Evaluation of Paediatric Patients with Protein Losing Enteropathy

A Single Centre Experience

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ABSTRACT

Objective: *The aim of the study is to evaluate paediatric patients with protein losing enteropathy (PLE).*
Methods: *Fourteen cases diagnosed as PLE were evaluated in terms of aetiologies, diagnostic methods, laboratory findings, treatment procedures and long-term prognosis.*
Results: *Four of the cases had coeliac disease, three intestinal lymphangiectasia, three giardia infection, one* H pylori *infection and three cytomegalovirus (CMV) infection. Histopathological examinations of duodenum specimens revealed total villous atrophy in four cases, lymphatic dilatation in three cases, severe nodular appearance in four cases and no pathology in four cases. All of the cases except patients with intestinal lymphangiectasia were controlled by the appropriate treatment given for the underlying disease. The cases with CMV infection were treated with only supportive treatment and gancyclovir therapy was not needed.*
Conclusion: *When proteinuria is not detected in well-appearing children admitted with oedema, PLE must be considered.*

Keywords: Children, hypoproteinaemia, protein losing enteropathy

Evaluación de los Pacientes Pediátricos con Enteropatía Perdedora de Proteínas

Experiencia Sola en un Centro

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RESUMEN

Objetivo: *El objetivo del estudio es evaluar a pacientes con enteropatía perdedora de proteínas (EPP).*
Métodos: *Catorce casos diagnosticados con EPP fueron evaluados en términos de etiologías, métodos de diagnóstico, resultados de laboratorio, procedimientos de tratamiento, y prognósis a largo plazo.*
Resultados: *Cuatro de los casos tenían enfermedad celíaca, tres padecían de linfangiectasia intestinal, tres sufrían de infección por giardias, uno tenía infección por* H pylori, *y tres presentaba infección por citomegalovirus (CMV). Los exámenes histopatológicos de especímenes duodenales revelaron atrofia de las vellosidades intestinales en cuatro de los casos, dilatación linfática en tres casos, apariencia nodular severa en cuatro casos, y ausencia de patología en cuatro casos. Todos los casos – excepto los pacientes con linfangiectasia intestinal – fueron controlados mediante el tratamiento adecuado para la enfermedad subyacente. Los casos con infección por CMV fueron tratados con tratamiento de apoyo, y no se necesitó terapia con ganciclovir.*
Conclusión: *Cuando no se detecta proteinuria en niños con buena apariencia ingresados con edema, hay que considerar principalmente la posibilidad de EPP.*

Palabras clave: Niños, hipoproteinemia, enteropatía perdedora de proteínas

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INTRODUCTION

Protein losing enteropathy (PLE), characterized by loss of serum proteins from the gastrointestinal tract because of defect in the tight junctions between enterocytes resulting from localized or systemic factors, obstruction in lymphatic

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flow and increase in pressure of the right side of the heart, includes a large group of diseases (1, 2). The most common causes of PLE include inflammatory bowel diseases, allergic gastroenteropathy and parasitic infestations; rarely, *Helicobacter pylori* and cytomegalovirus (CMV) infections can also result in PLE (3).

Most of the patients present with diarrhoea, chronic abdominal pain and oedema. Laboratory examinations reveal decreased serum albumin, immunoglobulins, transferrin, ceruloplasmin and iron levels. Cellular immunity is impaired. The measurement of fecal alpha-1-antitrypsin which is not normally detected in stool is a noninvasive test for confirming loss of protein from the gastrointestinal tract (4). The symptoms usually resolve spontaneously when the underlying disease is treated. The aim of this study is to evaluate paediatric patients with PLE.

SUBJECTS AND METHODS

Fourteen cases with PLE diagnosed between January 2000 and 2009 at the Department of Paediatric Gastroenterology in Sisli Etfal Training and Research Hospital (Istanbul, Turkey) were enrolled in this study. The cases that were admitted to our clinic with body swelling, abdominal pain and diarrhoea were evaluated retrospectively. Complete blood count (haemoglobin, haematocrit, leukocyte, lymphocyte, eosinophil, thrombocyte), biochemical tests (total protein, albumin, calcium, iron, total iron binding capacity, ferritin, immunoglobulins) and urinalysis were evaluated in all patients. Fecal alpha-1-antitrypsin determination was done by immunodiffusion method (Nor partigen, Behring Diagnostics, Germany). Upper gastrointestinal endoscopy was performed with paediatric gastroscope (Olympus Evis Exera CV-160). Rectal midazolam 0.5 mg/kg was given as premedication 30 minutes before endoscopy. Two biopsy specimens were obtained from each patient's stomach and duodenum by oeosophagogastroduodenoscopy and tissue specimens were fixed with 10% formaldehyde.

