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SEVERE CONGENITAL DIARRHEA SECONDARY TO TUFTING ENTEROPATHY. CASE REPORT

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Palabras clave: Diarrea neonatal; Recién nacido; Diarrea infantil; Anomalías congénitas; Enfermedades Intestinales; Enfermedades Raras.

María Angélica Wilches-Cuadros

Universidad del Rosario - School of Medicine
and Health Sciences - Department of Pediatrics
- Bogotá, D.C. - Colombia.

Laura González-Hakspiel

Paula Nausa-Suárez

María Paula Fernández

Paula Patiño-Ascencio

Alejandra Manrique-Guerrero

Universidad Autónoma de Bucaramanga -
Faculty of Health Sciences - Medical Program
- Bucaramanga - Colombia.

Ángela Milena Díaz-Díaz

Universidad Autónoma de Bucaramanga -
Faculty of Health Sciences - Medical Program
- Bucaramanga - Colombia.

Clínica FOSCAL - Pediatrics Service

- Floridablanca - Colombia

Derly Liseth Castro-Rojas

Centro de Inmunología y genética CIGE -
Medical Genetics Service - Medellín - Colombia

Corresponding author

Ángela Milena Díaz-Díaz. Departamento de Pediatría,
Clínica FOSCAL. Floridablanca. Colombia.

Email: adiaz558@unab.edu.co

RESUMEN

Introducción. La enteropatía en penacho es una causa rara de diarrea congénita en neonatos; esta se caracteriza por una alteración de la adhesión epitelial que ocasiona desprendimiento de enterocitos hacia el lumen y, en consecuencia, forma los característicos penachos. Se describe el caso de una paciente con esta patología.

Presentación del caso. Neonata de 15 días de vida, quien fue llevada por sus padres al servicio de urgencias de un hospital de tercer nivel debido a que desde su nacimiento tuvo deposiciones diarreicas y a causa de esto presentó deshidratación, pérdida de peso, acidosis metabólica e insuficiencia renal aguda. La paciente recibió manejo con alizaprida, loperamida, sulfato de zinc y probióticos, pero a los 75 días de tratamiento continuaba sintomática. Se le practicó una endoscopia de vías digestivas y una colonoscopia que mostraron aplanamiento de las vellosidades e infiltrado de células linfoides en la lámina propia. Los síntomas continuaron y la menor falleció a los 10 meses de nacida. El resultado del exoma *post mortem* reportó enteropatía en penacho.

Conclusiones. Ante la presencia de diarrea congénita, se debe sospechar de una enteropatía en penacho y considerar el estudio molecular temprano, pues este permite evaluar la posibilidad de realizar un trasplante intestinal o modificar el tratamiento según las necesidades de cuidado paliativo del paciente.

ABSTRACT

Introduction: Tufting enteropathy is a rare cause of congenital diarrhea in neonates. It is characterized by the abnormal distribution of epithelial adhesion molecules, which causes enterocytes to shed into the lumen, forming the characteristic tufts.

Case summary: A 15-day-old female neonate was taken by her parents to the emergency department of a tertiary care hospital due to diarrheal stools she had been experiencing since birth. The patient presented with dehydration, abnormal weight loss, metabolic acidosis, and acute kidney failure. She received treatment with alizapride, loperamide, zinc sulfate, and probiotics, but after 75 days of treatment she was still symptomatic. An upper tract endoscopy and colonoscopy were performed, finding flattening of the villi and lymphoid cells in the lamina propria. However, the symptoms persisted, and she died at the age of ten months. A post-mortem exome sequencing reported tufting enteropathy.

Conclusions. When congenital diarrhea is present, tufting enteropathy should be considered. An early molecular study would allow to evaluate the possibility of performing an intestinal transplant or modifying the treatment to meet the patient's palliative care needs.

INTRODUCTION

Congenital diarrhea is a rare disorder in neonates (1) and differs from acquired diarrhea due to its severity, chronicity, and dependence on nutritional support (2). This condition is caused by epithelial defects and alterations in neuroendocrine differentiation or immune dysregulation, digestion, and nutrient or electrolyte absorption or transport (1). It is classified as severe chronic diarrhea, with a high mortality rate, a difficult diagnosis, and an intractable course (3).

Tufting enteropathy is a rare cause of congenital diarrhea in neonates and is characterized by the abnormal distribution of epithelial adhesion molecules, which causes enterocytes to shed into the lumen, forming the characteristic tufts (3). The incidence of this disease in Europe varies from 1 case per 50 000 to 100 000 live births; however, a higher incidence is reported in patients of Arab origin (4).

