CASE REPORT

Two new mutations of the CLMP gene identified in a newborn presenting congenital short-bowel syndrome

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Summary Congenital short-bowel syndrome (CSBS) is a rare neonatal pathology associated with poor prognosis and high mortality rate. We describe a newborn presenting CSBS intestinal malrotation and chronic intestinal pseudo-obstruction syndrome (CIPS), compound heterozygous for two previously unreported heterozygous mutations in Coxackie and adenovirus receptor-like membrane protein (CLMP) gene, one in intron 1 (c.28+1G>C), the other on exon 4 (c502C>T, p.R168X). Both mutations are predicted to be pathogenic, leading to impaired splicing and the appearance of a premature stop codon, respectively. Our case is remarkable in that it concerns two heterozygous truncating mutations associated with a good clinical prognosis with a favorable cerebral and gastrointestinal outcome and a substantial enteral input at 8 months of age, despite a small intestine measuring only 35 cm.

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http://dx.doi.org/10.1016/j.clinre.2015.12.018
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We describe a newborn presenting congenital short-bowel syndrome (CSBS) intestinal malrotation and chronic intestinal pseudo-obstruction syndrome (CIPS), compound heterozygous for two previously unreported mutations in the Coxsackie and adenovirus receptor-like membrane protein (CLMP) gene.

Antenatal ultrasound examinations were normal and the girl, second child of related parents (third-degree cousins), was born at term weighing 3200 g. She was exclusively breast-fed. The meconium passed within 36 hours after birth, but the first yellow stools appeared only on day 5. Frequent postnatal yellow regurgitations were noticed.

On day 13, she presented upper gastrointestinal occlusion syndrome prompting transfer to the pediatric emergency unit. She had lost more than 10% of her birth weight and experienced bilious vomiting after meals. Her abdomen was bloated, tender, but supple, with no sign of hernia. She was asthenic, but apyrexic and hemodynamically stable. Abdominal ultrasonography showed normally positioned mesenteric blood vessels and no evidence of volvulus or pyloric stenosis. Feeding was continued via nasogastric tube at constant rate. Upper gastrointestinal transit time measured on day 22 (Fig. 1) suggested intestinal malrotation with intermittent volvulus. Laparoscopic surgery was performed, including division of Ladd’s bands, repositioning of the intestine and mesentery, and appendectomy.

Five days post-surgery, bilious vomiting recurred. Plain abdominal radiography showed several dilated jejunoileal loops with air-fluid levels. A second laparoscopy on day 27 revealed a short (35 cm), distended, atonic small bowel; ileocecal valve and colon were normal. Duodenal biopsies were normal on standard histologic and immunohistochemical examinations, with ganglion cells present in the myenteric plexus.

Gastrointestinal signs indicative of CIPS, including problems in initiating enteral feeding and impaired intestinal motility, persisted up to 3 months of age.

Parenteral nutrition was provided via central venous catheter. Despite CIPS, oral reflexes were stimulated from birth, allowing increasing oral food intake.

At 8 months, the child’s growth was normal. She received parenteral nutrition during 15 hours every day, additional spoon-fed pureed fruits and vegetables accounting for half her daily food intake. Intestinal transit was spontaneous, with no recurrence of CIPS, four firm stools being voided daily.

Cognitive skills and emotional and social behaviors were consistent with age.

Laboratory tests revealed no cytolyis or cholestasis and no notable fluid and electrolyte balance anomalies. Hepatic echography showed neither steatosis nor lithiasis.

A genetic screen identified two heterozygous mutations in CLMP, one in intron 1 (c.28+1G>C) inherited from the father, the other on exon 4 (c.502C>T, p.R168X) inherited from the mother. Both mutations are predicted to be pathogenic, leading to impaired splicing and the appearance of a premature stop codon, respectively. Neither has been reported previously, or is present in any of the available human genome variant databases.

Discussion

CSBS is a rare neonatal pathology associated with poor prognosis and high mortality rate. Only 37 cases have been reported since the first description by Hamilton et al. in 1969 [1]. CSBS is defined by a small intestine less than 75 cm long (or 60 cm, according to author) [2]. In our patient, it measured only 35 cm.

