Microvillus Inclusion Disease as a Cause of Severe Protracted Diarrhea in Infants

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Abstract

There are many etiologies responsible for severe intractable diarrhea in infancy, for instance, autoimmune enteropathy, microvillus inclusion disease, tufting enteropathy, food allergy, post-enteritis syndrome, chronic intestinal pseudo-obstruction, Hirschsprung's disease, intestinal lymphangiectasia, congenital sodium or chloride diarrhea, and congenital enzymatic deficiency. This article reports a case of microvillus inclusion disease in a Thai patient. He presented with severe intractable watery diarrhea with persistent metabolic acidosis. After extensive investigation, the diagnosis of microvillus inclusion disease was made, based on the ultrastructural findings of microvillus inclusions in the cytoplasm of the enterocyte on electron microscopic study. Various treatments were introduced to the patient without clinical improvement, including cholestyramine, metronidazole, probiotics, and octreotide. He was dependent on total parenteral nutrition and subsequently died from TPN-related complications. Even though it is a rare disease, it should be considered if an infant has chronic secretory diarrhea.

Key word : Microvillus Inclusion Disease, Chronic Secretory Diarrhea, Diagnosis, Ultrastructure Pathology

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Intractable diarrhea of infancy was first described by Avery et al in 1968[1]. The syndrome was characterized by diarrhea of more than 2 weeks' duration, age less than 3 months, and three or more stools negative for pathogenic bacteria, ova, and parasites. At that time, etiologies could not be identified in about 40 per cent of the cases. Recently, there have been many reports elucidating disease

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entities responsible for severe intractable diarrhea of infancy, for instance, autoimmune enteropathy[2], microvillus inclusion disease[3,4], tufting enteropathy[5], food allergy[4,6], post-enteritis syndrome [4], chronic intestinal pseudo-obstruction[4], Hirschsprung's disease[4,6], intestinal lymphangiectasia[4], congenital sodium or chloride diarrhea[7,8], and congenital enzymatic deficiency[9]. Even though the pathogenesis of this syndrome has been much discussed, treatment is still ineffective in a substantial number of these patients, requiring long-term parenteral nutrition and ultimately acquiring TPN-related complications.

In this article, we reported a male infant who was finally diagnosed as microvillus inclusion disease. The objective of this article is to remind physicians to include the possible diagnosis of microvillus inclusion disease in an infant who presents with severe secretory diarrhea, dehydration, and persistent metabolic acidosis.

CASE REPORT

A 2-week-old infant presented with chronic diarrhea and persistent metabolic acidosis. He was born to a full term (GA 41 weeks), uneventful pregnancy; his birth weight was 4200 grams. The first son in this family also died from diarrhea and clinical sepsis at the age of 13 days. The definite diagnosis was not available. He developed jaundice after 24 hours of life, which was subsequently diagnosed as G6PD deficiency. Since birth, he had had clinical sepsis, watery mucus diarrhea, severe dehydration, and metabolic acidosis. On physical examination, mild jaundice and mild abdominal distention were noted. The complete blood count showed hemoglobin 16.1 g/dl, white blood cell 35,800/mm^3 (neutrophil 58%, lymphocyte 42%), and platelet 764,000/mm^3. The metabolic panels included Na^+ 133 mEq/L, K^+ 4 mEq/L, Cl^- 106 mEq/L, and HCO_3^- 9 mEq/L. The liver function tests showed mild elevation of transaminases (AST 161 IU/L and ALT 94 IU/L) and conjugated hyperbilirubinemia (total bilirubin 8.33 mg/dl and direct bilirubin 5.68 mg/dl). The patient was treated with a course of antibiotics. All culture reports were negative. He still had massive watery diarrhea (up to 130 ml/kg/day) with occasional mucus stools. Despite the fasting state, diarrhea never stopped. Various treatments regarding severe protracted diarrhea were introduced to the patient without clinical improvement, including cholestyramine, metronidazole, probiotics, and octreotide. He was dependent on total parenteral nutrition. Concerning cholestatic jaundice, it was associated with sepsis and subsequently resulted from TPN-induced cholestasis. The esophagogastroduodenoscopy and colonoscopy revealed no gross abnormality. The duodenal biopsy showed marked villus atrophy with destruction of the brush border. There was also evidence of minimal chronic inflammatory cell infiltrate in the lamina propria. The colonic mucosal biopsy showed evidence of chronic nonspecific colitis. The electron microscopy revealed disorganized and markedly shortened microvilli with evidence of inclusion bodies, containing microvilli, in the enterocyte. Numerous vesicular bodies of various sizes were also noted. (Fig. 1.) This patient was finally diagnosed as microvillus inclusion disease. He was placed on total parenteral nutrition

