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Congenital short bowel syndrome: systematic review of a rare condition

Elisa Negri [a,*], Riccardo Coletta [a,b], Antonino Morabito [a,c]

[a] Department of Pediatric Surgery, Meyer Children's Hospital, University of Florence, Viale Pieraccini 24, 50139 Florence, Italy
[b] School of Environment and Life Science, University of Salford, Salford, United Kingdom
[c] Dipartimento di Neuroscienze, Psicologia, Area del farmaco e della Salute del Bambino NEUROFARBA, University of Florence, Viale Pieraccini 6, 50121 Florence, Italy

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ABSTRACT

Background: Congenital short bowel syndrome (CSBS) is a rare gastrointestinal disorder caused by intrauterine reduction of small bowel length whose etiology is still unknown. Chronic diarrhea, vomiting, and failure to thrive are the most important complications, arising from less absorptive intestinal surface. This review examines clinical features and outcomes of CSBS patients.
Methods: A PubMed and EMBASE research on CSBS was performed. Inclusion criterion was congenital short bowel diagnosis in a range of ages between 33 weeks of gestational age and 15 years old (IQR 38 days). Exclusion criteria were history of atresia of any part of the gastrointestinal tract and extensive surgical bowel resections. Qualitative and quantitative variables were collected and analyzed. Data were expressed in mean and IQR.
Results: Sixty-one patients were identified (38 males, 23 females) from 1969 to date. Mean bowel length was 58.24 cm (IQR 37.5). Malrotation of the midgut was seen in 98.4% of cases. Our data showed an interesting trend in improving the survival rate of these patients (from 28.5% before 2008 to 75% in the period after 2008). Sepsis was the most frequent cause of death reported (57.9%). Interestingly, 18 patients were genetically analyzed, finding mutations either in FLNA gene (38.8%) or in CLMP gene (61.1%).
Conclusions: CSBS is a condition that seems to be related to an autosomal recessive (CLMP) or an X linked (FLNA) type of inheritance. Advance in medical management seems to have improved survival of these children in recent years. Further genetic studies can better understand the causes of this disease aiming to create personalized treatment.
Type of study: Systematic review.
Level of evidence: Level IV.

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Contents

Congenital short bowel (CSB) is defined as a shortage of small bowel, present from birth, in children with intestinal continuity preserved, which leads to short bowel syndrome (SBS). It is a multisystemic disorder caused by malabsorption of nutrients as a result of inadequate length of small intestine, which is usually less than half expected for gestational age [1]. This disease has still an unknown etiology and its prevalence seems to be <1/1,000,000 [2].

Common features of CSBS include abdominal distension, chronic diarrhea, vomiting and failure to thrive. These signs are common to other pathologies and so this contributes to the difficulty in diagnosis. Unfortunately this condition can still lead to mortality, even if advances in surgical and medical management have showed an interesting trend in improving the survival rate of patients affected.

* Corresponding author at: University of Florence, Viale Pieraccini 24, 50139 Florence, Italy.
E-mail address: elisa.negri@unifi.it (E. Negri).

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The aim of this paper is to collect all data available about this pathology in an organized way and to identify common features and any key patterns to tackle CSBS in future patients. Furthermore, several etiological theories have been proposed over the past few decades and these will be analyzed.

1. Methods

A PubMed and EMBASE search of the literature was undertaken for all reported cases of CSBS using terms "congenital short bowel" and "congenital short gut". All papers that were directly reporting cases/series and reviews about CSBS were included in the study. Articles written in English and data about non-English papers, obtained through English reviews, were considered for the purpose of this study.

Inclusion criterion was congenital short bowel diagnosis in a range of age between 33 weeks of gestational age and 15 years old (IQR 38 days). Patients with history of gastrointestinal atresia and extensive surgical bowel resections, leading to SBS, were excluded.

Data were recorded in an organized chronological order in a Microsoft Excel database in preparation for our analysis. We divided patients in two groups, because according to literature, survival of SBS patients has increased with the introduction of target lipid parenteral nutrition, which occurred approximately in 2008 [1].

Patient's data were expressed in mean, IQR and percentage. Means were calculated for intestinal length and age at diagnosis. Percentage means were calculated for: gender, survival, parenteral nutrition usage, familiarity, consanguinity between parents and presence of malrotation of the midgut.

