CONGENITAL MICROVILLUS ATROPHY IN A 4 - MONTH - OLD GIRL*

*Yeşim Acar MD***, Deniz Ertem MD****, Evin Özgüven MD*****

*İmer Okar MD******, Rengin Ahıskalı MD*******, Ender Pehlivanoğlu MD********

SUMMARY: Acar Y, Ertem D, Özgüven E, Okar İ, Ahıskalı R, Pehlivanoğlu E. (Department of Pediatric Gastroenterology, Marmara University Faculty of Medicine, İstanbul, Turkey). Congenital microvillus atrophy in a 4-month-old girl. Turk J Pediatr 1999; 41: 495-500.

Congenital microvillus atrophy is a severe generalized enteropathy with ultrastructural abnormalities of the intestinal brush border. It is a rather new clinicopathological entity which needs to be differentiated from other enteropathies within the spectrum of intractable diarrhea of infancy. The presented case was a four-month-old girl with a chronic, intractable diarrhea, beginning at birth. The diagnosis was established only after the electron microscopic examination of small intestinal mucosa which revealed the characteristic features of the disease. Congenital microvillus atrophy is a rare autosomal recessively inherited disorder and bowel transplantation becomes a realistic option of treatment. Therefore, it should be specifically considered in the differential diagnosis of chronic intractable diarrhea of infancy. *Key words: congenital microvillus atrophy, intractable diarrhea, infant.*

Intractable diarrhea in infancy denotes a clinical symptom complex characterized by the onset of noninfectious diarrhea before three months of age which lasts longer than two weeks and results in severe malabsorption and malnutrition[1]. Within this group of heterogeneous patients, congenital microvillus atrophy is a specific entity with abnormal ultrastructural features of the small intestine that distinguish it from other causes of congenital diarrhea with normal ultrastructure of the enterocytes[2-6]. Clinical features of the disease are a protracted diarrhea starting at or soon after birth, which is resistant to all therapeutical interventions and results in failure to thrive[2,3,5]. The diagnosis of microvillus atrophy can be made by demonstration of abnormal periodic acid-Schiff (PAS) stained enterocytes on light microscopy, increased numbers of secretory granules in the apical cytoplasm of enterocytes, and the presence of microvillus inclusions detected on electron microscopic

* From the Department of Pediatric Gastroenterology, Marmara University Faculty of Medicine, İstanbul.

** Pediatric Gastroenterologist, Marmara University Faculty of Medicine.

*** Fellow in Pediatric Gastroenterology, Marmara University Faculty of Medicine.

**** Assistant Professor of Pediatrics, Marmara University Faculty of Medicine.

***** Professor of Histology, Marmara University Faculty of Medicine.

****** Assistant Professor of Pathology, Marmara University Faculty of Medicine

******* Professor of Pediatrics and Pediatric Gastroenterologist, Marmara University Faculty of Medicine.

examination of the small intestinal biopsy[2-5]. We present this case because congenital microvillus atrophy is a rare but perhaps an important cause of intractable diarrhea of infancy. It could be easily overlooked if it is not specifically considered.

Case Report

A four-month-old girl was transferred to the Department of Pediatric Gastroenterology and Nutrition at Marmara University School of Medicine for the evaluation of chronic diarrhea, beginning at birth. The patient was born at term to healthy, consanguineous Turkish parents with two healthy boys, after a normal pregnancy and an uncomplicated delivery. The infant was vigorous at birth and the birth weight was 2500 g. At home, the newborn breastfed poorly, had several loose, watery stools and began to vomit after the feeds. She developed peripheral edema within the first days of life which resolved spontaneously. At the end of the first month, the edema reappeared on the face, the diarrhea persisted and the severe episodes of vomiting led to a poor weight gain. At 10 weeks of age, the patient was taken to a local hospital where she was hospitalized because of pneumonia and was given an appropriate antibiotic therapy. During the hospital stay, the initial hemoglobin level was 6.5 g/dl, and she was transfused twice. Laboratory investigation revealed hypoproteinemia (total protein 5.9 g/dl, albumin 2.7 g/dl with a normal urine analysis. Thereafter, the patient was transferred to our unit for further investigation of the chronic diarrhea and hypoproteinemia.

