Gastroenterology and Hepatology From Bed to Bench.
2023 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

CASE REPORT

Not all enteropathies are coeliac disease! Report of an infant with microvillus inclusion disease

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ABSTRACT

Primary enteropathies of infancy comprise of epithelial defects including microvillus inclusion disease, tufting enteropathy, and enteroendocrine cell dysgenesis and autoimmune enteropathies. The diseases in this group cause severe chronic (>2-3 weeks) diarrhoea starting in the first weeks of life and resulting in failure to thrive in the infant. Duodenal biopsies show moderate villous shortening together with crypt hyperplasia which are the main features causing resemblance to coeliac disease.

We, hereby, report a term-born male infant of consanguineous parents. His two siblings died during infancy. He developed watery, urine-like diarrhea on the 3rd day of his life. On the postnatal 6th day he weighed 2750 grams, became dehydrated and had metabolic acidosis. Upper GI endoscopy performed on the postnatal 20th day appeared normal. Light microscopic examination of the duodenal biopsy showed moderate villous blunting, with mildly increased inflammatory cells in the lamina propria or and intraepithelial lymphocytosis. Enterocytes at the villous tips showed an irregular vacuolated appearance in the apical cytoplasm with patchy absence of the brush border demonstared by PAS and CD10. Electron microscopy revealed intracytoplasmic inclusions that were lined by intact microvilli in the apical cytoplasm of enterocytes. As he was dependent on TPN and aggressive intravenous fluid replacement he was hospitalized throughout his life. He died when he was 3 years and 4 months old.

Paediatric coeliac disease is in the differential diagnosis of primary enteropathies of childhood. The differentiation lies on duodenal biopsy interpretation together with genetic analysis to detect the underlying genetic defect in childhood enteropathies.

Keywords: Primary congenital enteropathy, Microvillus inclusion disease, Coeliac disease, Duodenal biopsy.

(Please cite as: **Kozan EN, Tuna Kırsaçlıoğlu C, Kuloğlu Z, Kansu A, Savas B, Ensari A. Not all enteropathies are coeliac disease! Report of an infant with microvillus inclusion disease. Gastroenterol Hepatol Bed Bench 2023;16(2):234-239. https://doi.org/10.22037/ghfbb.v16i2.2735).**

Introduction

Regardless of the cause, malabsorption syndrome refers to the clinical picture comprising diarrhoea, steatorrhea, malnutrition, weight loss, abdominal pain, and, anaemia. Undigested food produces diarrhea, due to its voluminous effect in the bowel lumen. Although all three major nutrients (fat, carbohydrate, and protein) may be malabsorbed, clinical symptoms usually only develop with carbohydrate and fat malabsorption. Small intestinal biopsy is an indispensable component of the diagnostic work-up of patients with malabsorption and/or chronic diarrhoea secondary to mucosal damage. Though, complete villous flattening usually indicates coeliac disease when coexisting crypt hyperplasia is present, there are entities which may cause villous flattening and crypt hyperplasia other than coeliac disease. The majority of disorders causing malabsorption, on the other hand, produce mild to moderate villus blunting and crypt hyperplasia without any specific diagnostic feature. Pathologists can also be faced with a patient with malabsorption or chronic diarrhoea and a biopsy that appears normal or near normal architecturally on microscopy. In the presence of IEL increase there are some disorders that can be diagnosed on light microscopy with very careful examination (1).