The biggest problem in data collection was publication bias, because there was a great variability in the availability of data reported in different articles screened. Variables not described were reported as not available (N/A). It is also apparent that descriptions of some patients are duplicated through subsequent publications. In these cases we consider the most recent one and the earlier articles were examined for additional details.

A Preferred Reporting items for Systematic Reviews and Meta-analyses (PRISMA) checklist was followed in the construction of the manuscript [4].

2. Results

Sixty-one patients were identified from 1969 to date, described in 38 full text articles. Intestinal length was reported in 53 cases, 38 male (62.3%) and 23 females (37.7%). The average mean bowel length was 58.24 cm (IQR 37.5). Age at diagnosis was included between 33 weeks of gestational age and 15 years old.

Malrotation of the midgut was seen in all but one case (98.4%). Fifty cases were diagnosed by laparotomy, 1 by laparoscopy and in 1 case barium meal is used alone for diagnosis. In 62% of patients a radiological examination was performed before surgery.

Signs or symptoms of functional obstruction and/or malabsorption were reported in 53 cases such as abdominal distension (96.2%), diarrhea (37.7%) and failure to thrive (77.3%).

Associated anomalies were found in 57.4% of CSBS patients such as bowel adhesions or bands (11 cases), pyloric hypertrophy (11 cases), persistent ductus arteriosus (PDA) (6 cases), central nervous system malformations (5 cases), mesenterium commune (4 cases) and absence of appendix (3 cases).

Interestingly, a simultaneous reduction of small bowel and colon length was reported in 3 cases. Four patients showed episodes of rectal bleeding.

Four patients underwent laparotomy for bowel occlusion caused by volvulus of ileum. In all these cases the intestine was vital and volvulus was reduced without intestinal resection, finding at the same time a small bowel pathologically short.

Twenty-four patients were reported to be alive at time of publication.

Considering cases published before 2008, 15 patients, out of 49, survived (30.6%). Of these 9 were thriving on a regular oral diet at follow up, 3 required mixture of parenteral and enteral nutrition and in 3 patients data about feeding outcome were not reported (N/A).

Analyzing publications after 2008, there was a much brighter outlook for survival; we identified 9 out of 12 children who survived (75%). Nutritional outcome was reported in 8 cases, that needed PN associated with oral nutritional support. The main reason for patients that did not receive PN was death at a very early age. These results are summarized in Table 1.

Surgical procedures were performed in only two cases. One underwent bowel-lengthening procedure and the technique used was the longitudinal intestinal lengthening and tailoring (LILT); nevertheless he died at 1 month of age for unspecified causes [37]. In the second patient small bowel tapering was performed at the age of 11 and at the age of 17 he remained in partial PN, but he expanded the amount of food he consumed orally [43].

Causes of death were described in 20 cases and they were mainly related to infective complications. Sepsis was reported in 11 cases. Other causes explained were: subocclusion (3 cases), malabsorption (3 cases), chest infection (1 case), convulsion plus cardiac arrest (1 case) and gastrointestinal bleeding (1 case).

A familial occurrence was discovered in 70.5% of patients affected by congenital shortage of bowel and all of these were siblings. Parents of 11 patients were consanguineous.

Eighteen patients included in the review were genetically analyzed. Genomic Deoxyribonucleic acid (DNA) was isolated from peripheral blood lymphocytes. Gene sequences of interest were amplified using Polymerase chain reaction and compared with the reference genomic sequence. Different homozygous and compound heterozygous losses of function mutations for the Coxsackie and Adenovirus receptor-like membrane protein (CLMP) were identified in 11 CSBS patients. This gene is located on chromosome 11 encoding a transmembrane protein that colocalizes with tight junction proteins and act as an adhesion molecule [5]. Eight cases were female and three males (Table 2).

In other seven male patients, a mutation in FLNA gene was found on X chromosome encoding the cytoskeletal protein filamin A. Filamin A is a widely expressed filamin that regulates cell shape by cross linking actin filaments and plays an important role in cell signaling and migration in response to environmental changes. FLNA has been reported to play an important role in vascular development and cardiac morphogenesis, but its role in intestinal development is still unclear [5].

This mutation is identified with an X linked pattern of inheritance (except for case described by Siva et al. where it occurred for the first time in the family) [6] (Table 3).