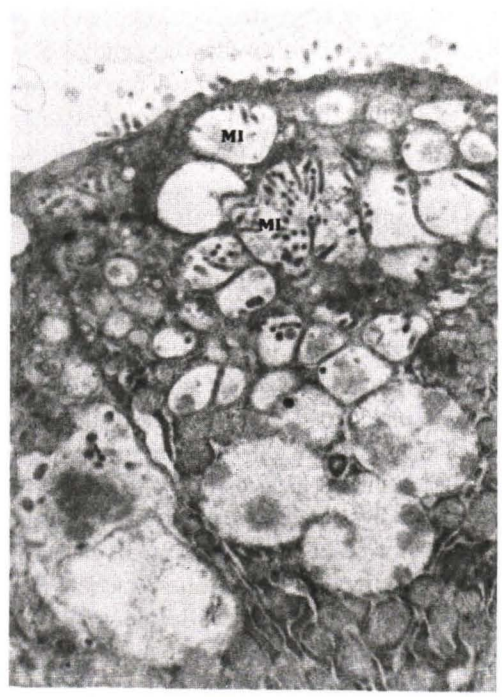

Fig. 1. The electron microscopy shows disorganized and markedly shortened microvilli with evidence of inclusion bodies, containing microvilli, in the enterocyte. Numerous vesicular bodies of various sizes are also noted. (MI=microvillus inclusion body)

for 2 months and ultimately died from TPN-related complications.

DISCUSSION

As mentioned above, microvillus inclusion disease is one of the rare diseases contributing to intractable diarrhea during infancy. It was first recognized in 1978 by Davison et al, who described a group of infants presenting with an apparently familial enteropathy characterized by protracted diarrhea from birth, failure to thrive, and hypoplastic villous atrophy[10]. Cutz E et al, subsequently, reported a group of patients with the same clinical syndrome and first termed the condition, microvillus inclusion disease, according to the typical electron microscopic findings in small bowel biopsy[3]. After that, sporadic articles reported this condition with different names, including congenital microvillus atrophy[11], microvillus inclusion disease[3] and familial microvillous atrophy[12].

A patient with microvillus inclusion disease is usually born after a full term, uneventful pregnancy. The average birth weight is slightly low, with the mean of 2970 grams, reported from the largest series of Phillips AD et al[12]. Polyhydramios is not observed during pregnancy, whereas, it is frequently seen in congenital sodium or chloride diarrhea. This may suggest postnatal development of the disease, triggered by environmental factors in a genetic predisposed child. Regarding this issue, a report of this disease in two male siblings from a consanguinous family, suggested that microvillus inclusion disease is a genetic disease inherited by autosomal recessive[13]. In our case, the mother reported that her older child died from diarrhea and sepsis during the neonatal period. This might clue a physician, taking care of a patient born to a family with a history of protracted secretory diarrhea, to think of some rare disease entities, such as microvillus inclusion disease, and decide to do more specific investigations. Genetic counseling is mandatorily required, although there is no prenatal diagnosis available now.

Most patients usually develop symptoms of severe watery diarrhea, dehydration, and metabolic acidosis within the first week of life. However, there was a report of late-onset microvillus atrophy beyond the newborn period, but it seemed to be less severe [12]. The patient still has profuse watery diarrhea despite nothing being given by mouth. A stool output is usually greater than 100 ml/kg/day. Stool electrolytes comprise high sodium and chloride concentration, similar to those noted in congenital sodium diarrhea. These lead to fluid and electrolyte imbalances, particularly severe dehydration, hyponatremia, and metabolic acidosis. In severe cases, mucus may be noted in the stools[12,14].

