

# A case of protracted diarrhea in a newborn: a diagnostic challenge

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## Abstract

Congenital diarrhea comprises a broad range of pathologies and often requires a thorough workup and immediate treatment. Although rare, microvillous inclusion disease (MVID) should be included in differential diagnosis of this presentation in the neonate. We report the case of a 36-week newborn who developed signs of severe dehydration and lethargy, requiring fluid resuscitation and total parenteral nutrition. MVID was diagnosed by recognition of profuse secretory diarrhea after an exhaustive etiological investigation, confirmed by DNA analysis.

## Introduction

Protracted diarrhea presenting in the neonatal period poses a diagnostic challenge not only because it is a rare and potential life threatening condition, but also because its differential diagnosis is broad.<sup>1-4</sup>

Congenital diarrheal disorders are a group of rare inherited enteropathies that usually present in the neonatal period as a severe and chronic diarrhea, frequently requiring parenteral nutrition support and should be included in the differential diagnosis of this condition.<sup>3,5</sup> Microvillous inclusion disease (MVID) is one of the most severe congenital diarrheal disorders, caused by a genetic defect in enterocyte differentiation and polarization.<sup>2,5,6</sup> It is an autosomal recessive disease and results from a molecular defect in the MYO5B gene, coding for a protein of the cytoskeleton determinant of cell polarity.<sup>7</sup> Its exact prevalence is unknown although it is more common among consanguineous families.<sup>3,6</sup>

The diagnosis is made by typical findings on small bowel biopsies, which show villus atrophy with relatively little crypt hyperplasia and an absence of marked inflammatory infiltrate in the lamina propria. There is atrophy of the enterocyte brush border with accumulation of

periodic acid-Schiff (PAS) positive secretory granules within the apical cytoplasm on light microscopy and typical microvilli inclusions in the cytoplasm on electron microscopic (EM).<sup>3,8</sup>

## Case Report

A 36-week gestation female caucasian newborn was delivered to a 26-year-old primigravida mother by spontaneous vaginal delivery. Pregnancy was uneventful. Parents were not related and reported to be healthy. There was no family history of gastrointestinal disease.

Amniotic fluid was stained with thick meconium and resuscitation included tracheal suctioning and positive pressure ventilation. Birth weight was 2800 g (50<sup>th</sup> percentile) and the Apgar score was 4, 6 and 7 at 1, 5 and 10 min respectively. After stabilization she was transferred to the neonatal intensive care unit on nasal continuous positive airway pressure. Her physical examination was unremarkable except for marked pallor. Full blood count showed normocytic normochromic anemia with 10.6 g/dL hemoglobin and 31.9% hematocrit, C-reactive protein, kidney function tests and serum electrolyte levels were within normal limits. There were no signs of hemolysis or fetomaternal hemorrhage on flow cytometric quantification. Histopathological examination of the placenta revealed chorioamnionitis. She received intravenous antibiotics and blood transfusion.

After the first few hours she was stable, with no respiratory distress, on spontaneous breathing. On day two she was well and oral feeding was started with both breast and formula feeding. Less than 24 hours later, she was irritable, lethargic, with signs of severe dehydration and had lost 25% of her body weight. Paradoxically she seemed to have an adequate urine output. Investigation showed hyperchloremic metabolic acidosis (pH 7.18; HCO<sub>3</sub> 12.3 mmol/L; base excess -14.9 mmol/L, Cl<sup>-</sup> 129 mmol/L) due to hypernatremic dehydration (Na<sup>+</sup> 155 mmol/L). Glucose and lactate levels were within normal ranges and sepsis workup was negative. Some loose watery bloodless stools with mucus were then noticed. She was kept *nil per os*, given volume expansion with normal saline and initiated fluid and sodium bicarbonate replacement therapy. She was then given total parenteral nutrition (TPN) via a central venous line, on which she became dependent.

Attempts to deliver oral feeding resulted in weight loss, hyponatremia and metabolic acidosis. Urinary catheterization was performed and we realized that the diarrhea was so profuse that it was initially misinterpreted as urine. It persisted despite fasting with a stool output up to 120 ml/kg/day, which was replaced

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with intravenous fluids. She also had high sodium requirements, up to 10 mmol/kg/day. Stool reducing substance was negative, fecal pH was 8, Na<sup>+</sup> concentration in stools was high (83 mmol/L, normal 20-30 mmol/L), fecal ion gap [Stool osmolality - 2 × (stool Na<sup>+</sup> + stool K<sup>+</sup>)] was <50. Persistence of diarrhea during fasting with elevated stool sodium content and a decreased fecal ion gap confirmed a secretory diarrhea pattern. On day 19 she initiated octreotide, with no improvement. By this time she also developed cholestasis and a catheter-related sepsis. An exhaustive etiological investigation was performed including repeated blood, stool and urine cultures (with culture for cytomegalovirus), metabolic screen, immunoreactive trypsinogen levels, renal, hepatic and endocrinological testing, specific serum cow milk IgE levels, testing for immunodeficiency and autoimmune enteropathy, cerebral, abdominal, cardiac and renal ultrasound, the results of which was all normal. A congenital enterocyte defect, specifically MVID seemed the most likely diagnosis; therefore an endoscopy with duodenal biopsy was planned and performed on day 12. Duodenal sections revealed an unspecific inflammatory enteropathy. A further biopsy performed when she was three-month old showed microvillus atrophy, but again there was no evidence of abnormalities of the enterocyte cytoplasm detected by PAS staining and

EM examination did not show significant changes.

DNA sequencing revealed compound heterozygous mutations of MYO5B gene, confirming the diagnosis of MVID. Both parents were heterozygous carriers and genetic counseling was offered. She was discharged home at three months of age with TPN, with liver function deterioration by five months. She died at the age of nine months due to septic shock secondary to a catheter-related infection.

## Discussion and Conclusions

Microvillous Inclusion Disease is characterized by severe diarrhea, which typically appears in the first days of life (early onset form); a late-onset form is also described, beginning in the first three months.<sup>3</sup>

In its typical form MVID causes severe dehydration and metabolic acidosis, which need immediate treatment.<sup>3,8-10</sup> Diarrhea is secretory in type but mucosal atrophy can cause osmotic diarrhea during feedings, making oral alimentation impossible in the most severe type.<sup>3</sup> Stools are so watery and profuse that can be mistaken with urine,<sup>1</sup> as occurred in this case.

Patients' survival depends on fluids and TPN and apart from supportive measures there are no currently effective options except for intestinal or combined liver and intestinal transplantation, which have been successfully used recently in these patients.<sup>11,12</sup>

Combined analysis with light and transmis-

sion electronic microscopy showing typical histological findings is the gold standard for diagnosis.<sup>3,13</sup> However, lesions are sometimes focal or delayed,<sup>13</sup> which can explain the absence of typical histological changes in this case.

The authors emphasize the difficulties encountered upon the diagnosis of a newborn with MVID. In a case of protracted diarrhea of the newborn, after a thorough negative workup, this diagnosis should be considered even if biopsy findings are inconclusive.

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