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CLINICAL CASE

Microvillous inclusion disease as a cause of severe congenital diarrhea. Case report

Enfermedad por inclusión microvellositaria como causa de diarrea congénita severa. Caso clínico

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Abstract

Introduction: Congenital diarrheas correspond to a severe and low frequency digestive disease, with a high mortality. They start a few days or months after birth, leading to intestinal insufficiency and dependence on parenteral nutrition. It must be highly suspected in newborns or infants with diarrhea and severe electrolyte disorders. The diagnosis is based on clinical, endoscopic, histologic and eventually genetic findings. Treatment is supportive with intensive correction of electrolyte imbalances as well as parenteral nutrition. **Objective:** To present a case report of congenital diarrhea identified as microvillous inclusion disease presenting in the neonatal period. **Case report:** Male patient currently 3 years of age, son of consanguineous parents. At 10 days of age presents a severe secretory diarrhea, requiring treatment in a critical care unit and parenteral nutrition. Initially he also presented with Fanconi syndrome, which improved afterwards. The suspicion of congenital microvillous inclusion was confirmed later by optic and electronic microscopy, and inmunohistochemistry. A succesful evolution was later achieved maintaining home parenteral nutrition after discharge. **Conclusion:** We present the first known case in Chile of congenital diarrhea due to microvillous inclusión disease and his evolution.

Keywords:
Intractable diarrhea infants;
Intestinal failure;
Microvillous inclusion disease

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Introduction

The microvillus inclusion disease belongs to the group of refractory diarrhea in infants that produce intestinal insufficiency during the first days or months of life. It is generated by a severe congenital alteration of the intestinal epithelium resulting in a massive watery diarrhea and a permanent malabsorption that normally lead to a lifelong dependency of total parenteral nutrition (TPN).

The microvillus inclusion disease was described for the first time in 1978 by David Andersen et al., who reported a group of 5 infants with severe persistent diarrhea of neonatal stating and common characteristic findings in the intestinal histology[1,2]. Nowadays its prevalence is estimated in <1:1000.000 and there are few known cases in the world[3]. The autosomal recessive inheritance is known and it is associated with consanguinity[4]. There is a slight preponderance of female gender. In general, the pregnancy and childbirth occur with no associated pathology, still oligohydramnios has been described in some cases.

There is a neonatal presentation with early onset during the first hours or days of life and a later apparition at 2-3 months[3]. The clinic is characterized by severe watery diarrhea of secretory type with massive volume losses up to 300 mL/kg/day and big amounts of electrolytes producing quickly the dehydration and serious metabolic imbalance. Moreover, there is an enzymatic deficit in the luminal edge that generates osmotic diarrhea.

Within differential diagnosis, other causes of intractable diarrhea in infants should be considered, such as congenital ones caused by transport defects, epithelial dysplasia or tufting enteropathy, autoimmune enteropathy, IPEX syndrome, as well as allergies, infections, and post infectious enteropathy[5,6].

For the diagnosis, a combination of optical and electronic microscopy of duodenum, jejunum, and colon are used. In the first one, with hematoxylin and eosin stain, it is observed a hypoplastic atrofia that may vary, accumulation of secretory granules with positive periodic acid Schiff (PAS) stain in the apical cytoplasm of enterocytes and no inflammatory infiltrate. The crypts still stay intact. The pathognomonic changes that are intracytoplasmic vacuoles with included microvilli and absence or shortage of microvilli in the luminal edge are recognized using the electronic microscopy. It also can be practice an immunoreactive stain that recognizes a neutral peptidase CD-10, that in this disease, is located within the cytoplasm of enterocytes unlike normal intestine and other intestinal pathologies, which it is normally found on the surface[8,9,10].

In 2008, a common mutation was identified in most of the patients in the MYO5B gene that codes for the Myosin Vb protein, which it is expressed in all epithelia and is involved in the protein transport towards cell surface and in the cell polarity[11,12,13,14]. Therefore, it is postulated that the impairment of the protein transport will be the cause of the disease, altering the correct development and the regeneration of the epithelial membrane. The severity of the disease is marked by the careful replacement of electrolyte losses and the TPN treatment. Multiple complications are described,, such as liver damage, nephrocalcinosis, delay in psychomotor development and dead within the first year of life, among others[15,16,17]. An intestinal transplant is a therapeutic option, alone or in combination with liver, even acceptable survivals can be achieved with TPN at home[18,19,20,21,22]. In the literature, there is a report of only one patient in which the long-term parenteral nutrition was successfully suspended[23]. The current survival described in a series of cases is 70%, with more than a half of patients who have received intestinal or liver-intestine combination transplants[21]. The greatest cause of death is the sepsis.