The correct diagnosis requires a high index of suspicion and some specific investigations. On light microscopic study of small bowel or colonic biopsies, severe villous atrophy with crypt hypoplasia and minimal inflammatory cell infiltration in lamina propria are noted[3,10-12]. Abnormal Periodic Acid Schiff (PAS)[3,11,12] and alkaline phosphatase activity[15] stains of the apical epithelial cytoplasm are also helpful for establishing the diagnosis. The glycocalyx and alkaline phosphatase activity stained by PAS and indoxyl phosphate-tetrazolium methods, respectively, are absent in the bush border, whereas, there is aggregation of material staining positive located in the apical cytoplasm of enterocytes. However, the specific diagnosis is based on the finding of microvillus inclusion body in the cytoplasm of enterocytes, frequently observed in the epithelial cells lining from upper crypts to villi, by the electron microscope. Numerous vesicular bodies of various sizes are also noted. The surface microvilli appear markedly shortened and disorganized[3,16].

The pathogenesis of this condition is still unknown. Nonetheless, a failure of migration of the vesicle, which is derived from the golgi complex, to the apical surface of the enterocyte in order to form microvilli, has been postulated[3]. In addition to secretory component of diarrhea, this, in part, can lead to a component of malabsorption due to the loss of bush border enzymes. Michail S et al demonstrated a complete absence of Na-Hydrogen exchanger-3 (NHE-3) and an extreme decrease in NHE-2 and SGLT-1 (sodium-glucose transporter-1) mRNA expression in human enterocytes with this disease [17]. These facts may explain the massive secretory diarrhea, similar to the patient with congenital sodium diarrhea.

There have been many medical treatments used, but none have been effective and curative, including steroids, human colostrum, oral antibiotics, cimetidine, epidermal growth factor, and octreotide. With the advent of a new immunosuppressive

therapy, FK 506, there have been reports of successful combined small bowel-liver transplantation (14,18). Patients could be fed enterally and discontinued parenteral nutrition after the surgery. This seems to give new hope for this fatal and rare condition.

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โรคไมโครวิลลัส อินคลูชัน: สาเหตุท้องเสียเรื้อรังในเด็ก

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ภาวะท้องเสียเรื้อรังในเด็กสามารถเกิดจากโรคต่าง ๆ ได้มากมายเช่น autoimmune enteropathy, microvillus inclusion disease, tufting enteropathy, food allergy, post–enteritis syndrome, chronic intestinal pseudo–obstruction, Hirschsprung's disease, intestinal lymphangiectasia, congenital sodium or chloride diarrhea และ congenital enzymatic deficiency บทความนี้รายงานผู้ป่วยเด็กไทย 1 รายที่มารับการรักษาด้วยเรื่องถ่ายเหลวเป็นน้ำเรื้อรัง และมีภาวะความเป็นกรดในเลือดที่ไม่ตอบสนองต่อการรักษา ผู้ป่วยได้รับการวินิจฉัยขั้นสุดท้ายโดยการตรวจชิ้นเนื้อลำไส้เล็กด้วยกล้อง–จุลทรรศน์อิเลคตรอน พบมีความผิดปกติระดับ ultrastructure ที่เข้าได้กับโรค microvillus inclusion disease ผู้ป่วยได้รับการรักษาโดยใช้ cholestyramine, metronidazole, probiotics และ octreotide ผลการรักษาไม่สามารถลดปริมาณอุจจาระลงได้ ผู้ป่วยยังคงต้องได้รับสารอาหารทางหลอดเลือด และเสียชีวิตในที่สุดจากภาวะแทรกซ้อนของการให้สารอาหารทางหลอดเลือด ถึงแม้ว่าภาวะนี้จะพบได้ไม่บ่อย แต่ควรจะคิดถึง และให้การตรวจพิเศษต่อไป ถ้าเด็กมีอุจจาระเหลวเป็นน้ำเรื้อรังและไม่สามารถหาสาเหตุจากการตรวจทางห้องปฏิบัติการณ์เบื้องต้นได้

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