The physical examination showed a malnourished infant with a weight of 3530 g and a length of 53 cm. Both measurements were below the 3rd percentile and her nutritional index was 45 percent. She appeared pale with edema on cheeks, tibiae, and dorsum of feet and hands, and had hepatosplenomegaly.

Initial laboratory studies showed anemia (hemoglobin 9.3 g/dl), leukocytosis (18700/mm^3), elevated transaminases levels (AST 83 U/L, ALT 66 U/L), hypoproteinemia (protein 5.0 g/dl, albumin 2.0 g/dl), and elevated cholesterol and triglyceride levels (203 mg/dl and 319 mg/dl, respectively). Her renal functions and serum electrolyte levels were within normal ranges with a normal arterial blood gas analysis. Further investigations revealed normal glucose homeostasis, and normal serum lactate, pyruvate and ammonia levels. Her urine analysis did not reveal any reducing sugar, ketone or protein in the urine. Serum and urine amino acid profiles were normal. The circulating autoantibodies, including antinuclear, antimitochondrial, antismooth muscle and anti liver-kidney microsomal antibodies were all negative. Thyroid function tests and serum immunoglobulin levels were within normal ranges. The examination of the stool showed a normal pH and chymotryptic activity, and there was no pathological alpha1-antitrypsin excretion. The repeated stool cultures were negative for any pathogenic microorganism. The quantitative sweat chloride test was normal. Screenings for hepatitis A, B, C viruses and cytomeglovirus were also negative.

On the clinical course, the patient's diarrhea and vomiting persisted, and enteral feeding was not tolerated. Total parenteral nutrition (TPN) was initiated and the patient became TPN dependent with only minimal tolerance to enteral feeding. The upper and lower gastrointestinal endoscopies performed at this time were macroscopically unremarkable. The histopathological examination of hematoxylin and eosin (H&E) stained esophageal, gastric, duodenal and rectal biopsies were normal under light microscopy (Fig. 1). On the electron microscopy (EM), however, the ultrastructural examination of the duodenal mucosa revealed partial microvillus atrophy on the apical membrane of the enterocytes (Fig. 2). After the diagnosis of microvillus atrophy was confirmed by the EM, the duodenal specimens which were stained with periodic acid-Schiff (PAS) revealed an abnormal accumulation of PAS-positive material within the apical cytoplasm of the epithelium under light microscopic examination (Fig. 3).

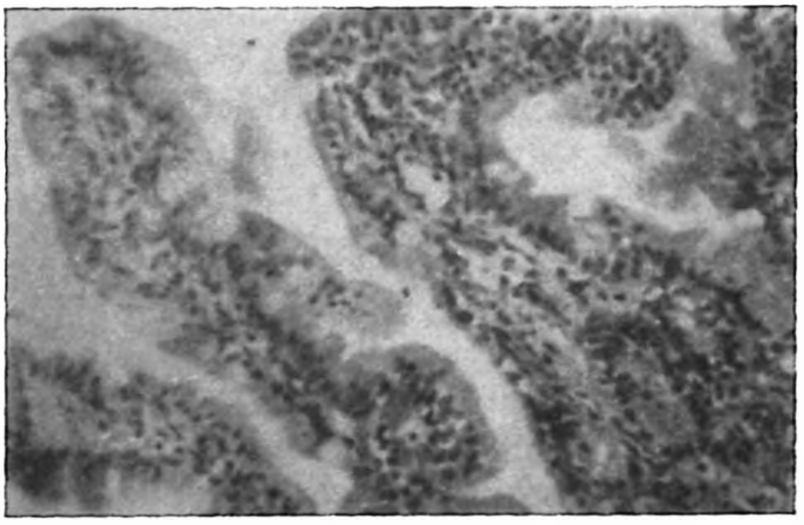

Fig. 1: The light microscopic appearance of the proximal small intestinal mucosa was normal in the patient with congenital microvillus atrophy (H&E x 40).