Statistical analysis

Statistical analysis was performed using SPSS 11.5 software (SPSS Inc, Chicago, IL, USA). Results were expressed as means ± SD.

RESULTS

The age of patients ranged from 24 months to 228 months (median: 127 months) and the age at diagnosis ranged from 2.5 months to 120 months (median: 24 months). The male: female ratio was 1. The allergy and nutrition history were not remarkable. The growth parameters were normal in all patients except in four cases with the diagnosis of coeliac disease. Anaemia was determined in all patients except two cases. Eosinophilia was detected in two and lymphopenia was in three of the cases. Serium Ig G, Ig A, Ig M, total protein, albumin and calcium levels were below normal for similar age group in all cases. The median fecal alpha-1-antitrypsin was 4 g/stool (normal < 2 g/stool) and it was high in all of the cases. Four cases had coeliac disease, three intestinal lymphangiectasia, three giardia infection, one *H pylori* infection and three CMV infection. The demographic, aetiologic and laboratory characteristics of the cases are shown in the Table.

Table: The characteristics of cases with protein losing enteropathy

Age (year)	2.95 ± 2.56
Gender (male/female)	1:1 (7/7)
Primary disease	
Coeliac disease	4
Intestinal lymphangiectasia	3
Giardiasis	3
H pylori	1
Cytomegalovirus infection	3
Laboratory findings	
Haemoglobin (g/dL)	10.2 ± 0.7
Haematocrit (%)	30.6 ± 1.2
Total protein (g/ dL)	3.9 ± 0.8
Calcium (g/ dL)	8 ± 1.3
Albumin (g/ dL)	1.98 ± 0.26
Ferritin (ng/ml)	5.3 ± 0.95
Fecal alpha-1-antitrypsin (g/stool)	4 ± 1.59

Histopathological examinations of specimens from the duodenum revealed total villous atrophy in four cases, lymphatic dilatation in three, severe nodular appearance in four and no pathology in four cases. Two of the cases with CMV infection had hypertrophic giant folds and hyperaemia in the corpus and immunohistological examination showed inclusion bodies in gastric biopsy specimens.

DISCUSSION

Protein losing enteropathy is a disorder which is characterized by loss of serum proteins from the gastrointestinal tract. Although the frequency is not known, limited number of cases have been reported in the literature. In aetiology, infections (*H pylori*, CMV, rotavirus and parasitic infestations) and inflammatory bowel diseases, malignancies, cardiac diseases and connective tissue diseases are the main causes (5, 6).

Cytomegalovirus infections cause loss of protein due to gastric hypertrophy and intestinal lymphangiectasia (7, 8). Detection of CMV DNA by polymerase chain reaction (PCR) in biopsy specimens is a more sensitive indicator than antigenaemia and serological tests for diagnosis (9). In our study, upper gastrointestinal endoscopy of a two-year old boy who was admitted with eyelid oedema and bilateral leg swelling demonstrated hypertrophy and oedema of the gastric folds. When the underlying causes were examined, it was determined that CMV Ig M and CMV DNA were positive. The examination of gastric biopsy specimens of the case whose fecal alpha-1-antitrypsin was 2.2 g/stool revealed intense polymorphonuclear leukocytes, lymphoid follicules and aggregates. We could not show the decrease in gastric glands and dilatations between glands. This can be explained by the fact that biopsy specimens were taken

superficially. Cytomegalovirus-associated PLE has a good prognosis in children. It has been reported that it could be treated usually within several weeks with supportive treatment including albumin infusion, high protein diet and proton pump inhibitors [PPI] (10, 11). In the study conducted by Megged and Schlesinger, children with PLE in the literature were evaluated and they recommended that gancyclovir be given only to newborns with an immature immune system, immunocompromised patients and those who do not improve with supportive therapy (12). Supportive treatment and PPI were used in the treatment of our patients with PLE and we observed that oedema started to resolve within 24 hours. The cases in whom clinical improvement was seen after two to three weeks with this treatment were discharged from hospital.