As previously noted by Gonnaud et al. the severity of CSBS seems to be related with the type of genetic abnormalities. Patients with mutation in CLMP presented a pathological phenotype restricted to the intestine with a length of small bowel included between 26 cm and 76 cm, respectively 10% and 31% of what is expected for gestational age. Differently patients with mutation in FLNA presented multiple congenital abnormalities, usually involving central nervous system and a longer length of intestine both as an absolute (45 cm–237 cm) and as a % of the expected (18%–33%) (Tables 2–3).

Gargiulo et al. described the association of mutation in FLNA with short intestine and chronic idiopathic intestinal pseudoobstruction. They analyzed full thickness ileal and colonic biopsies finding abnormal argyrophilic neurons in the myenteric and submucosal plexus [42].

3. Discussion

Several theories have been proposed to answer the elusive question of what causes CSBS. A comprehensive definition of short bowel syndrome can help to understand this rare disease. In fact SBS and CSBS

Table 1
Result

Case	Year of Publication	Bowel length (cm)	Age at presentation	PN usage	Outcome	Cause of death	Nutritional outcome
1	1969 [16]	40	7 months	N	**A** > 7 y.o.		Normal diet
2	1969 [16]	30	3 weeks	N	**D** at 1 month	N/A	
3	1970 [10]	30	3 months	Y	**D** at 5 months	Pneumonia and pulmonary hemorrhage	
4	1973 [11]	70	7 weeks	Y	**D** at 20 weeks	N/A	
5	1973 [28]	42	3 days	N	**D** at 35 days	Malabsorption	
6	1974 [34]	106	22 days	N/A	**D** at 25 days	N/A	
7	1974 [35]	40	5 days	Y	**D** at 2 months	N/A	
8	1974 [35]	45	15 days	Y	**D** at 7 months	N/A	
9	1974 [35]	70	N/A	N/A	**D** at 4 days	N/A	
10	1974 [35]	25	N/A	N/A	**D** at 3 weeks	N/A	
11	1976 [9]	40	1 day	N	**D** at 1 day	Convulsion and cardiac arrest	
12	1976 [9]	75	6 days	Y	**D** at 5 months	Chest infection and septicemia	
13	1976 [40]	70	18 days	N/A	**D** at 22 days	Subocclusion	
14	1976 [40]	N/A	7 days	N/A	**D** at 16 days	Subocclusion	
15	1976 [40]	50	15 days	N/A	**D** at 7 months	Subocclusion	
16	1976 [41]	N/A	N/A	Y	**D** at 5 months	Sepsis associated with TPN	
17	1976 [41]	60	N/A	N	**D** at 6 weeks	N/A	
18	1978 [36]	65	N/A	N	**D** at 5 months	N/A	
19	1984 [12]	65	18 days	Y	**D** at 2 mouths	Gram negative sepsis	
20	1984 [12]	72	6 weeks	Y	**A** > 5 y.o		22 months: lactose free normal diet
21	1984 [18]	45	Unknown	Y	**D** at 3 months	Malabsorption	
22	1984 [18]	45	1 day	N	**D** at 6 weeks	N/A	
23	1984 [26]	24	32 days	Y	**D** at 55 days	Pseudomonas aeruginosa sepsis	
24	1984 [26]	27	2 days	N/A	**D** at 5 months	N/A	
25	1985 [31]	45	1 day	Y	**D** at 2 months	Malabsorption	
26	1986 [13]	69	5 weeks	Y	**A** > 7 y.o		28 months: total enteral nutrition
27	1990 [3]	112	1 month	N	**D** at 1 month	Gastrointestinal bleeding	
28	1990 [3]	70	6 h	Y	**D** at 6 months	Klebsiella sepsis	
29	1990 [3]	237[a]	3 months	Y	**A** > 18 y.o		High calorie diet
30	1991 [27]	54	2 months	Y	**A** > 4 y.o.		4 years: normal food intake
31	1993 [37]	30	2 days	Y	**D** at 4 months	N/A	
32	1993 [37]	39	N/A	Y	**D** at 6 months	N/A	
33	1993 [37]	30	N/A	Y	**D** at 1 month	N/A	
34	1996 [38]	30	1 day	Y	**A**		TPN
35	1997 [25]	50	1 day	Y	**A** > 3 y.o		N/A
36	1998 [17]	25	4 days	Y	**D** at 6 months	Pneumonia, sepsis	
37	1998 [39]	35	2 days	Y	**D** at 9 weeks	Gram negative sepsis	
38	1999 [32]	47	9 days	Y	**A** > 1 y.o.		N/A
39	2001 [15]	42	1 day	Y	**D** at 5 months	Severe liver dysfunction and sepsis	
40	2001 [15]	51	3 days	Y	**D** at 1 month	Fulminating sepsis	
41	2001 [15]	95[a]	2 months	N/A	**A** > 14 y.o.		N/A
42	2001 [15]	35	2 days	Y	**D** at 9 weeks.	Gram - sepsis	
43	2002 [6]	228.6 [a]	N/A	Y	**A** > 40 y.o.		35 years: total enteral nutrition
44	2004 [29]	20	4 days	Y	**A**		5 months: total enteral nutrition
45	2004 [23]	56	4 months	Y	**A**		Parenteral and enteral nutrition
46	2006 [30]	30	5 days	Y	**A** > 7 y.o.		Total oral feeding
47	2007 [42]	N/A	3 days	Y	**A** at 18 y.o.		Parenteral and enteral nutrition
48	2007 [42]	N/A	1 day	Y	**D** at 8 mounts	N/A	
49	2008 [14]	50	6 weeks	Y	**A** > 2 y.o.		24 months: regular oral diet
50	2010 [24]	25	26 days	Y	**D** at 26 days	Severe disseminated sepsis	
51	2010 [43]	115[a]	2 weeks	Y	**A** > 19 y.o.		17 years: PN, expanded the amount of food he consumes orally
52	2010 [43]	45	20 w.g.a.	N	**D** 33 w.g.a.	N/A	
53	2010 [43]	68	N/A	N	**D** at 6 weeks	N/A	
54	2011 [33]	80	12 weeks	Y	**A**		PN and oral nutritional support
55	2012 [19]	N/A	N/A	Y	**A**		N/A
56	2012 [19]	N/A	N/A	Y	**A**		N/A
57	2012 [19]	N/A	N/A	Y	**A**		N/A
58	2012 [19]	N/A	N/A	N/A	**A**		N/A
59	2016 [20]	35	13 days	Y	**A** > 8 months old		8 months: PN for 15 h every day and enteral nutrition
60	2016 [5]	76	3 months	N/A	**A**		N/A
61	2016 [5]	26	38 days	N/A	**A**		N/A

