Case 11	4,5	3 month	F	-	-	+	-	ND	ND	Only BF
Case 12	9	Since birth	M	+	+**	+	-	ND	ND	4 months BF
Case 13	3	1 month	F	-	+**	-	-	ND	ND	Only BF
Case 14	10	5 month	F	-	-	+	-	-	-	4 months BF
Case 15	3	Since birth	F	+	+	-	-	ND	ND	Only BF
Case 16	3	1 month	F	-	+**	+	-	ND	ND	Only BF
Case 17	11	8 month	F	-	+**	+	+	+	+	5 months BF
Case 18¥	4	Since birth	F	+	+	+	-	+	++	Only BF
Case 19	5	2 month	F	-	+	+	-	ND	ND	Only BF
Case 20	8	6 month	F	-	+	+	-	ND	ND	Only BF
Case 21	4	2,5 month	M	-	+	+	-	ND	ND	Only BF
Case 22	8	5 month	M	-	+**	+	-	ND	ND	2 months BF
Case 23	14	11 month	M	-	+	+	-	ND	ND	6 months BF
Case 24	3,5	1 month	M	-	+**	+	-	ND	ND	Only BF
Case 25	6	25 day	M	-	+**	+	+	+	-	No BF
Case 26#	6,5	15 day	M	-	+	+	-	ND	ND	BF
Case 27	4	Since birth	F	-	+	+	-	ND	ND	Only BF

*: Penicillin allergy present in family, **: stool with mucus, ND: Not Done, ¥: Cystic Fibrosis, #: CMV infection, BF: Breast Fed

(CT), abdominal MRI angiography, abdominal USG, Meckel scintigraphy, and upper and lower gastrointestinal contrast graphies were all reported as normal. Upper and lower gastrointestinal endoscopy were performed in another center. In these evaluations, colonic mucosa not fully visualized, reported as fragile and a couple of telangiectatic lesions were seen. Non-specific microscopic examinations were reported for endoscopic biopsies. The case admitted to our ER (emergency room) with bloody stool with mucoid diarrhea. Macroscopic view of stool was mucous and bloody state. In physical examination, abdominal tenderness and perianal aphthous lesions to form abscess were significant. The stool was rich in leukocytes and erythrocytes in microscopic examination. Stool culture was negative for Yersinia, Salmonella, Shigella and *Escherichia coli*. *Clostridium difficile* toxin was negative. Laboratory findings were as follows: leukocyte count: 11800 mm^3, platelets: 464000 mm^3, erythrocyte sedimentation rate (ESR): 38 mm/hour, and C-reactive protein (CRP): 40 mg/dl. Total protein: 6.7 g/dl, albumin: 3.8 g/dl, renal function tests, and hepatic function tests were all normal. Meckel scintigraphy was reevaluated as normal in our clinic. Abdominal USG showed diffuse intestinal wall thickness. Upper gastrointestinal endoscopy was normal. Biopsy specimens of the bulbus and duodenum showed an increase in eosinophil count. White exudative ulcers, either local or diffuse, were noted in colonoscopy through the distal colon. Proximal colon and terminal ileum were normal in colonoscopy. LM examination of the distal colon revealed cryptic inflammation, abscess and pseudomembrane formation. Uveitis was not detected in the ophthalmologic examination. Pathergy test was negative. HLA B5 and HLA B25 were reported as negative. FMF mutation was not detected. IgD of 5.2 mg/dl (0-25) was normal. There was no response to fully

hydrolyzed cow's milk formula. The patient was diagnosed as inflammatory bowel disease (IBD) and/or intractable colitis. Under steroid administration, his symptoms diminished and 5-acetylsalicylic acid (ASA) treatment was started. The patient returned to the ER with mucoid and bloody stool one month after discharge. A second colonoscopy was similar to the first except for regression in white ulcerative lesions. Repeat microscopic examination was parallel to the first. The patient's condition worsened after the second colonoscopy. Findings were as follows: fever, leukocytosis (24000 mm^3), thrombocytosis (617000 mm^3), high ESR: 80 mm/hour, high CRP: 134 mg/dl, and excessive bowel dilatation in abdominal X-ray. The patient was considered as toxic megacolon, antibiotics were started, and the condition was taken under control. Finally, the patient was considered as Behçet's disease. Colchicine treatment was started. The case is now 4 years old, has attained a normal growth pattern and all symptoms are under control.

