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REGULAR ARTICLE

Nutritional therapy complications in children with ultra-short bowel syndrome include growth deficiency but not cholestasis

Katarzyna Olszewska[1], Janusz Ksiazyk (j.ksiazyk@ipczd.pl)[1], Dariusz Kozlowski[2], Magdalena Pajdowska[2], Malgorzata Janusz[1], Maciej Jaworski[2]

1.Department of Paediatrics, Nutrition and Metabolic Diseases, The Children's Memorial Health Institute, Warsaw, Poland
2.Department of Biochemistry, Radioimmunology and Experimental Medicine, The Children's Memorial Health Institute, Warsaw, Poland

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Correspondence
Janusz Ksiazyk, MD, PhD, Department of Paediatrics, Nutrition and Metabolic Diseases, The Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04-730 Warsaw, Poland.
Tel: +48 22 815 12 16 |
Fax: +48 22 815 12 12 |
Email: j.ksiazyk@ipczd.pl

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ABSTRACT

Aim: Children with ultra-short bowel syndrome (USBS) have not been extensively studied to date because the condition is rare. The aim of the study was to assess the nutritional status of children with USBS receiving home parenteral nutrition, using citrulline serum concentration and cholestasis.

Methods: We studied 17 patients with USBS, with a median age of 6.6 years and median duration of parenteral nutrition of 6.6 years. The study was carried out at The Children's Memorial Health Institute, Warsaw, from January 2014 to January 2015.

Results: The median standard deviation score (SDS) was −1.2 for body mass according to chronological age, −1.72 according to height and −0.59 according to height for age. Patients requiring seven days per week parenteral nutrition had a citrulline concentration below 10 μmol/L. Decreased bone-mineral density was observed in 87% of the patients. Low values of 25-hydroxyvitamin D were found in 53% of the children. None of the patients had elevated conjugated bilirubin levels above 34.2 μmol/L.

Conclusion: Children with USBS were growth deficient according to their chronological age, with frequent abnormal bone mineralisation and vitamin D deficiency. Children requiring parenteral nutrition seven days a week had citrulline concentrations below 10 μmol/L. Cholestasis was not seen.

INTRODUCTION

Patients with short bowel syndrome (SBS) are potential candidates for small-intestine transplantation. Surgery is particularly indicated if they have ultra-short bowel syndrome (USBS), which is the most severe form of the syndrome and normally indicates that they have a residual small bowel length that is less than 20 cm (1), or they would need long-term parenteral nutrition (PN) (2). For the purposes of this study, we have defined USBS as a residual small bowel length of below 10 cm. Intestinal failure-associated liver failure, sepsis, thrombosis and an increased number of surgical interventions appear to make the prognosis worse for these patients, but fish-oil lipid emulsions have been reported to open up new perspectives on the prevention of liver failure (3). Tremendous advances in the provision of PN have resulted in significant improvements being reported in the survival and quality of life of affected children (4). Cholestasis has been defined as elevated serum conjugated bilirubin of more than 2 mg/dL (34.2 μmol/L) in parenterally fed patients (5). The ability to predict patients' potential for successfully being weaned off PN, or biomarkers that indicate it could be reduced, would be useful for clinicians. Citrulline is an amino acid that is mainly produced by enterocytes of the small bowel from glutamine-derived from intestinal lumen and smaller amounts come from the blood supply (5). It plays a significant role in detoxification of ammonia and the production of urea, because citrulline is

Abbreviations
25(OH)D, 25-hydroxyvitamin D; BMD, Total body bone mass density; BMI, Body mass index; DXA, Dual-energy X-ray absorptiometry; ESPGHAN, The European Society for Paediatric Gastroenterology, Hepatology and Nutrition; PN, Parenteral nutrition; SBS, Short bowel syndrome; SDS, Standard deviation score; USBS, Ultra-short small bowel syndrome.

