Clinical Case Report

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Congenital intestinal atresias with multiple episodes of sepsis

A case report and review of literature

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Abstract

Introduction: Hereditary multiple intestinal atresia associated with severe combined immunodeficiency (MIA-SCID) is a very rare disease caused by deleterious mutations in the tetratricopeptide repeat domain-containing protein 7A gene *TTC7A*. It is characterized by intestinal obstruction, sepsis, and a poor prognosis. Insights into phenotype–genotype correlations could help to guide genetic counseling and increase our knowledge of the natural history of this disease.

Case presentation: We report the case of a newborn in which his fetal magnetic resonance imaging showed jejunal atresia and microcolon and an abdominal x-ray at birth confirmed intestinal obstruction. The clinical course was complicated by multiple episodes of sepsis, and laboratory investigations showed SCID. The genetic analysis identified a homozygous c.53344_53347 mutation in the *TTC7A* gene compatible with MIA-SCID syndrome. The patient required 3 operations because of new intestinal atresias in the first months of life. She underwent bone marrow transplantation at 8 months of age but died of liver failure secondary to graft-versus-host disease.

Conclusion: Immunologic assessment and genetic screening for *TTC7A* mutations are important in patients with MIA. Greater knowledge of the functions of the TTC7A protein will have important therapeutic implications for patients with MIA-SCID syndrome.

Abbreviations: MIA = multiple intestinal atresia, TPN = total parenteral nutrition, SCID = combined immunodeficiency.

Keywords: exome, gastrointestinal tract, neonatal sepsis, parenteral nutrition

1. Introduction

Hereditary multiple intestinal atresia (MIA) (OMIM #243150) is a severe, very rare, congenital disease that involves multiples atretic injuries in diverse segments of the gastrointestinal tract, from the stomach to the rectum.[1,2] Approximately 10% to 15% of cases occur in association with severe combined immunodeficiency (SCID) and recurrent sepsis (MIA-SCID syndrome,).[3,4] According to a PubMed search, just 21 cases of MIA-SCID have been published[4–13] since the first case was described by Moreno et al[5] in 1990. All the cases to date have involved disruption of the epithelial barrier along the gastrointestinal tract, inversion of apicobasal polarity of the epithelial cells, and signs of intestinal epithelial apoptosis. Total parenteral nutrition (TPN) dependence and repeated episodes of sepsis are associated with a very poor prognosis and death occurs before the age of 2 years in 70% of patients.[4–13]

In 2013, Samuels et al[6] identified the causative gene of MIA, the tetratricopeptide repeat domain-containing protein 7A gene *TTC7A*, through whole-exome sequencing. Since then, 20 mutations have been identified: skipping of exons 7, 12, and 18, p.L823P, p.Y105fs, p.K254fs, p.L823P, p.S678X, p.Q712X, p.L399P, p.Q277X, p.A832X, p.S539L, p.Y336X, p.L493fsX13, p.A558GfsX7, p.E71K, p.Q526X, and p.A832T.[7–13] However, the relation between *TTC7A* mutations and phenotype in patients with MIA-SCID syndrome remains to be clarified.

We present a complicated case of MIA-SCID in an infant girl. The girl's parents provided informed consent to the publication of this case. There were no other ethical requirements.

2. Case report

A preterm female infant was born by vaginal delivery to healthy nonconsanguineous parents at 32 weeks of gestation. This was the first pregnancy of the mother, aged 35 years. The antenatal ultrasound at 6 months of gestation had shown a cystic malformation of the pelvis (25 × 94 cm) suggestive of dilated colon. Subsequent magnetic resonance imaging of the fetus confirmed jejunal atresia and microcolon. Chorionic villus sampling showed a normal female karyotype (46 XX).

The birth weight was 1610 grams and the 10-minute Apgar score was 9. On admission, the patient had stable respiratory and

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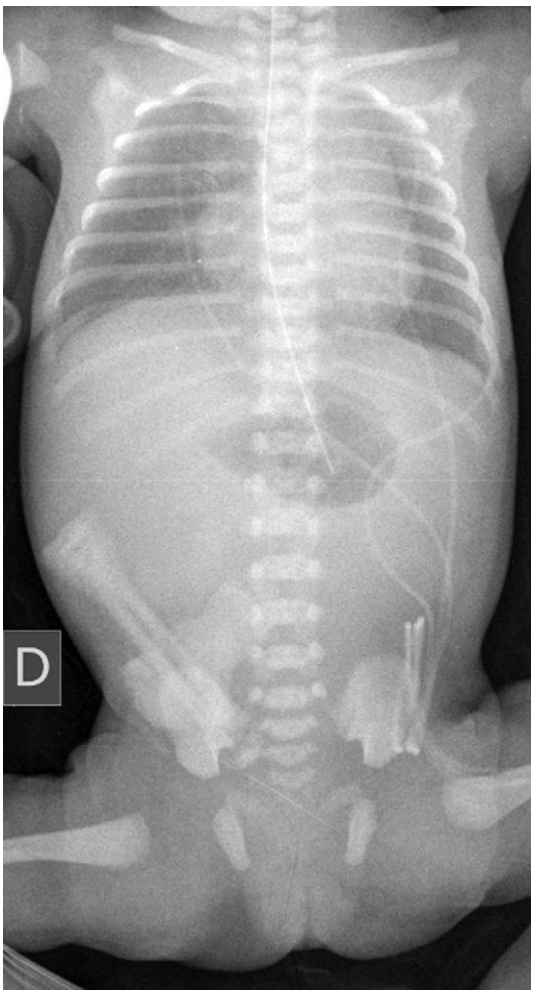