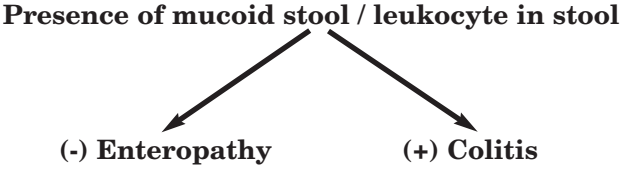
IIC- Infantile Ulcerative Colitis

A 21-month-old girl admitted to our clinic. She had diarrhea since birth, which turned to mucoid and bloody stool state after 6 months. The patient received amebiasis treatment before admittance, her parents were consanguineous, and her sister had FMF diagnosis. In physical examination, the patient seemed pale and weak. Body weight was 5880 g (<3 p) and height was 64 cm (<3 p). Stool examination was rich in leukocytes and erythrocytes, *Clostridium difficile* toxin was negative, and stool cultures for Salmonella, Shigella, Yersinia, and E. coli were negative. Laboratory findings were as follows: WBC: 22000 mm^3, Hb: 7.4 g/dl, mean corpuscular volume (MCV): 56, RBC: 4.23 x 10^6, PLT: 800000/mm^3, total protein: 5.2 g/dl, and albumin: 3.2 g/dl; hepatic and renal function tests were all normal. ESR: 45 mm/hour, CRP: 75 mg/dl and immunoglobulin levels were normal, and serology for CD was negative. During colonoscopy, the terminal ileum was considered as normal; colonic mucosa showed hyperemia, fragility, edema and ulcerative lesions. Biopsy specimens of colonic mucosa revealed inflammation with cryptitis and crypt abscess formation. Infectious reasons were ruled out. Cow's milk elimination was not helpful; thus, the patient was considered as an infantile colitis, and steroid treatment was started at a dosage of 1 mg/kg/day. While steroid dosage was being reduced, 5-ASA was started. After 2 months, the patient returned with increased symptoms. The reendoscopy and biopsies showed no regression in colonic mucosa. Thus, a steroid dosage of 2 mg/kg/day was administered. FMF mutation was found heterozygote for M694V. We thought that the FMF association might worsen the clinical state in IBD so colchicine was given. The patient is still under colchicine, 5-ASA and azathioprine treatment. The patient reached 10 p for body weight and height and has had no symptoms for last 24 months. Follow-up schedule is arranged for every 3 months to evaluate long-term steroid usage side effects like osteoporosis, hypertension and diabetes.

DISCUSSION

Persistent diarrhea in infancy may be caused by a multitude of diseases concerning different systems. Specific diagnosis can be attained with biochemical and genetic assays, endoscopic evaluation and biopsies, which can be safely employed in infants. Yet, sound clinical assessment of the cases and simple laboratory measures such as stool testing allow proper selection of specific diagnostic options.

A) The first step in a patient with persistent diarrhea may be macroscopic and microscopic stool examination in order to differentiate colitis and enteropathy.



Infantile colitis has to be considered in infants presenting with mucoid or bloody diarrhea. Cow's milk allergy, infectious diseases, vasculitis, IBDs, ischemic colitis, microscopic colitis, eosinophilic colitis, occasionally syndromic diarrhea, and Behçet's disease have to be considered in the evaluation of an infant with colitic state (3).

Cow's milk allergy represents the major group in our series presenting with colitic diarrhea. In infants with cow's milk allergy, growth and development are usually not impaired. In our series, there was no numerical difference between the colitis- and enteropathy-type cow's milk protein allergy, with each group consisting of 11 patients. In such patients, response to cow's milk elimination for 2-3 weeks should be considered before further, more invasive diagnostic testing is attempted. Ulcerati-

ve colitis patient with infantile onset and infantile Behçet's disease are rare reasons for infantile colitis. Each of these two diseases was represented by one case in our series. Infantile ulcerative colitis presented with bloody diarrhea, anemia, thrombocytosis, and increased acute phase reactants. Ruling out dietary hypersensitivity and infectious etiologies is important for the diagnosis of this colitis. IBD and FMF share common clinical and biologic features, such as recurrent and periodic symptoms and an abnormal regulation of apoptosis (4,5). An increasing number of studies have been published recently indicating that IBD is more common and severe in patients with FMF. Cattan et al. (6) reported that the FMF and IBD association in non-Ashkenazi Jews is 8-to-14-fold higher than expected. These authors suggested that the genes responsible for one disorder could have a modifying effect on the other inflammatory disease (6). FMF is reported as a possible modifying factor in treatment-resistant and early-onset ulcerative colitis in infancy and childhood. FMF heterozygosity was detected in our patient and colchicine treatment helped in the control of the disease (7,8).