It is presented a case of congenital diarrhea identified as microvillus inclusion disease of neonatal presentation and its evolution.

Clinical case

36-weeks preterm born male infant with 27-years old first-time mom, with gestational diabetes and no others pathologic histories during the pregnancy. Caesarean section because of acute fetal distress. Apgar 9-9. Parents are blood relatives, the mother is an immediate niece of the patient's father. History of deceased infants in the family (the maternal grandfather's brothers) with no known diagnosis. He presented a respiratory distress syndrome and a screening was performed with negative infectious results, receiving empirical antibiotic treatment for 7 days. Diarrhea started with liquid stools, mucous, with no blood at 10 days of life, and severe dehydration.

He required an invasive ventilatory support, vasoactive drugs for 3 days, and empirical antibiotherapy to suspicious of unproven, necrotizing enterocolitis. The gastric tube feeding and TPN were initiated and it was obtained a laboratory study that showed a severe metabolic acidosis with a normal anion gap, hypokalemia, normal metabolic and negative infectious screening, a normal hormonal and immunity study, normal glycemia, and he was HIV-negative. Positive glucosuria and proteinuria. The patient continued with frequent mucous stools with a volume loss to diarrhea estimated in 190cc/kg/day, refractory at enteral fasting. Reducing substances in stools were positive; electrolytes in stools

with Na 120meq/L, CI 67meq/L, stool osmotic gap 30, compatible with secretory diarrhea. Congenital diarrhea with Fanconi syndrome cataloged as transitory was proposed as a diagnosis since subsequently glucosuria and proteinuria decreased. The upper digestive endoscopy was performed at the age of 4 months, finding in the duodenum an aspect compatible with villus atrophy and it was confirmed the final diagnosis of microvillus inclusion disease with optical and electronic microscopy and also immunohistochemistry study (see Figure 1). Since his admission receiving TPN, he has had multiple changes of the central venous catheter (CVC) due to catheter-related infections. The patient evolved with a macroscopic hematuria, evidencing nonobstructive, bilateral renal lithiasis, reason why he received an urinary alkalinizer. At 5 months he presented symptoms of acute abdomen, suspecting a volvulus, however, in the ward was confirmed a diffuse necrosis in a large part of the small intestine due to necrotizing enterocolitis, getting resected 120 cm, remaining 45 cm of jejunal intestine and 25 of distal ileum. At 6 months he presented a massive upper gastrointestinal bleeding, demonstrating a gastric ulcer, probably associated with a prolonged fasting, and a therapeutic endoscopy was carried out. At 10 months the patient was discharged, with Broviac catheter and PTN at home, receiving daily a large amount of additional supplements of electrolytes and bicarbonate (endovenous via: Sodium: 8 meq/kg, Potassium: 4 meq/kg, and Bicarbonate: 7 meq/kg/day. enteral via: Sodium bicarbonate: 6 meq/kg/day), along with iron in an intermittent way, and megadoses of vitamin D. He receives an enteral stimulus through gastrostomy with highly hydrolysate milk and chicken mash, and rice and some vegetables by mouth. Currently, he is 3 years old and is cared for by his parents at home. He has required some rehospitalizations due to sepsis associated with CVC, thrombophlebitis, obstructive bronchitis syndrome, and acute pyelonephritis. He presents compensated chronic malnutrition with low height (T/E: -2.76 z-score; P/E: -1.4 z-score, and P/T: 0.64 z-score) and language delay. He attends kindergarten and performances his daily activities with a backpack adapted to parental feeding. To date, no hepatopathy. Genetic counseling was provided to the parents.