Fig. 2: Electron microscopy revealed a partial microvillus atrophy (arrows) on the apical membrane of the enterocyte (x 25,000).

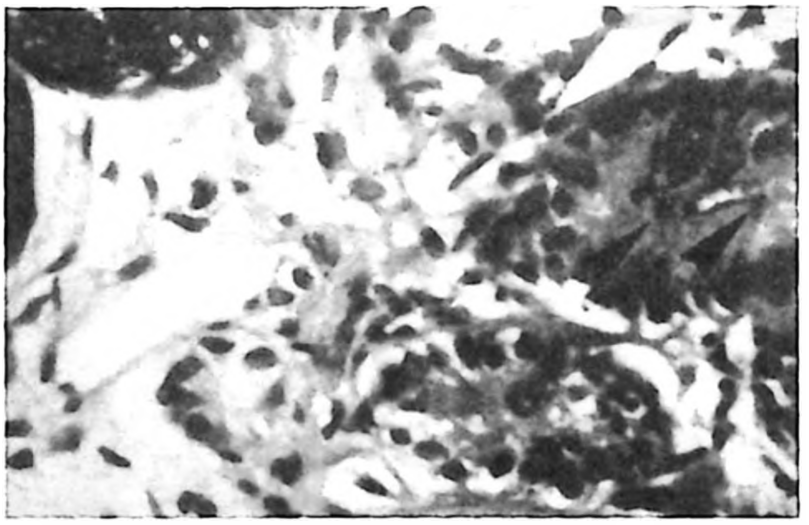

Fig. 3: Abnormal accumulation of PAS-positive material (arrows) in the apical cytoplasm of epithelial cells seen in duodenal specimen (PAS x 40).

The hepatic biopsy which was performed because of persistent hepatomegaly and increased transaminases levels showed diffuse macrosteatosis. The patient was still receiving TPN when she died due to gram-negative sepsis at eleven months of age. Unfortunately, a postmortem work-up could not be performed.

Discussion

Congenital microvillus atrophy or microvillus inclusion disease is an autosomal recessive disorder, associated with a high mortality. It may be the most common cause of severe, refractory diarrhea in the neonatal period[1,2,6,7]. Although the basic defect is not known, it has been suggested that there is a defect in the transport of substances normally destined for the brush-border, which then build up within the cells[2,3,8]. This defect may represent an inborn error of intracellular transport which leads to aberrant assembly of the components of the enterocyte surface membrane[2,8]. The characteristic features of the disease include a thin mucosa, an abnormal accumulation of PAS-positive material within the apical cytoplasm of epithelial cells, an increase in epithelial cell secretory granules, and the presence of microvillus inclusions[3-5,9]. Although intracytoplasmic inclusions are one of the diagnostic features of microvillus atrophy, they are not limited to this disease[3]. There are also published case reports showing ultrastructural abnormalities of congenital microvillus atrophy without inclusions[5]. However, the accumulation PAS-positive material within the apical cytoplasm of intestinal cells, which has only been reported in microvillus atrophy, appears to be a specific defect of this disease[3,8].

Intractable diarrhea of infancy may result from a variety of known disorders including infections, inflammatory conditions, enzymatic defects, hormonal and metabolic diseases, and anatomical abnormalities[1,6,9]. It is therefore important

to exclude these disorders through apropriate investigations. The diagnosis of congenital microvillus atrophy as a cause of intractable diarrhea of infancy has to be established on the ground of the morphological and ultrastructural features which are characteristic for the disease[3,4,9,10]. Since the H&E-stained sections did not show any characteristic features, the abnormalities which could be detected by PAS stain can be easily overlooked[3]. Ultrastructural abnormalities can involve not only the small and large intestinal epithelia but also the biliary epithelium[3,10]. At present, the only reliable way of diagnosis could be the electron microscopic examination of jejunal or rectal biopsy specimens[2,3,5].