The etiology of Behçet's disease is unknown and appears in genetically sensitive individuals with triggering of environmental factors. Unfortunately, a specific diagnostic test is not available. Pediatric Behçet's disease patients with gastrointestinal manifestations are diagnosed with clinical conclusion after exclusion of similar situations. Finally, our patient was considered as Behçet's disease according to two major findings (recurrent oral aphthous lesions and perianal ulcers) and 1 minor finding (gastrointestinal manifestation) described in the revised Behçet's disease diagnosis criteria in 2005 (9). Behçet's disease diagnosis is more difficult in childhood because findings like uveitis and positive pathergy test are rare in comparison to adults. Although the major relevant zone presenting lesions in Behçet's disease is the ileocecal area, in our case, the distal colon was involved. Several agents have been tested in the treatment of Behçet colitis, but none has been shown to be convincingly effective. Colchicine may be used with modest success to treat the other organ involvement but is insufficient for the treatment of colitis. However, our patient is in remission status with colchicine treatment alone and is now 4 years old. The case is interesting with its features like distal type colitis, response to colchicine treatment and infantile onset (10). Differential diagnosis of infantile colitis type persistent diarrhea requires colonoscopy and biopsy after exclusion of infectious states and food allergies.

B) After ruling out colitis type persistent diarrhea, enteropathy should be considered. The second step is deciding whether the enteropathy is osmotic or secretory type (Figure 4). Secretory diarrhea is usually associated with large volumes of watery stool and persists even when oral food is withdrawn. In contrast, osmotic diarrhea is dependent on oral feeding, and stool volumes are usually not as massive as in secretory diarrhea (3).

C) In osmotic type diarrhea, it is important to identify the responsible factor. Fat, carbohydrate and protein malabsorptions may result in persistent osmotic diarrhea due to increased intraluminal osmolarity. The easiest way for screening the factor is to look for stool pH, reducing substance, fat, and stool alpha-1 antitrypsin level. In carbohydrate malabsorptions, pH is <5 and reducing substance is positive. Sugar chromatography shows the carbohydrate type that fails absorption. Sucrose isomaltose deficiency, glucose galactose malabsorptions and lactase deficiency are examples of carbohydrate malabsorptions. Alpha-1 antitrypsin presence in stool indicates protein-losing enteropathy. Bile acid malabsorptions, ABL, CF, and lipase deficiency present as fat malabsorptions. Isolated pancreatic lipase deficiency, lymphangiectasia and CF are kinds of protein-losing enteropathies. In some diseases, all three components may be seen together, such as malnutrition, acrodermatitis enteropathica, short loop syndrome, CD, and food allergies (3). In our series, gastrointestinal endoscopy and biopsies led to the diagnosis of CD, IL and ABL. Cow's milk al-

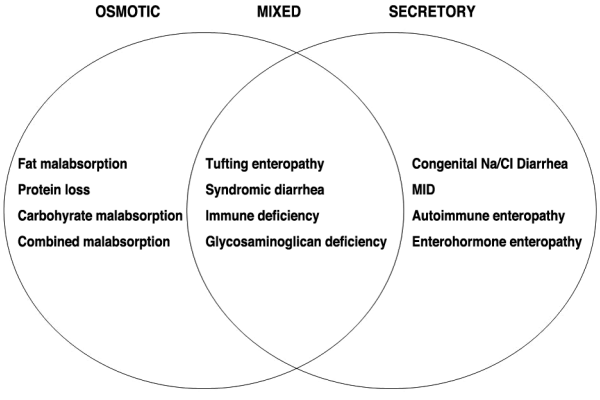


Figure 4. Classification of intractable enteropathies

lergy was the most relevant disease in our enteropathy group and colitis group. A single case was further investigated after being diagnosed as enteropathy type cow's milk protein allergy due to relatively poor response to dietary regulations. During the follow-up period, albumin levels diminished under dietary treatment and breastfeeding. As seen in this case, as one of the major reasons for hypoalbuminemia during breastfeeding in the case of consanguinity, CF has to be kept in mind.

There is no data about celiac prevalence in Turkey; however, a survey about celiac prevalence in primary school aged children has been carried out by our clinic. The presence of chronic diarrhea, poor weight gain and abdominal distention after introduction of gluten to the infant diet are the major characteristics of all our cases. Endoscopic biopsies led to diagnosis of the disease and all patients showed improvement with gluten-free diet.