Received: 16 January 2023 *Accepted*: 15 March 2023
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Primary enteropathies of infancy comprise of epithelial defects including microvillus inclusion disease, tufting enteropathy, and enteroendocrine cell dysgenesis and autoimmune enteropathies. The diseases in this group cause severe chronic (>2-3 weeks) diarrhoea starting in the first weeks of life and resulting in failure to thrive in the infant. The diarrhoea is either "intractable" that is chronic, unexplained diarrhoea or "protracted" describing infants with loose and frequent stools which resolves despite intial severity. Both forms are usually associated with malabsorption. Causes of intractable or protracted diarrheoa in infancy can be classified as entities showing a normal villus/crypt axis, and those associated with villous atrophy. Congenital defects in the transport of sodium, chloride, glucose/galactose and bile acids, and congenital enterokinase deficiency can cause prolonged diarrhoea in the neonates while enterocyte defects many of which have been recently described may also cause similar symptoms (2, 3). Microvillus inclusion disease (MVID) is one of the most frequent causes of intractable diarrhea with persistent villous atrophy and indefinite dependence on total parenteral nutrition (TPN) from early infancy. The disease was first described by Davidson et al in 1978 as severe secretory diarrhoea occurring during the first week of life with villous atrophy in the intestinal biopsy (4). It has been demonstrated that *MYO5B* gene located on 18q21 encoding myosin Vb which regulates the organization of intracellular transport and cell surface polarity in epithelial cells is mutated. Most reported cases involved small intestine while colonic involvement may also be present. Duodenal biopsies show moderate villous shortening together with crypt hyperplasia which are the main features causing resemblance to coeliac disease. However, unlike coeliac disease there is very little if any intraepithelial lymphocytosis and mild lamina propria inflammation. Changes in the enterocytes are typically found at the villous tips rather than villous bases and crypts. Light microscopy shows an irregular vacuolated appearance in the apical cytoplasm of the enterocytes with extensive or patchy absence of the brush border (3-5).

We, hereby, present a paediatric case of MVID diagnosed and followed-up with duodenal and colonic biopsies.

Case report

Male infant, term born vaginally, weighing 3065 grams, without polyhydramnios. He was the fourth child of consanguineous parents (first degree cousins). The first sibling of the patient died intrauterine at 39 weeks (bowel obstruction?). One sister died due to chronic watery diarrhea. He has one healthy older sister.

He developed watery, urine-like diarrhea on the 3rd day of his life.

On the postnatal 6th day he weighed 2750 grams,

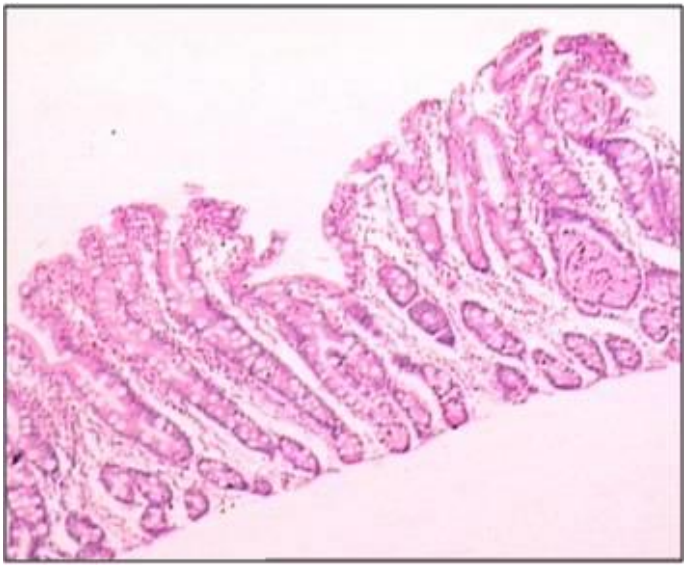

Figure 1. Duodenal biopsy with villus loss, crypt hyperplasia and minimal inflammation (H&E; x100).