The following is the case of a neonate with tufting enteropathy who presented with intractable diarrhea of infancy and died at 10 months of age despite receiving multiple treatments.

CASE PRESENTATION

A 15-day-old female neonate from Bucaramanga (Colombia), mestizo, was taken by her parents to the emergency department of a tertiary care hospital because due to explosive, abundant, watery, yellowish liquid stools without mucus or blood since birth. Seven days prior to the consultation, the patient presented postprandial vomiting, irritability, jaundice, and nursing strike, so the parents started supplementation with milk formula at home.

Relevant perinatal history included that this was the mother's second pregnancy, that she had adequate antenatal care and that the patient was born by vaginal delivery at 40 weeks, weighed 3 245 grams, and Rh incompatibility tests were positive.

The patient was admitted to the emergency room in fair health, with blood pressure of 61/38 mmHg, heart rate of 158 bpm, respiratory rate of 56 rpm, temperature of 35.4°C, oxygen saturation of 90% on room air, glucose level at 232 mg/dL, and weight of 2 800 grams (13% weight loss since birth). Physical examination showed sunken fontanelle, dry oral mucosa, marked intercostal retractions with scarce panniculus adiposus, scaphoid abdomen with hepatomegaly, hypotrophic limbs, and pallor on the elbows; the rest of the examination was normal. Due to the suspicion of late-onset neonatal sepsis, the girl was immediately hospitalized in the neonatal intensive care unit (NICU), where laboratory tests were requested and oxygen support, fluid resuscitation, and empirical antibiotic therapy were initiated.

The test results on admission reported a normal blood count with the following values: hemoglobin: 18.9 g/dL, hematocrit: 56.2%, leukocytes: 18970/mm³,

neutrophils: 6499/ μ L, lymphocytes: 8157/ μ L and platelets: 81000/ mm^3 . Prerenal acute kidney failure with creatinine of 1.61 mg/dL and BUN of 40.5 mg/dL was also identified. Total bilirubin was 5.91 mg/dL, direct bilirubin was 1.41 mg/dL, and indirect bilirubin was 4.5 mg/dL. C-reactive protein, transaminases, and electrolytes were normal and arterial blood gas levels showed metabolic acidosis with the following values: pH: 7.29; PaCO₂: 22.7 mmHg; PaO₂: 103.4 mmHg; HCO₃: 10.8 mmol/L; base excess: -13 μ mol/L. On the day of admission, two blood cultures were also taken, which were negative after 5 days of incubation.

Once stable in the NICU, enteral feeding was restarted; although it was initially tolerated, with a gradual increase in intake, the patient again presented with abundant liquid stools and hypovolemic shock. She was given alizapride (3 mg/kg/day for 8 days), loperamide (0.08 mg/kg every 12 hours for 8 days), zinc sulfate (5 mL every day for 10 days), and probiotics; however, no improvement was achieved.

After 15 days of hospitalization, the patient was assessed by the genetics department, which requested further tests to rule out inborn errors of carbohydrate metabolism, aminoacidopathies, metabolic acidemias, cystic fibrosis, among others. Seliwanoff's test was negative, while qualitative amino acid urine tests were positive for sodium nitroprusside. Plasma and urine amino acid quantification tests were also requested, which yielded nonspecific results (Tables 1 and 2).

Table 1 Altered quantitative plasma amino acids

Amino acid	Value obtained (μ mol/L)	Reference value (μ mol/L)
Aspartic acid	22	2-14
Glutamic acid	230	32-185
Serine	235	83-212
α -Aminoadipic acid	15	<5
Glycine	527	103-386
Sarcosine	9	<5
Arginine	179	30-147
γ -Aminobutyric acid	1	<1
α -Aminobutyric acid	37	4-30
Phenylalanine	103	31-92
Ornithine	206	19-139
Lysine	427	70-258

Source: Own elaboration.

Table 2 Altered quantitative amino acids in urine.

Amino acid	Value obtained ($\mu\text{mol}/\mu\text{ol}$ creatinine)	Reference values ($\mu\text{mol}/\mu\text{ol}$ creatinine)
Alanine	431	27-313
Glycine	2988.31	133-894
Valine	56.56	3-43
Isoleucine	23.57	2-21
Threonine	287.52	12-145
Serine	638.67	34-329
Phenylalanine	44.78	7-42
α -Aminoadipic acid	160.26	7-110
Ornithine	120.19	2-19
Lysine	549.11	4-80
Histidine	841.35	69-392

Source: Own elaboration.