Figure 1. Abdominal x-ray at birth confirming intestinal obstruction.

hemodynamic status. Her abdomen was soft and nondistended and palpation did not elicit pain. There were no palpable masses. An abdominal x-ray at birth confirmed intestinal obstruction associated with bilious nasogastric tube drainage (Fig. 1). The first surgical intervention, performed on day 1 of life, showed a dilated stomach and duodenum in addition to multiple jejunal and ileal atresias and intestinal malrotation. Jejunostomy and ileostomy were performed with resection through 20 cm of cecum (Fig. 2). Histopathological examination showed the classic aspect of intestinal lumen fibrosis but normal innervation. TPN and antibiotic therapy were established in the postoperative period.

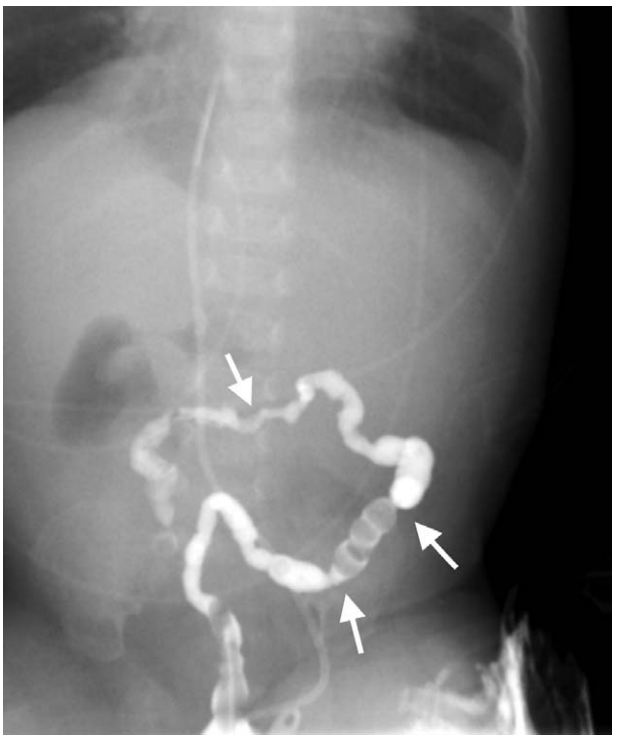

Figure 3. Ileal atresias detected by lower gastrointestinal tract radiography in the first month of life, after the first operation.

At 1 month of life, after a failed attempt to start trophic enteral feeding, a new ileal atresia with secondary microcolon was detected by lower gastrointestinal tract radiography (Fig. 3). A second surgical intervention identified additional atretic lesions in the ileal segment requiring ileocecal valve resection and another anastomosis. The remaining small bowel was about 25 to 30 cm in length. A skin abrasion around the stoma was detected after

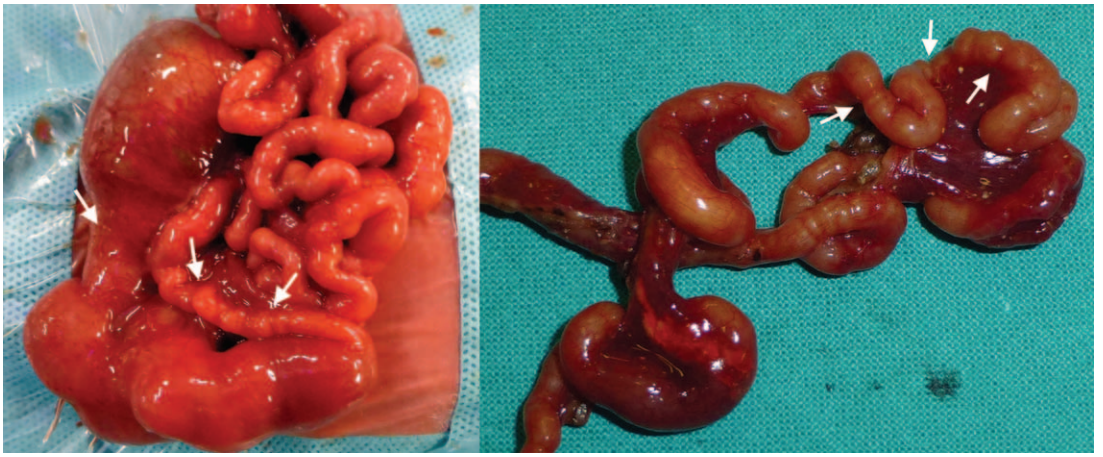

Figure 2. Multiple intestinal atresias observed in the macroscopic examination during the first surgical intervention. (A) Preresection; (B) postresection.