became dehydrated and had metabolic acidosis. Then he was referred to the neonatal intensive care unit. His mean fecal volume was 1100 cc/day (400 cc/kg/day). (Expected 5-10 cc/kg/day in a healthy infant.) In his stool, potassium was 20mEq/L, sodium was 84mEq/L and chlorine was below 20mEq/L. His stool osmotic gap was within the normal range (82 mOsm/kg). His diarrhea continued in the fasting state. A normal appearance was found in the upper GI endoscopy performed on the postnatal 20th day. Light microscopic examination of the duodenal biopsy showed moderate villous blunting, with mildly increased inflammatory cells in the lamina propria and intraepithelial lymphocytosis (Figure 1). Enterocytes at the villous tips showed an irregular vacuolated appearance in the apical cytoplasm with patchy absence of the brush border (Figure 2). The surface epithelial brush border showed an abnormal pattern of staining by PAS (Figure 3) and CD10 (Figure 4) instead of its normal linear staining pattern. Electron microscopy revealed intracytoplasmic inclusions that were lined by intact microvilli in the apical cytoplasm of enterocytes. These inclusions were associated with poorly developed surface brush border microvilli. (Figure 5).

When he was 1 month old, he weighed 2700 grams (Z score: -4.3) and was 53 cm (Z score: -1.8) tall. He

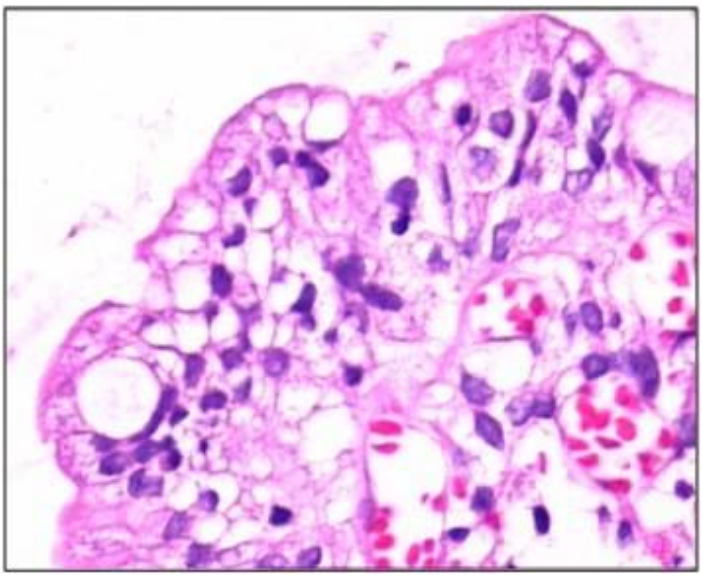

Figure 2. Surface epithelium showing vacuolization in the apical cytoplasm of enterocytes (H&E; x200).

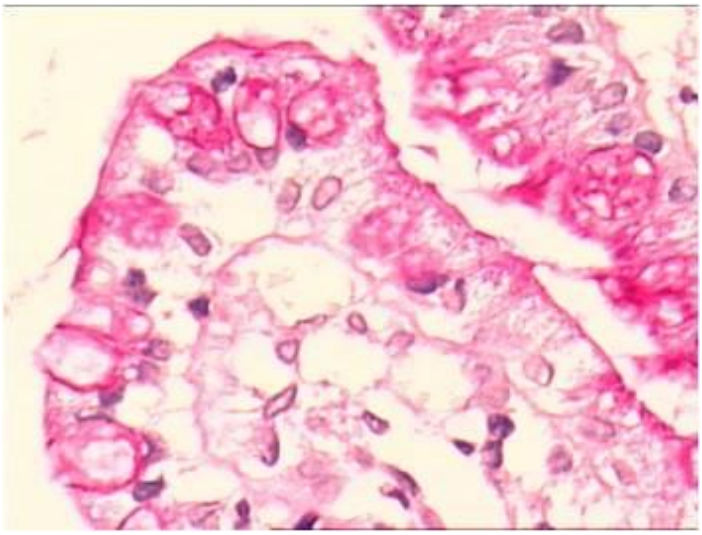

Figure 3. Apical cytoplasmic vacuolization of surface enterocytes (PAS; 200).