At one week of age, the patient underwent an abdominal ultrasound, followed by a brain magnetic resonance imaging and echocardiogram two weeks later, all of which were normal. There were no cataracts in the fundus and the pilocarpine iontophoresis test (at three different times) was normal.

The patient was also assessed by the pediatric nephrology service at one month of life, which diagnosed high anion gap metabolic acidosis and negative urinary anion gap and suggested a high probability of an inborn error of metabolism rather than tubular acidosis.

After a 75-day hospital stay, during which she was readmitted to the NICU three times due to hypovolemic shock caused by diarrhea following the administration of various nutritional formulas, the patient, who was already 3 months old at that time, weighed 3.59kg and measured 52cm (standard deviations for weight-for-age, height-for-age and weight-for-height were -3.99, -4.03, and -0.61, respectively), which indicated failure to thrive. Additionally, chronic diarrhea and infectious episodes persisted.

At that point, she was evaluated by the pediatric gastroenterology service, which diagnosed intractable diarrhea of infancy and started treatment with ondansetron (0.15 mg/kg/dose for 5 days) and requested a pancreatic enzyme replacement therapy for 2 months (lipase), but no improvement was observed. Endoscopy and colonoscopy were also performed, identifying flattening of the villi in the bulb, in the second portion of the duodenum, and in the last 5 centimeters of the ileum mucosa. Biopsies were taken during these last two examinations, which were processed with electron microscopy, revealing ileum with lymphoid cells in the lamina propria, without microscopic abnormalities. Based on the results, ultrastructural changes suggestive of microvillous inclusion disease or altered lipid transport were ruled out.

As previously stated, the patient developed hypovolemic shock several times as a result of diarrhea, which required fluid resuscitation, prolonged total parenteral nutrition, and gastrostomy feeding. A new amino acid test showed altered aminoaciduria, as well as aminoacidemia with increased oligosaccharides in urine, for which exome sequencing was indicated.

At 10 months of age, vascular access was lost and the only treatment option available was a transhepatic catheter, which her parents rejected due to the high morbidity associated with the procedure. The day after this event, the child died without a known diagnosis, but 2 months later, the exome sequencing report indicated a mutation and deletion of the *EPCAM* gene (Table 3), which encodes an epithelial adhesion molecule expressed in the cell membrane. It has been reported that these pathogenic variants cause tufting enteropathy with subsequent diarrhea. Figure 1 shows the clinical course and management of the patient during her hospital stay.