Table 1

Laboratory results for patient with multiple intestinal atresia-severe combined immunodeficiency syndrome at 3 months of life.

Parameter	Level	Normal range
Lymphocytes, cells/μL)	1200	4000–6100
$CD3^+$, cells/μL	450	2400–3300
$CD4^+$, cells/μL	312	1600–2200
$CD8^+$, cells/μL	96	820–1600
$CD19^+$, cells/μL	276	1000–1600
$CD16/56^+$, cells/μL	220	270–1100
IgG, mg/dL	35	223–1099
IgM, mg/dL	11	0–73
IgA, mg/dL	8	0–100

this second operation. The wound worsened despite topical antibiotics, antifungals, and steroids, and at 3 months of life, the gastrointestinal tract was reconstructed and the ostomies were closed by end-to-end anastomosis. Bilious nasogastric tube drainage continued to be observed, even with TPN. Additional evidence of intestinal atresia was detected by contrast radiography. The patient's clinical course was complicated by multiple episodes of sepsis caused by central lines or intestinal bacteria, such as *Enterobacter cloacae* and *Pseudomona aeruginosa*. Laboratory investigations at the age of 3 months showed severe T-cell lymphopenia and profound hypogammaglobulinemia (Table 1), confirming the diagnosis of SCID. Genetic analysis confirmed a homozygous c.53344_53347 mutation in the *TTC7A* gene, compatible with MIA-SCID syndrome. At 4 months of life, the patient developed moderate hepatic impairment, with laboratory results showing a maximum conjugated bilirubin level of 3.3 mg/dL, GOT 130 UI/L, GPT 120 UI/L, and prolonged prothrombin time. The patient underwent bone marrow transplantation at 8 months of life but died of liver failure secondary to graft-versus-host disease.

3. Discussion

We have presented a new case of MIA-SCID with a homozygous c.53344_53347 mutation in the *TTC7A* gene. Clinical manifestations of hereditary MIA develop in the first 3 months of life, but in most cases, they are present from birth.[3–8] Atresias in MIA can occur in any segment of the gastrointestinal tract, but they are most common in the small bowel. Treatment consists of early surgical intervention to restore the continuity of the gastrointestinal tract through resections and anastomoses. Surgery and short-bowel syndrome, however, are an indication for TPN, which is associated with an increased risk of cholestasis, liver cirrhosis, and hepatic failure.[13,14] Patients with MIA also have altered immune system development and function. Only 6 living patients with MIA-SCID have been described in the literature. The oldest of these, presented by Bigorgne et al,[8] was 8 years old and had severe T-cell and B-cell and mild natural killer cell lymphopenia. Transplantation was contraindicated due to severe bronchiectasis.

There is limited experience with attempts to restore the immune system in patients with MIA-SCID syndrome. Gilroy et al[15] described donor immune reconstitution after liver-small bowel transplantation in a 16-month-old boy with MIA-SCID. The boy achieved complete enteral autonomy and normal liver function and showed no evidence of allograft rejection 2 years post-transplant. Three of the cases of living patients with MIA-SCID were described by Chen et al[7] in 2013. The patients were 12, 22, and 24 months old and had multiple episodes of sepsis except the 22-month-old patient achieved reconstitution of T-cell immunity after bone marrow transplantation at 3 months of life. The last known living patient was described by Agarwal et al[10] in March 2014. At the time of writing, the infant was 5 months old and had undergone multiple surgical interventions and 4 episodes of sepsis.

Our patient died at 8 months of life following bone marrow transplantation. The cause of death was liver failure secondary to graft-versus-host disease, a high-risk complication of transplantation.[16,17] She had a homozygous c.53344_53347 mutation in the *TTC7*A gene. This homozygous mutation had been described in 4 other patients with a similar phenotype, and they all died within the first year of life.[6,7,9] Other mutations identified in MIA-SCID syndrome have been associated with significant phenotypic variations. A recent study showed *TTC7A* mutations in 5 children from 3 unrelated families with very early onset inflammatory bowel disease associated with apoptotic enterocolitis.[11] None of them, however, had MIA-SCID syndrome, suggesting genotype-phenotype correlations in this disease.

In conclusion, *TTC7A* mutations should be investigated in patients with multiple intestinal atresias with or without SCID. Certain homozygous mutations may suggest a more common phenotype. Surgery is currently the treatment of choice for MIA, but it is associated with multiple complications. Particular attention should be paid to intestinal sepsis, which is the main cause of death in these patients. Further clarification of the role of the TTC7A protein in both the immune system and intestinal mucosa could improve the prognosis of patients with hereditary MIA and SCID.

Author contributions

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Validation: Olalla López-Suárez.
Writing – original draft: Adolfo Bautista-Casasnovas, María-Luz Couce.
Writing – review & editing: María-Luz Couce.

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