was defecating 14-18 times a day. He was fed only with TPN and was receiving aggressive intravenous fluid replacement. He developed cholestasis but that regressed at 5 months of age. By the age of 2 months, he started to have abdominal distension and pseudo obstructions. Surgical full thickness ileal and colonic biopsies were taken. Histopathological features of ileal biopsy were similar to the previous biopsy with no muscular or neurologic abnormality. Microvillus inclusions were detected by electron microscopy. Colonic biopsies were normal with no epithelial abnormality. Homozygous c.1323-2A>G mutation of the *MYO5B* gene was detected by genetic analysis. He weighed 3080 grams at 4 months, 3180 grams at 5 months, and 9400 grams at 13 months. His stool volume was above 250 ml/kg per day. He was defecating 2-6 times a day. He was still fed only with total parenteral nutrition and was receiving aggressive intravenous fluid replacement. When he was 3 years old, he weighed 10800 grams (Z score: -2.8) and was 82 cm (Z score: -3.9) tall. Because he was dependent on TPN and aggressive intravenous fluid replacement he was hospitalized throughout his life. He developed complications such as catheter-related sepsis, iron deficiency anemia, catheter-related thrombosis, vitamin D deficiency, hepatosteatosis, and non-selective proteinuria.

His psychomotor development was also below what

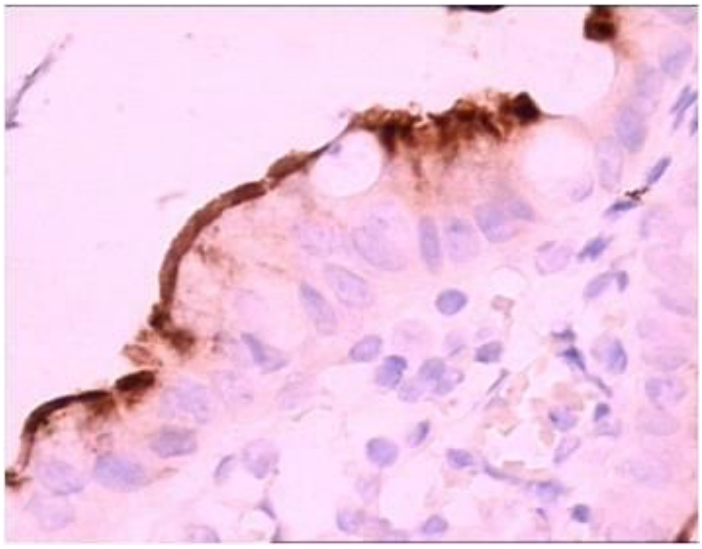

Figure 4. Smudgy staining of apical cytoplasm (CD10 immunohistochemistry; x200).

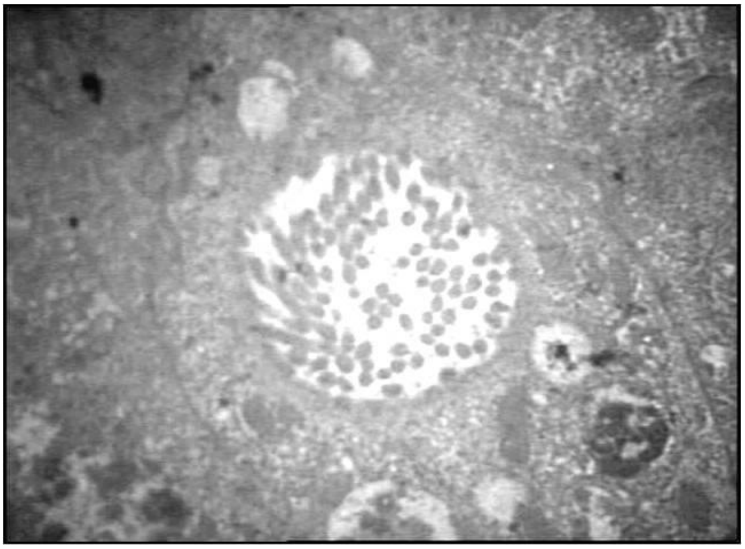

Figure 5. Microvillus inclusions in enterocytes (electron microscopy).

was expected for his age. He started walking at 18 months of age. At the age of 3, he could only use a few words. He has never started oral feeding. He died when he was 3 years and 4 months old.