The pathogenesis of CSBS is not fully understood. Organogenesis of the middle segment of the primitive intestine occurs between 5 and 10 weeks of gestation, starting by elongation of the intestinal loops, followed by their physiological herniation into the umbilical cord, double rotation and finally reintegration into the fetal abdominal cavity. Hamilton et al. suggested that in CSBS, elongation, rotation and herniation of the small intestine are interrupted or delayed due to lack of space within the umbilical cord [1]. In 96% of cases, CSBS is associated with intestinal malrotation [3].

A defect in neuroenteric development was postulated by Tanner et al. given the myenteric plexus abnormalities observed on autopsy [4]. As in our patient, CSBS is often associated with various intestinal motility disorders [5].

In several reported cases, CSBS was associated with other congenital malformations including hypertrophic pyloric stenosis, appendiceal agenesis, aperistalsis, dextrocardia, hemivertebrae and persistent ductus arteriosus [6—9].

Van Der Werf et al. demonstrated that mutations in CLMP cause a recessive form of CSBS [10]. CLMP encodes a tight-junction membrane protein, and is expressed in the intestine during embryonic development. Mutations in CLMP prevent normal positioning of this protein on the cell membrane. Studies in zebrafish showed that such mutations resulted in less proliferation of the small intestinal

Figure 1 Upper gastrointestinal transit on day 22.
cells during human development, leading to a shortened small intestine at birth and absence of goblet cells in the intestinal epithelium [10]. Our patient was compound heterozygous for two previously unreported CLMP gene mutations. Most CSBS patients present private truncating mutations, and no genotype/phenotype correlation has been established.

The usual clinical picture of CSBS comprises bilious vomiting, poor weight gain, diarrhea or signs of gastrointestinal obstruction. Onset of intestinal volvulus associated with acute mesenteric ischemia is rare. Hasosah et al. suggested that a short small intestine might prevent significant twisting and ischemia of intestinal loops [3].

In retrospect, we recognize that during the first laparoscopic operation, resolution of volvulus was unexpectedly easy and surgery duration was shorter than usual. In laparoscopic surgery for volvulus, the possibility of CSBS should therefore be considered if repositioning of the intestine and mesentery is “too easy”.

Care of children presenting CSBS, or acquired short-bowel syndrome, is based on prolonged parenteral nutrition, despite its associated non-negligible morbidity and mortality. Early introduction of enteral feeding is indispensable to rapidly reinforce mechanisms favoring adaptation of the short small bowel [11–13]. Semi-elemental diets containing hydrolyzed proteins and oligosaccharides, and providing lipids partly as medium-chain triglycerides are appropriate. Long-chain triglycerides stimulate mucosal hyperplasia and biliopancreatic secretions.

The prognosis of CSBS patients has improved with progress in therapeutic nutrition. Based on the 12 cases reported since 2000, survival beyond one year of age is 66%, compared to 24% before 2000.

The severity of CSBS seems to depend on the type of genetic abnormalities. CSBS patients with loss-of-function mutations in CLMP could have a phenotypic form restricted to the intestine with a reduced length of the small intestine (30 to 54 cm) and with an earlier in life diagnosis made, whereas patients with mutations in Filamin A (FLNA) are more likely to have multiple congenital abnormalities, but a longer small intestine (55 to 235 cm). Chromosomal abnormalities have also been described in cases of CSBS associated with multiple congenital abnormalities: (achenia, dextrocardia, hemivertebrae and persistent ductus arteriosus) [14].

Our case is remarkable in that it concerns a child with CSBS achieving a highly favorable cerebral and gastrointestinal outcome with substantial enteral input at 8 months of age, despite a small intestine measuring only 35 cm and two previously unreported mutations in CLMP. Finding two heterozygous truncating mutations associated with a good clinical prognosis does not imply a favorable prognosis for all compound heterozygotes. Further research might reveal such correlations.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

We especially acknowledge all the physicians (Dr Cremlieux, Billiemen, Destombre, Trapes), the surgeons (Varlet, Lopez) and the geneticists (Touraine, Alves, Hofstra) who participated in the diagnosis and care of the baby.

We also thank Dr. Paula Harry, PhD for her writing assistance.

Of course, we finally thank the parents of this baby who permit us to report this case.

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