Intestinal lymphangiectasia has to be considered in the differential diagnosis when the hypoproteinemia, edema and diarrhea triad is present in a patient. In our cases with IL, Cases 1, 2, 4, and 5 had dilated lymphatic channels. In Case 3, signs and symptoms, laboratory findings and endoscopic evaluation led to the diagnosis of the case as IL, but histopathologically dilated lymphatic channels were not visualized in LM. The golden standard is to show dilated lymphatics histopathologically. LM is not always sufficient to show dilated lymphatic ducts. EM evaluation makes the diagnosis definite. Exclusion of other protein-losing enteropathies and endoscopic findings led us to the diagnosis of IL (11). Abdominal imaging techniques such as USG and CT can help identify the underlying cause and can demonstrate PIL. Mazzie et al. (12) reported CT findings of an IL patient for the first time in 2003. In our cases, abdominal USG was performed in all 4 patients. Cases 3 and 5 had ascites, Case 4 had a thickened intestinal wall, and Cases 1 and 2 had normal sonographic evaluation. IL treatment is dietary intervention with high protein, low fat and use of MCT. In addition to this treatment, octreotide might be useful. There is no consensus regarding the dosage of octreotide in IL treatment. Unfortunately, follow-up studies on this point are not present in the literature but some case reports have been noted. Thus, start-up dosage for octreotide treatment and intervals are not clear. Octreotide dosage was between 50-200 micrograms in our cases. Treatment dosage was assayed according to the patient's clinical condition and demand for albumin replacement. No complications were observed throughout the treatment period. Despite the relatively short-term follow-ups and small number of cases, we may declare the fact that early diagnosis of IL resulted in extended usage of octreotide (11,12). Malnutrition due to chronic diarrhea and vitamin deficiencies is observed in ABL patients, resembling CD. However, low lipid profile can be addressed to lipid transport abnormalities. Fat-soluble vitamin deficiencies due to absorption defect are also observed in these patients. Endoscopic findings are not specific; however, diffuse white granular pattern is representative. In LM examination, small bowel epithelial cells show lipid accumulation. These findings are seen in both ABL and hypobetalipoproteinemia. ABL and homozygote hypobetalipoproteinemia are hard to differentiate due to clinical and laboratory findings. Genetical analysis is necessary, and our two cases are still under genetic investigation (13).

D) Persistent enteropathies, whether osmotic or secretory type, necessitate endoscopic evaluation and biopsy in the early stages. LM and EM examinations are helpful for diagnosis of MID and autoimmune enteropathy. The most common disease among the neonatal enteropathy group is MID. EM examination of small bowel biopsy specimens is the gold standard for diagnosis of MID. All LM and EM findings including villous atrophy may become evident in a period. In Case 2, the first biopsy was efficient for the diagnosis; however, Case 1 needed a full year and the diagnosis was made after the second biopsy. The case is being followed with a prediagnosis of congenital diarrhea. After exclusion of immune deficiencies, transport defects, short loop syndrome, cow's milk protein allergy, metabolic diseases, and CF, although initial pathological signs did not point to it, the diagnosis of MID was not excluded. Late manifestation of pathological findings in a patient surveyed for congenital diarrhea may delay the definite diagnosis (14).

Cystic fibrosis is the most common etiologic factor for pancreatic failure in the infantile age group. Genotype and phenotype association is mostly done in pancreatic manifestations of CF. Pancreatic enzyme activity has to drop below 10% for the appearance of pancreatic insufficiency clinical state. CF infants have nearly 65% pancreatic insufficiency at birth. Cases with pancreatic insufficiency are distinguished by weight gain difficulties in the

first 6 months of life, diarrhea, hypoalbuminemia, and clinical state of malabsorption. Pancreatic enzymes could be assayed from stool for the pancreatic insufficiency diagnosis; however, the easy method is stool fat analysis. Both of our cases in this series were chronic diarrhea patients recognized by the presence of fat in stool and pancreatic insufficiency in the clinical foreground (2).

In conclusion, in all age groups, diarrheas lasting more than 14 days have to be accepted as persistent diarrhea apart from diarrheal type and are worth investigating. Diarrheas occurring in infants aged 0-24 months, in other words the infantile period, result in growth retardation and malnutrition. Congenital type diarrheas are also present among this group, and fatal results may occur without bowel transplantation.

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