There are only a few studies which reported that there was a relationship between *H pylori* and PLE (13–19). *H pylori* is the most important cause of antral gastritis and duodenal ulcer in children (12). Although it is not known exactly by which mechanism *H pylori* causes loss of protein, it has been suggested that loss of protein has resulted because of intense inflammation in the gastric mucosa (16–18). The diagnosis is made by detection of positive fecal anti-Hp IgG and serum Hp IgG or demonstration of *H pylori* in biopsy specimens (11). Triple drug therapy with amoxicillin, clarythromycin and PPI is used in the treatment of *H pylori* infections (20). A seven-year old girl in our study who did not have proteinuria had high fecal alpha-1-antitrypsin level and positive Hp antigen (detected by immunochromatography). The endoscopy of this case revealed severe nodular appearance and *H pylori* was demonstrated in histopathologic examination of biopsy specimens. The complete resolution of her complaints was observed while the patient was on treatment with triple drug therapy.

Malabsorption is a well-known complication of giardiasis, but PLE is not common. It is considered that mucosal damage of the small intestine by giardia results in PLE (21). It has been reported in the literature that treatment with metronidazole alone as monotherapy is successful in the treatment of giardiasis (21–23). In our study, we detected that three cases (2, 2.5 and 9 years old) that were admitted with generalized body swelling had giardiasis. Fecal alpha-1-antitrypsin results were 3.3, 3.2 and 4 g/stool, respectively. The cases whose biopsy specimens of the small intestine revealed villous shortening and blunting were treated with metronidazole. It was observed that oedema gradually resolved and complete recovery occured within 10 days.

It was well known that coeliac disease, in which hypoalbuminaemia is frequently seen, is a more complex disease than a simple malabsorption. In recent studies, it was reported that nongastrointestinal manifestations were more common than specific malabsorption symptoms and the atypical cases diagnosed are gradually increasing (24). Making a diagnosis becomes easier by using serological tests (anti-endomysium IgA, antigliadin IgA and IgG) and histopathological examinations of duodenal biopsy specimens. In our study, four cases aged from one year to four years and admitted with swelling of the abdomen and legs, had growth retardation. They had high fecal alpha-1-antitrypsin level (4.5, 4.8, 8.2 and 2.4 g/stool, respectively) and also high serum anti-endomysium Ig A and antigliadin Ig A levels. The cases were diagnosed as coeliac disease according to the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria and started on a gluten-free diet. In addition to diet, human albumin was given 0.5 g/kg/day for two consecutive days. The cases whose oedema resolved within one week were still on follow-up without any problem.

Intestinal lymphangiectasia, which is characterized by dilated lymphatics, obstruction of intestinal lymphatic vessels and increase in lymphatic pressure, is an important cause of PLE in children (25). It has been reported that it might occur as obstruction defect of lymphatics congenitally (primary) or secondary to congestive heart failure, constrictive pericarditis, pancreatitis, tumour infiltration, amyloidosis and sarcoidosis (26–29). Besides endoscopic findings such as white spots on the mucosa, white villi and chylous fluid, it is very important to see dilated lymphatics in the mucosa and submucosa at histopathologic examinations of biopsy specimens (30). In treatment, low-fat diet, especially rich in medium chain fat and protein, is recommended. If it is secondary, the treatment is based on underlying disease and if it is primary, in addition to substitution therapy and octreotid, surgical treatment may be useful in chosen cases (30–32). In our study, three cases (aged 2.5 months, one year and three years) were admitted with profuse diarrhoea, fever and abdominal distention. The history of the first case revealed parental consanguinity but the others did not. The third case has had surgery for bowel cyst when he was 40 days old. All three cases had hypoalbuminaemia, hypoglobulinaemia, low serum ferritin, iron and calcium levels and also high fecal alpha-1-antitrypsin levels (4, 4 and 4.2 g/stool, respectively). Their upper gastrointestinal endoscopy showed punctate white dots in the duodenal mucosa. Histopathologic examinations of duodenal biopsy specimens showed that significant dilatation at the tips of villi resulted in lacteal formation which is compatible with intestinal lymphangiectasia. The albumin levels were very low (1.2, 0.8 and 2.2 g/dL, respectively). Therefore, enteral feeding product containing middle chain fatty acids (0.5 g /kg/day) was given to all three cases. Diarrhoea resolved within four days and a rise in serum albumin level was observed. On the tenth day, complete clinical response was achieved and laboratory improvement was observed. Two of the cases except the three-year old girl died because of septicaemia during the second year of follow-up.

In conclusion, in well-appearing children admitted to hospital with oedema, if proteinuria is not detected, PLE must be considered. Therefore, in our opinion, it is necessary to evaluate fecal alpha-1-antitrypsin level, a noninvasive test,

in patients with clinical suspicion of PLE. Appropriate treatment should be given according to underlying disease and these patients should be followed-up after diagnosis.

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