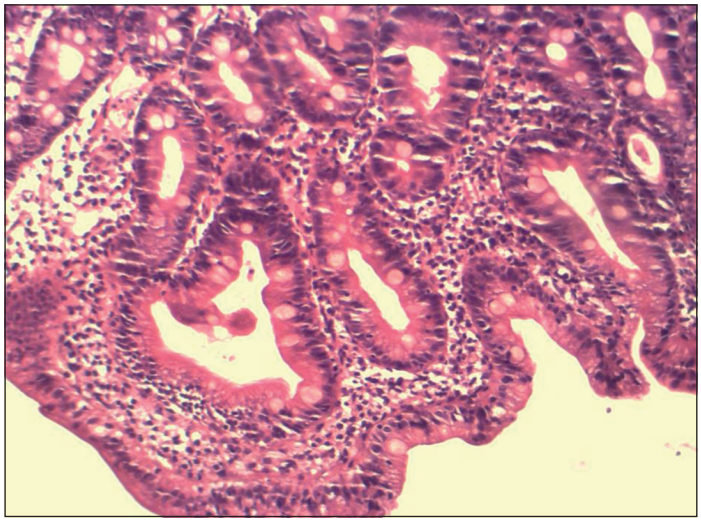

Figure 1a. Light microscopy, with Hematoxilina and Eosin stain, magnification 10x. Duodenal mucosa with subtotal villous atrophy, without inflammation.

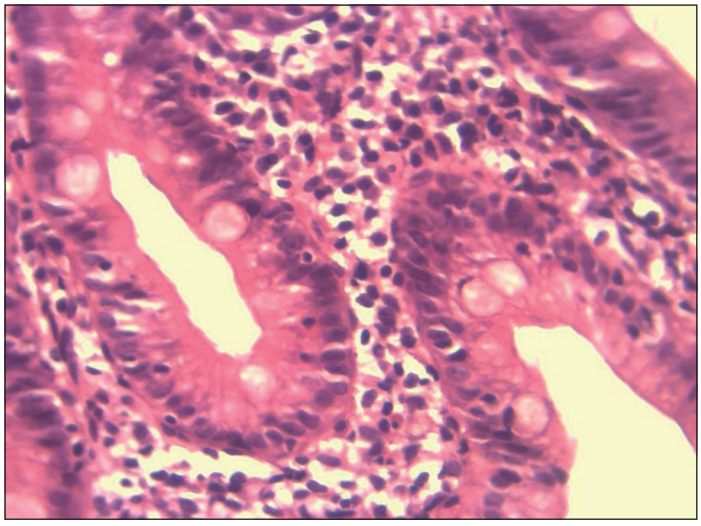

Figure 1b. Light microscopy, with Hematoxilina and Eosin stain, magnification 40x. Duodenal mucosa with subtotal villous atrophy, without inflammation.

Discussion

The congenital diarrhea of neonatal presentation means a rare and severe pathology that initially requires a careful stabilization with electrolyte replacement and then an exhaustive etiological research. In the presented case, it was discarded at first infectious, hormonal, immunological, and metabolic causes. Posteriorly, it was suspected microvillus inclusion disease due to the characteristic of secretory diarrhea, provided by the differential diagnosis with osmotic diarrhea (for example, due to an enzyme deficiency; see algorithm) and because of the quantified losses of electrolyte in stools, which were incompatible with other entities as congenital sodium or chloride diarrhea. The final diagnosis was achieved through optical and electronic microscopy, along with immunohistochemistry, with previously described characteristics in the reported cases in the world literature. The genetic analysis could also have helped, but it is not available in Chile yet. The Fanconi syndrome, mentioned in the world literature in two similar cases [15], was transitory and it was attri-

buted to tubulopathy due to severe dehydration. The nephrocalcinosis is a known complication related to intestinal malabsorption [16]. The necrotizing enterocolitis is also an associated entity published in a previous case, but the patient, in that case, had other risk factors as great prematurity and a fatal outcome. In our case, a short intestine was generated, it did not mean a major change in the patient management, mainly based on TPN.

Conclusion

It is presented the first case, to the best of our knowledge, of a patient with microvillus inclusion disease diagnosticated and managed in Chile and its evolution. Thanks to the implementation of TPN at home, it is provided an acceptable life quality for the patient and his family in the context of a severe congenital diarrhea with high mortality.