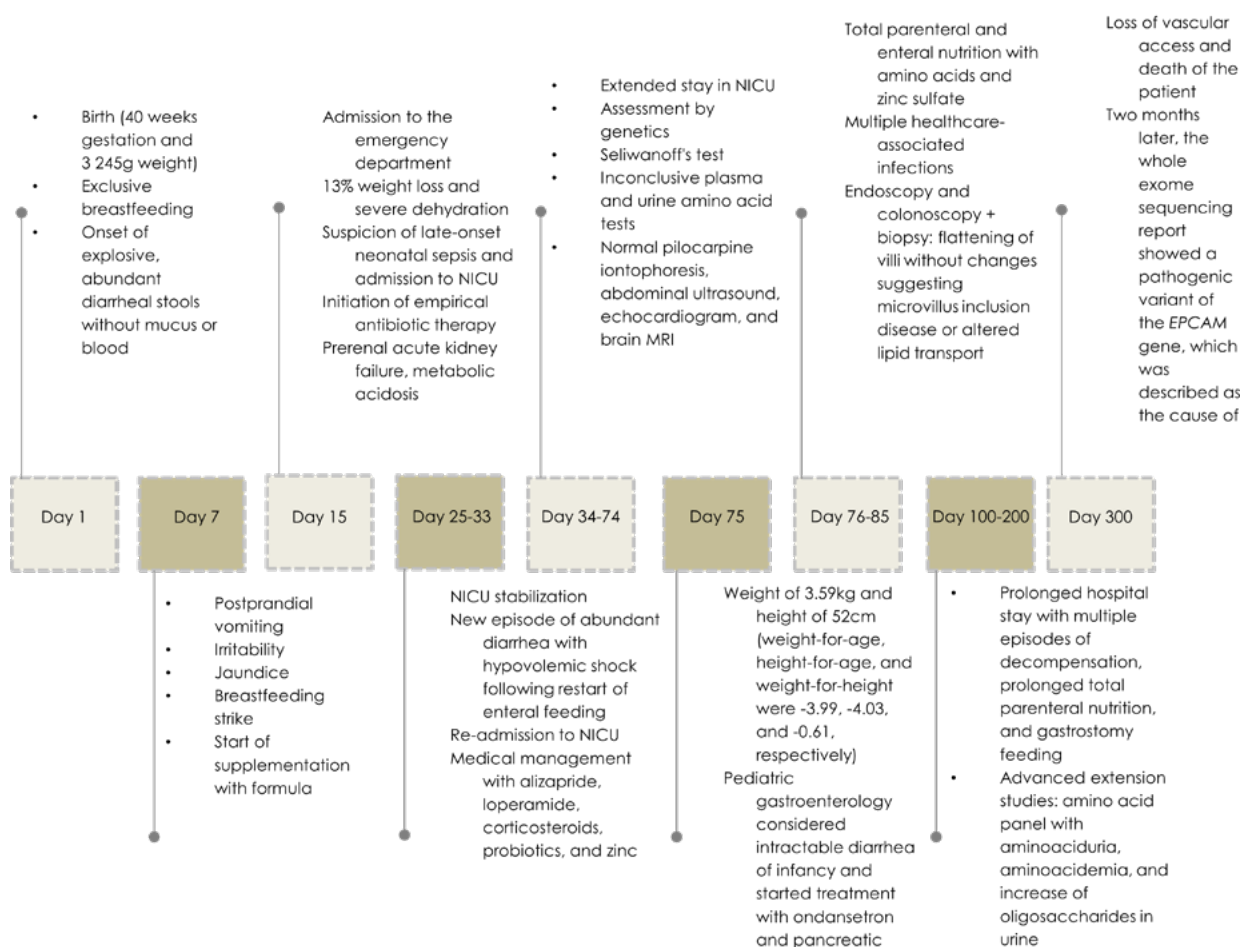


Figure 1 Timeline.

NICU: neonatal intensive care unit; NMR: nuclear magnetic resonance; SD: standard deviation.

Source: Own elaboration.

Table 3 Exome sequencing.

Gene	Variant	Zygosity			Inheritance	MAF (%)	Prediction <i>In silico</i>	Classification
		Case	Mother	Father				
<i>EPCAM</i>	c.492-3C>G;p.?	het.	-	het.	AR, AD	-	Affecting splicing	Unknown meaning
<i>EPCAM</i>	Del.exon 1-3	het.	het.	-	AR, AD	-	-	Probably deleterious

HET: heterogeneous; AR: autosomal recessive inheritance; AD: autosomal dominant disorder; MAF: minor allele frequency.

Source: Own elaboration.

DISCUSSION

Tufting enteropathy, also known as intestinal epithelial dysplasia, is an autosomal recessive genetic disorder that is usually caused by mutations in the *EPCAM* gene, a type I transmembrane surface glycoprotein antigen expressed on the basolateral membrane of multiple epithelial and plasma cells (5). This gene is located in the 2p21 locus, and when it mutates, it causes abnormal development of the intestinal mucosa (6), which is caused by changes in epithelial adhesion molecules and causes enterocytes to shed into the lumen, resulting in the formation of tufts (7). This disease occurs during the first few months of life and manifests with chronic watery diarrhea that persists despite intestinal rest (8) and feeding with breast milk or formula (5). It usually causes a deterioration in the patient's growth and is related to other alterations involving the epithelium (9).

Although mutations in the *SPINT2* gene have also been described, the most involved gene, as in the case presented here, is *EPCAM* (10). It encodes a typical adhesion molecule that is connected to the actin cytoskeleton, is directly associated with the tight junction protein claudin-7 and facilitates intestinal barrier formation by recruiting claudins in cell-to-cell junctions (5). Most mutations are located in exons 3, 4, or 5 and lack the extracellular domain or the transmembrane domain. Some deletions in the gene or exon have also been reported, which are related to the degree of involvement caused by the disease (10).

Mutations associated with tufting enteropathy appear to lead to the loss of cell-surface *EPCAM* protein (4), which is consistent with the immunopathological findings of the present case. Since this is an autosomal recessive disorder, mutations in both alleles are required to express the disease. The exome report in the present case showed a variant of uncertain significance and another probably pathogenic, which, in addition to the clinical findings, allow confirming diagnosis of this condition.