Legend: Y = yes; N = no; A = alive; D = death; N/A = not available; w.g.a = weeks of gestational age; y.o = years old.
[a] In these cases bowel was measured respectively at 14, 6, 15 and 10 years old.

can be considered multisystemic conditions caused by suboptimal absorption of nutrients owing to inadequate small intestinal length [1].

Normal intestinal length is best expressed as a percentage of predicted intestinal length for gestational age rather than the absolute length in centimeters. Struijs et al. studied 108 patients between 24 weeks of gestational age and 5 years old undergoing laparotomy and determined values for all predictor variables: postconception age, weight and height. Small bowel length increased from a mean of 70 cm in those aged 24 to 26 weeks postconception to 423.9 cm in those aged 49 to 60 months [7].

Table 2
Results

Case	CLMP type of mutation	Sex	Bowel length (cm)	Associated conditions
30	Homozygous deletion of 12,483 bp including exon 2	F	54	Common mesentery
35	Missense variant located in exon 4 leading to an amino acid substitution [c.410G > A;p.(C137Y)] and a splice site variant located two base pairs upstream of exon two (c.29-2A > G)	F	50	None
38	Homozygous del (with presumed inversion) in intron 1	M	47	Gastroesophageal reflux
46	[c.230 del A (p.E 77 Gfsx24)], exon 3 heterozygous frameshift c.821G > A, exon 6 Heterozygous splice site mutation	F	30	N/A
49	c.666C > T(p.R222X), exon 5 homozygous nonsense mutation.	M	50	None
55	c.371 T > A(pV124D), exon 3 homozygous missense mutation	M	N/A	N/A
56	Homozygous del (with presumed inversion) in intron 1	F	N/A	N/A
57	c.666C > T (p. R222X), exon 5 homozygous nonsense mutation	F	N/A	N/A
59	2 Heterozygous mutations: intron 1 (c.28 + 1 > C), exon 4 (c502C > T, p. R168X)	F	35	None
60	Homozygous nonsense variant in exon 4 [c.508c > T;p.(R170*)]	F	76	Ureteropelvic junction obstruction
61	Homozygous nonsense variant in exon 4 [c.508c > T;p.(R170*)]	F	26	Ureteropelvic junction obstruction

Legend: genetic mutations; F = female; M = male; N/A = nonavailable.