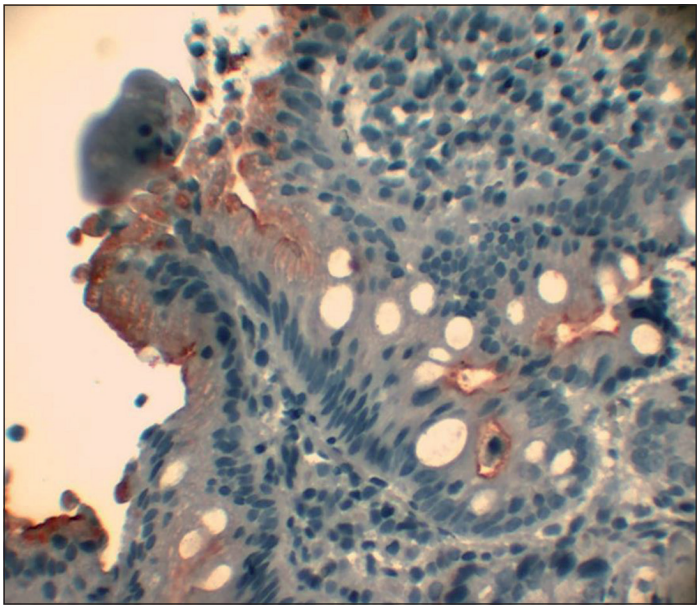

Figure 2. CD 10 Immunostaining. Intense marking CD10+ of the luminal line inside of the enterocytes, characteristic of the microvillus inclusion disease.

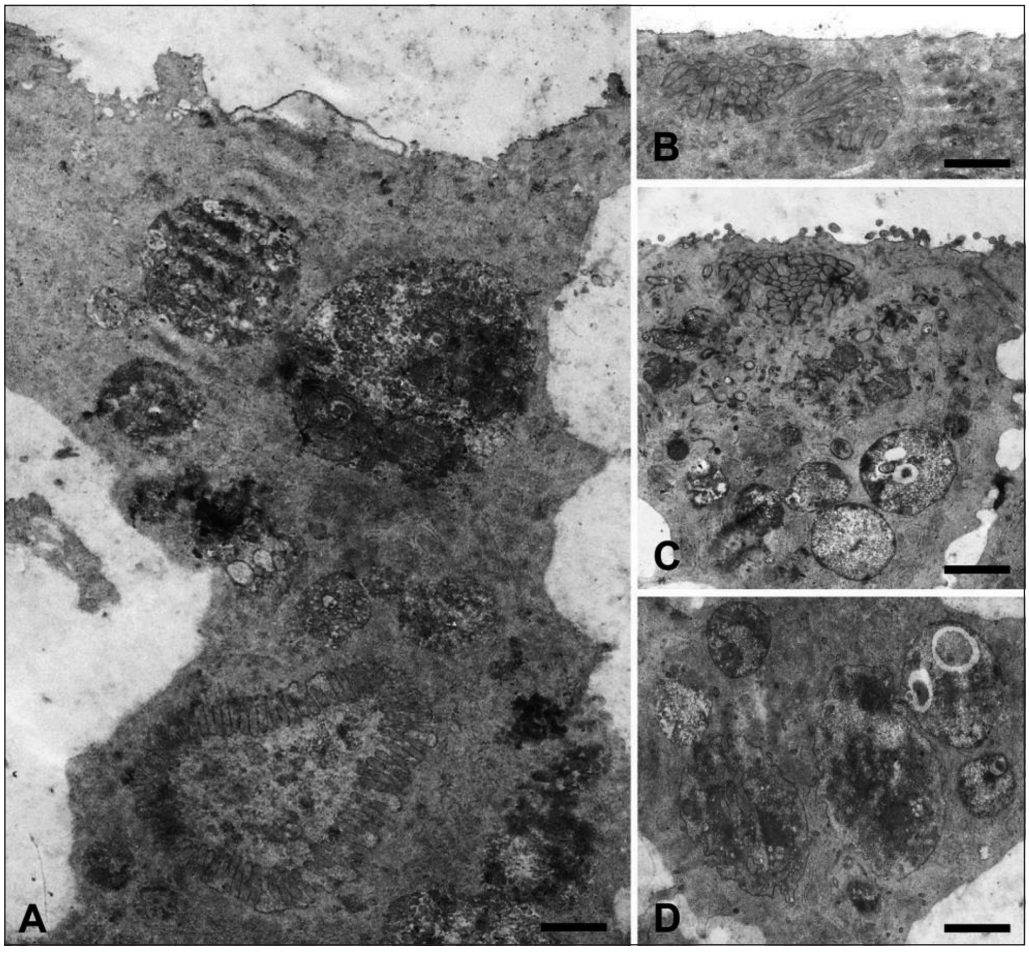

Figure 3a. Electron microscopy (markers=1um): **A.** Intestinal epithelial cell and his apical border without MV; inclusions and vacuoles with autophagy vesicles inside. **B.** Apical border with inclusiones. **C.** Few microvilli on the apical border, inclusiones and digestive vacuoles. **D.** Digestive vacuoles (autophagic).