Currently, no treatment is available, and patients with congenital microvillus atrophy are supported by total parenteral nutrition and intravenous fluids for the replacement of their massive intestinal losses[2-5]. The majority of the affected patients eventually die of septic complications or hepatic insufficiency stemming from TPN-induced cholestasis[2,3,5,6]. Recently, Oliva et al.[11] reported the first successful intestinal transplant for microvillus inclusion disease in a patient 2.5 years old. Thereafter, Herzog et al.[12] published their experience for a combined bowel-liver transplantation in a seven-month-old infant with microvillus atrophy. Advancements in immunosuppressive therapy have allowed the small bowel transplantation to become a realistic option, with a good survival of both patients and grafts[11,12].

We present this case because congenital microvillus atrophy is a rare but perhaps one of the most common causes of intractable diarrhea of infancy. It could be easily overlooked if it is not specifically considered. It is important to recognize and diagnose infants with congenital microvillus atrophy because small bowel transplantation becomes a realistic option for the future treatment of these patients.

REFERENCES

1. Guarino A, Spagnuolo MI, Russo S, et al. Etiology and risk factors of severe and protracted diarrhea. J Pediatr Gastroenterol Nutr 1995; 20: 173-178.
2. Cutz E, Rhoads JM, Drumm B, Sherman PM, Durie PR, Forstner GG. Microvillus inclusion disease: an inherited defect of brush-border assembly and differentiation. N Engl J Med 1989; 320: 646-651.
3. Phillips AD, Schmitz J. Familial microvillous atrophy: a clinicopathological survey of 23 cases. J Pediatr Gastroenterol Nutr 1992; 14: 380-396.
4. Phillips AD, Jenkins P, Raafat F, Walker-Smith JA. Congenital microvillous atrophy: specific diagnostic features. Arch Dis Child 1985; 60: 135-140.
5. Raafat F, Green NJ, Nathavitharana KA, Booth IW. Intestinal microvillus dystrophy a variant of microvillus inclusion disease or a new entity. Hum Pathol 1994; 25: 1243-1248.
6. Nizet V, Priebe CJ. A newborn girl with watery diarrhea, weight loss, and severe metabolic acidosis. Curr Opin Pediatr 1994; 6: 163-167.
7. Reifen RM, Cutz E, Griffiths AM, Ngan BY, Sherman PM. Tufting enteropathy: a newly recognised clinicopathological entity associated with refractory diarrhea in infants. J Pediatr Gastroenterol Nutr 1994; 18: 379-385.

8. Phillips A, Fransen J, Hauri HP, Sterchi E. The constitutive exocytotic pathway in microvillus atrophy. J Pediatr Gastroenterol Nutr 1994; 17: 239-246.
9. Bell SW, Kemer JA Jr, Sibley RK. Microvillus inclusion disease. The importance of electron microscopy for diagnosis. Am J Surg Pathol 1991; 15: 1157-1164.
10. Rhoads JM, Vogler RC, Lacey SR, et al. Microvillus inclusion disease. In vitro jejunal electrolyte transport. Gastroenterology 1991; 100: 811-817.
11. Oliva MM, Perman JA, Saavedra JM, Young-Ramsaran J, Schwarz KB. Successful intestinal transplantation for microvillus inclusion disease. Gastroenterology 1994; 106: 771-774.
12. Herzog D, Atkison P, Grant D, Paradis K, Williams S, Seidman E. Combined bowel-liver transplantation in an infant with microvillus inclusion disease. J Pediatr Gastroenterol Nutr 1996; 22: 405-408.