The actual length of small intestine required for optimal absorption is still controversial; however, bowel length < 100 cm in the first year of life is regarded as abnormal. Less than 40 cm traditionally requires therapy according to the practice of most centers [8].

Intestinal malrotation and intestinal obstruction are 2 quite prominent features of congenital short bowel syndrome. Both are investigated by contrast study and follow through tests [9–11]. It is thought that the malrotation may be a cause of early embryological problems concerning growth of the digestive midgut and the resulting vascular occlusion [11]. It's important to underline that in our review in the one case that was noted that malrotation was not commented on, it was not excluded, and so may well have been present [6]. According to these, we can state that in cases where congenital short bowel syndrome is suspected, an upper gastrointestinal contrast study should be done to investigate malrotation, which is almost universally present. If malrotation is found, an open or laparoscopic Ladd's procedure is indicated to prevent intestinal obstruction.

Reworking what we know thanks to the literature on SBS, we think that it could be also very useful to perform mucosal biopsies to evaluate bowel in functional terms of absorptive capacity. The human small intestine is organized with a proximal-to-distal gradient of mucosal structure and nutrient processing capacity. Certain nutrients undergo site-specific digestion and absorption, such as iron and folate in the duodenum/jejunum vs vitamin B12 and bile salts in the ileum. Depending on the segment(s) of intestine missed, malabsorption can be nutrient specific (eg, vitamin B 12 or fat) or sweeping, with deficiencies in energy, protein, and various micronutrients [45]. Understanding the histological characteristics of the CSBS remnant bowel, may help clinitians to predict long term nutritional needs. This is important to individualize patient management and to predict parenteral nutrition dependence.

Diarrhea, vomiting and failure to thrive are essential signs and symptoms indicative of the illness, and should certainly be looked for when questioning the diagnosis of CSBS [13,14]. No other intestinal deviations have been noted with this condition. A rare association between synovial lipomatosis and CSBS was noted in a patient with 20-year history of painless swelling of the knees, wrists, and hands [6].

CSBS has still no defined etiology. The first hypothesis revolves around looking at the embryological development of the primitive midgut between weeks fifth and tenth. The primitive midgut (digestive tube) undergoes considerable elongation and rotation through 180° and is contained within the intraumbilical coelom. By week 10 the tube returns to the abdominal cavity [13,15,16]. Dorney et al. were the first to propose that if the primitive midgut was not fully contained within the intraumbilical coelom throughout this gestation period, then it would consequently result in curtailment of the small bowel length, as the process of elongation and rotation would be very limited [13]. It has also been suggested that vascular occlusion or insult to the primitive midgut during in utero development may cause injury to the small bowel and hence at birth cause a shortened bowel length [14,17]. Recently, the role of a genetic component has also been widely postulated by several authors. The literature on this subject seems to suggest an autosomal recessive pattern of inheritance as both genders are affected by the condition. Interestingly, many CSBS cases seem to occur in siblings or via the product of unaffected consanguineous parents [3,9,15,18].

Van Der Werf et al. described in 7 CSBS patients a loss-of-function mutation in Coxsackie and adenovirus receptor-like membrane protein (CLMP). CLMP is a tight-junction associated protein that is expressed in the intestine of human embryos throughout development. To understand how loss of function of CLMP leads to CSBS, a series of zebrafish experiments was performed. CLMPa ortholog was expressed in the intestine of zebrafish embryos and knockdown of this ortholog resulted in a shortened and maldeveloped intestine with absence of goblet cells [19]. Loss-of-function mutations in CLMP cause CSBS in human beings, likely by interfering with tight-junction formation, which disrupts intestinal development [19]. The presence of these mutations was confirmed in a subsequent work in a newborn presenting CSBS, malrotation and intestinal pseudoobstruction [20].