Discussion

Microvillus inclusion disease (MVID) is an extremely rare autosomal recessive disease characterized by intractable, severe diarrhea within the first weeks of life resulting from congenital defects of intestinal epithelial differentiation. MVID was first described by Davidson et al. in 1978 as a congenital enteropathy characterized by severe diarrhea and villus atrophy in the small intestine biopsies (4). Identification of mutations in the *MYO5B* gene was an important step in understanding the pathophysiology of the disease (5). *MYO5B* gene encodes myosin Vb, which by interacting with RAB small GTPases (RAB8a, RAB10, RAB11), regulates the organization of intracellular transport and cell surface polarity in epithelial cells. The identification of t-SNARE STX3 as the second gene causing MVID has led to the understanding of the apical exocytic pathway in epithelial cells in the pathophysiology of the disease (6). Both the *MYO5B* and *STX3* genes are involved in apical trafficking.

MVID often presents with intractable watery diarrhea, leading to weight loss, and metabolic acidosis due to loss of bicarbonate. It has an early onset form that appears in the first days of life and a late-onset form that appears in the second or third months of the life. Complications do not occur frequently during pregnancy, but polyhydramnios has been reported in some of the cases. Diarrhea is the main, life-threatening symptom. The stool volume varies between 150-300 ml/kg/day. Although cholestatic liver disease is reported in one third of the cases like in our case, most of the patients do not have additional organ malformations or additional clinical symptoms (2-9).

Despite many similarities in clinical presentation and clinical course to other childhood enteropathies including tufting enteropathy and enteroendocrine dysgenesis, histopathological evaluation of duodenal biopsy allows the differential diagnosis (1, 3). Diagnosis of MVID is based on findings in light and electron microscopy. In light microscopic examination, moderate to severe villus atrophy usually accompanying crypt hyperplasia is observed in small intestinal biopsies. An irregular vacuolated appearance in the apical cytoplasm of enterocytes and patchy or extensive absence of brush border is commonly present. The surface epithelial brush border shows an abnormal smudgy pattern of staining histochemically by PAS and immunohistochemically by CD10, polyclonal CEA, alkaline phosphatase, villin or anti-Rab11 stains (3-8). EM reveals absent or short stubby microvilli, vesicular structures located in the apical cytoplasm of enterocytes containing microvillus inclusions, and subapical granules containing dense amorphous material (3, 9). Though duodenal biopsy is diagnostic in most cases of MVID, similar pathology may also be found in colonic biopsies as well like in our case.

The main goal of treatment is to replace lost fluid and nutrient. Therefore, patients are dependent on total parenteral nutrition (TPN) throughout their lives. Intestinal transplantation is the only known effective long-term treatment. Our case was also TPN-dependent leading to his hospitalization throughout his lifetime. However, the life expectancy is short due to infections secondary to immunosuppressive therapy and complications related to TPN. Most of the patients die in the first 3 years of their life (10). Unfortunately, our case died before the age of four, though he did not receive immunosuppressive therapy.

In coeliac disease clinical presentation varies from full-blown malabsorption with weight loss, diarrhoea and steatorrhoea to more subtle symptoms such as folate or iron deficiency anaemia, flatulence, episodic diarrhoea, loose stools, neurologic problems, osteoporosis and vitamin K and D deficiencies in as many as 50% of patients. In children, usually within few months of introducing the child to wheat-based foods the classic syndrome of chronic diarrhoea, steatorrhoea, abdominal distension and failure to thrive appears between 6 months and 2 years of age. More commonly weight (40% below 10^{th} centile) but also growth (25% below 10^{th} centile) are affected in these children (1). Therefore, paediatric coeliac disease is in the differential diagnosis of primary enteropathies of childhood. The differentiation lies on duodenal biopsy interpretation together with genetic analysis to detect the underlying genetic defect in childhood enteropathies.

Conflict of interests

The authors declare that they have no conflict of interest.

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