The characteristic feature of tufting enteropathy is the presence of focal epithelial "tufts" composed of tightly packed enterocytes that surround the apical

plasma membrane and result in a tear configuration of the affected epithelial cell (7). Hypoplasia and total or partial villi atrophy are commonly associated complications. Moreover, abnormalities of the basement membrane, accumulation of secretory granules in the apical cytoplasm of enterocytes without inflammatory infiltrate, crypt hyperplasia, and normal or slightly increased density of inflammatory cells in the lamina propria may be observed (5,11,12).

In patients with this disease, electron microscopy identifies pathognomonic changes such as the presence of intracytoplasmic vacuoles with microvilli and absent or abnormal microvilli at the luminal border (13). In cases of tufting enteropathy, the number of intraepithelial lymphocytes is not increased, unlike what happens in celiac disease or autoimmune enteropathy (8). In addition, sometimes the characteristic tufts may be absent in early childhood, as in the case of the patient reported here, so a biopsy is required to establish the correct diagnosis (6,9).

The differential diagnoses for diseases with persistent diarrhea and villous atrophy that should be ruled out include congenital chloride diarrhea, congenital sodium diarrhea, and microvillous inclusion disease. In the latter, besides atrophy, positive periodic acid-Schiff (PAS) stained granules are observed in the apical surface of enterocytes with atrophic bands that represent microvillus inclusion in histology (9,12,14). The first two differ in that there is usually no history of polyhydramnios in tufting enteropathy, but there is a history of consanguinity and no electrolyte alterations in blood and feces (9). Similarly, tufting enteropathy differs from glucose-galactose malabsorption in that the latter improves with one hour of fasting and symptoms can be managed through diet modification (9,14), and from autoimmune enteropathy in that it does not respond to immunosuppressive therapy (9).

Tufting enteropathy rapidly threatens the patient's life due to dehydration and the water-electrolyte disorders it causes (9), as in the reported case, which resulted in the patient's death due to metabolic decompensation. In patients with this disease, administering elemental formulas or hydrolyzed proteins exacerbates diarrhea, so they quickly become dependent on permanent parenteral feeding.

Regarding the management of tufting enteropathy, intestinal transplantation is indicated in patients with liver disease associated with intestinal failure with recurrent catheter-related sepsis (indication still under debate) and thrombosis of two or more central vascular access sites (15). Genetic counseling should be offered since this condition is related to the presence of parental consanguinity or heterozygous carrier status in asymptomatic parents (9). In cases in which transplant is contraindicated, long-term palliative care with home parenteral nutrition is prescribed (9).

Finally, molecular studies are recommended because they have improved diagnostic techniques and reduced the performance of invasive and costly procedures (5).

Among the strengths of this case report, it is noted that a pathogenic approach was taken using different advanced extension tests, which clarified

the various etiological possibilities and, eventually, established a diagnosis of the disease. The patient also received a multidisciplinary treatment, allowing for a comprehensive approach to her disease. On the contrary, limitations include the scarcity of data on the subject due to the few cases reported and the delay in obtaining the results of advanced studies, which led to a late diagnosis that did not allow making interventions aimed at modifying the prognosis and/or improving the patient's survival.

CONCLUSION

Congenital diarrhea is a rare disease that usually appears in the neonatal period. It is severe, chronic and difficult to treat, and it predisposes to multiple complications due to the nutritional involvement of the patient, resulting in high morbidity and mortality. Furthermore, due to the rarity and scarcity of cases reported in the literature, knowledge about this disorder is limited, as is its diagnosis.

In cases of refractory congenital diarrhea, genetic defects in enterocytes should be suspected early in order to perform a molecular analysis, as these new diagnostic methods are more efficient and have reduced invasive and costly procedures.

In this sense, in the presence of congenital diarrhea, tufting enteropathy should be suspected, and an early molecular study should be considered because it allows evaluating the possibility of performing an intestinal transplant or modifying the treatment based on the patient's palliative care needs.

To date, no specific treatment for tufting enteropathy has been described; however, a timely diagnosis allows for the possibility of performing, if indicated, an intestinal transplant on an experimental basis or providing timely therapy to avoid complications such as advanced life support measures and prolonged suffering of patients and their families. Genetic counseling should also be offered to parents because this is an autosomal recessive disease.

ETHICAL CONSIDERATIONS

Informed consent was obtained from the mother of the patient, who authorized the publication of the medical history data for the preparation of this case report.

CONFLICTS OF INTEREST

None stated by the authors.

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