On the other hand, it had been noticed that in some affected family only males developed the disease. A different series of 3 patient (2 of

Table 3
Results

Case	FLNA type of mutation	Sex	Bowel length (cm)	Associated conditions
29	2 bp del in second exon (c.16–17 del TC)	M	237	Rectal bleeding
43	2 bp del in second exon (c.16–17 del TC)	M	228.6	Synovial lipomatosis
47	2 bp del in exon 2 (c.65–66 del AC)	M	N/A	Pyloric hypertrophy, asymmetrical spastic diplegia
51	Partial duplication of first 28 exons	M	115	Bifid uvula, PDA, partial agenesis corpus callosum, patent foramen ovale
52	Partial duplication of first 28 exons	M	45	None
53	Homozygous for a nonsense mutation in exon 43 [c.7021C > T; Q2341X]	M	68	Left diaphragmatic defect, dysmorphic facies, spina bifida occulta, posterior fossa arachnoid cyst, proximally placed thumbs
58	2 bp del second exon (c.16–17 del TC)	M	N/A	N/A

Legend: genetic mutations; M = male; N/A = non available.

which familiar) with no CLMP mutations was studied and a novel 2 base pair deletion was identified in the second exon of FLNA associated with an X-linked pattern of inheritance. Male patients with CSBS with mutations in FLNA have usually associated multiple congenital anomalies [21].

FLNA encodes a cytoskeletal protein that binds to actin and has a well-characterized role in the cytoplasm. It regulates cell shape by cross-linking actin filaments and plays an important role in cell signaling and migration in response to environmental changes. A role for FLNA has also been recently discovered in the nucleoli, where it inhibits ribosomal RNA transcription. FLNA has been reported to play an important role in vascular development and cardiac morphogenesis, but its role is still unclear in intestinal development. It is reported that FLNA is able to interact with the tyrosine kinase-like orphan receptor 2 (Ror2) and showed that this interaction is required for filopodia formation and migration. Since disruption of Ror2 expression has been shown to lead to a shortened small intestine in mice, it is tempting to hypothesize that FLNA mutations leading to CSBS disrupt the FLNA–Ror2 interaction and impair cell migration [22].

Similar to SBS patients, early and long-term TPN can markedly increase the survival rate of CSBS. Referral to a specialist center is strongly recommended because intestinal rehabilitation programs offer the multidisciplinary experience to maximize medical and surgical management of these complex and rare patients. The results produced agree with previous studies, which outlined a greater likelihood of a worse prognosis if the symptom onset presents in the very early stages of the patients' life, whereas a delayed presentation of symptoms would provide a better advantage for survival [23].

From our results we understand that nutritional support is the medical management able to influence survival the most. Every patient who reached total enteral nutrition was treated at first with total parenteral nutrition. Oral feeding with elemental diet was then introduced and the amount of food was progressively increased base of the individual need.

Literature shows that, in children with intestinal failure, reaching tolerance to oral feeding is considered a big problem. These patients suffer from a condition called food aversion, defined as an excessive or extreme and consistently negative reaction to oral fluids or diet, which interferes with nutrition requirements. Food aversion pathogenesis seems to be related to the lack in development of oral feeding skills during the first year of life because usually these patients experienced feeding by nasogastric tube or by gastrostomy. Owing to this consideration, we believe that in short bowel patient oral feeding has to start as soon as possible. This comment was also stated previously in publication made by the senior author. Recent studies suggest that a powerful tool to overcome food aversion seems to be the so-called Messy Play Therapy. This treatment uses the senses to gradually desensitize children to different smells and textures within play, without the pressure to taste or eat. In our experience, children treated have gone from not tolerating any intake to tolerating an oral diet, which means enjoying their mealtimes [44].

It is important to mention that this review present some publication biases. The main problem in data collection was the absence of heterogeneity from the papers analyzed. In addition, a meta-analysis was not possible owing to the different data collection methods found in all the papers identified. Finally, studies examined did not show a clear outcomes data in terms of improvement in the clinical condition owing to TPN or to any other medical or surgical strategies.

4. Conclusion

Since entering the 21st century, the entire confidence in approaching the condition of CSBS has increased. The results produced within this report confirm the advances that have been successfully made. Despite CSBS being a severe and rare disease with still an unknown etiology, patients affected from this condition benefit from the experience coming from the multidisciplinary management of SBS.

We believe that the results from the genetic studies strongly suggest the need to further research investigating the role of CLMP in intestinal elongation, as this might provide future therapeutic strategies for CSBS patients.

Conflict of interest

There are no conflicts of interest.

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