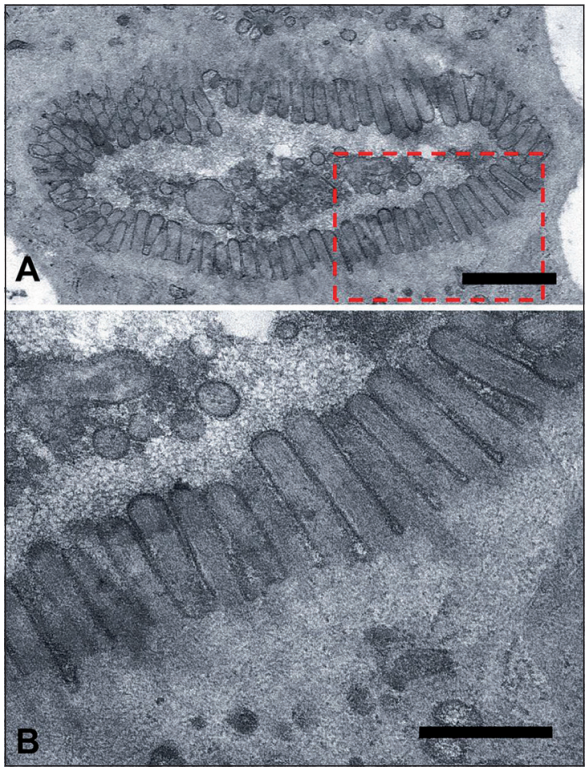

Figure 3b. Electron microscopy (Markers in A = 1 um; B = 0.5 um). **A.** Citoplasmic vacuole with microvilli. **B.** Magnification of picture A. Microvilli cover the luminal surface of the vacuole.

Ethical responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

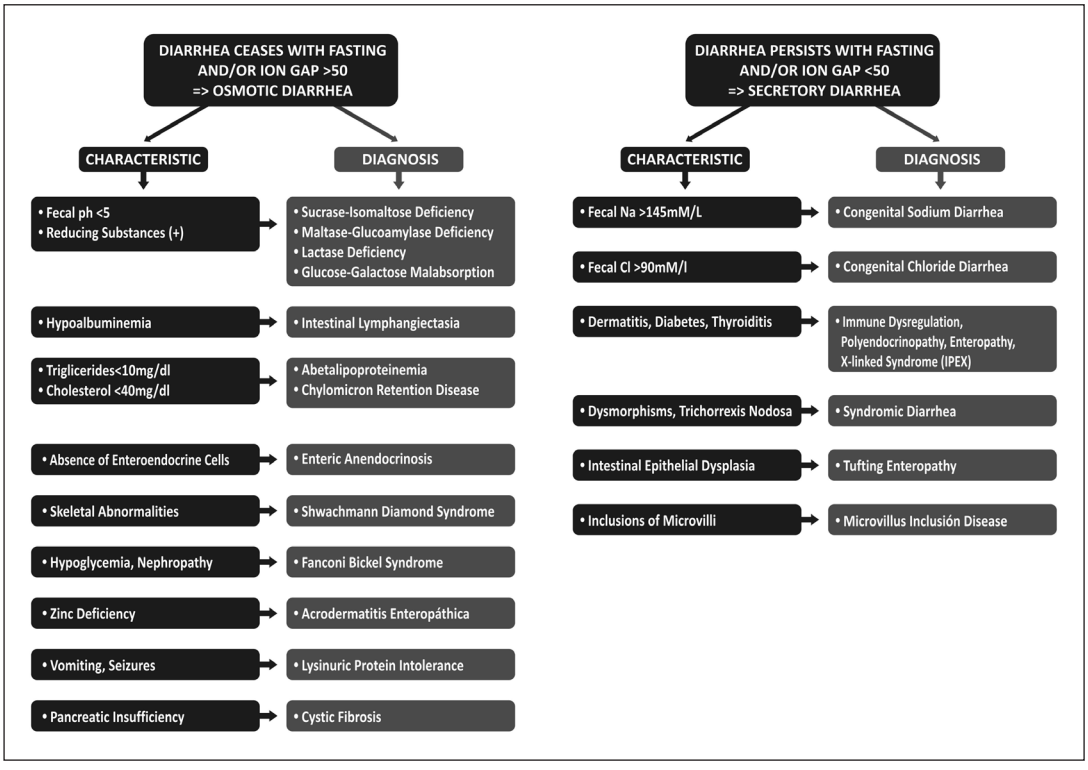

Figure 4. Algorithm for the differential diagnosis of congenital diarrhea using the stool osmotic gap.

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