Key notes

- Children with ultra-short bowel syndrome have not been extensively studied to date because the condition is rare.
- This Polish study of 17 children at a median age of 6.6 years found that growth impairment was seen in all of the children with this condition, but the subjects did not display cholestasis.
- We also observed that children requiring parenteral nutrition seven days a week had citrulline concentrations below 10 μmol/L.

converted in the kidney to arginine, but it is also a potent factor in producing nitric oxide (6,7). In clinical studies, both the chronic and acute reductions of enterocyte mass have been correlated with low plasma citrulline concentration (8). The plasma citrulline level is considered to provide a marker of bowel length and enteral tolerance in children with SBS, when serum levels exceed 19 μmol/L (9), and it has been reported to predict independence from PN when a cut-off level of 15 μmol/L is reached (10). This was confirmed in a paper about the markers of enteral adaptation in short bowel syndrome (11). One study stated that a citrulline serum concentration of more than 20 μmol/L was a prognostic marker for weaning adult patients off PN (12). Plasma citrulline concentration is not affected by liver diseases and protein-energy malnutrition (13), but it can be affected by catheter-related bloodstream infections in children with intestinal failure (14). Growth failure has not been a primary subject in previous studies concerning children with USBS, but a study that assessed a limited number of patients revealed deficient z-scores for weight and height and reported that most of them had high values of conjugated bilirubin (15).

The aim of this study was to evaluate nutritional treatment outcomes in children with USBS, by measuring plasma citrulline concentration and selected nutritional data, such as anthropological measurements, bone mass density, vitamin D and evaluating liver function tests.

METHODS

The study subjects

There were 17 patients (nine males) with USBS aged 0.8–14.2 years (median 6.6 years) who were eligible for the study and two cases were excluded: one because of late intestinal resection at the age of three years and one because the parents refused their consent. Home PN was implemented in all of our patients, based on the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines (16). The median duration of PN was 6.6 years (range 0.8–14.2 years). The patients' median gestational age was 37 weeks (range 25–40 weeks) and 10/17 (59%) were born premature. The median birth weight was 2850 g (range 1300–3960 g).

The inclusion criteria were having a small intestine of up to 10 cm at the time of resection, according to the current definition of USBS (17), undergoing an intestine resection in the first two months of life and receiving PN for at least six months after their resection. The exclusion criteria were abnormal renal function, symptoms of sepsis at the time of study entry and urea cycle disorders. Ethical approval was obtained from the Ethics Committee of our hospital and informed consent was obtained from the subjects' parents. The patients' characteristics are summarised in Table 1 and the characteristics of PN and the types of lipid emulsion are summarised in Table 2.

Study procedures

Nutritional status and growth were evaluated based on anthropometric measurements and related to the growth charts (18). Body mass measurement standard deviation scores (SDS) were related to chronological age and height for age, which was described as the child's age in relation to their height when plotted at the 50th percentile on a growth chart. The anteroposterior spine and total bone mass density (BMD) of eight children were measured by dual-energy X-ray absorptiometry (DXA) using a Prodigy

Table 1 Clinical characteristics of the patients

Case number	Male (M); Female (F)	Age (years)	Age at resection (day, month)	Primary diagnosis	Residual length of small bowel (cm)*	Presence of ileocecal valve	Colon intact
1	M	5.1	3rd day	Mesenteric volvulus	0	No	Yes
2	F	6.6	1st month	NEC	6	Yes	Yes
	M	1.2	2nd month	Intestinal volvulus	10	Yes	Yes
4	M	11.3	1st month	Mesentery defects	10	No	Not
5	F	12.8	1st month	Mesenteric volvulus	5	No	Not
6	F	12.3	1st day	Gastroschisis	7	No	Not
7	M	10.8	3rd day	Intestinal volvulus	4	Yes	Yes
8	F	13.8	3rd day	Intestinal atresia	8	No	Not
9	F	7.7	1st month	NEC	4	Yes	Yes
10	M	1.0	14th day	Mesenteric volvulus	10	Yes	Yes
11	M	2.1	3rd day	Mesentery defects	7	Yes	Yes
12	M	3.1	1st day	Mesenteric volvulus	0	No	Not
13	M	1.1	19th day	NEC	6	No	Yes
14	F	11.3	1st month	NEC	10	Yes	Yes
15	M	4.2	3rd day	Intestinal atresia	0	No	Yes
16	F	0.8	2nd day	NEC	4	No	Not
17	F	14.2	2nd day	Mesenteric volvulus	2	No	Yes

NEC = Necrotising enterocolitis.
*The duodenum was not included in the remnant bowel length.

Table 2 Characteristics of PN and type of lipid emulsion

Case number	Length of PN (months)	Days of PN/week (days of PN with lipid emulsion)	Proportion of energy intake provided by PN (%)	Type of lipid emulsion
1	61.2	7 (5)	100	SMOFLipid/ Omegaven
2	79.4	7 (5)	75	SMOFLipid
3	14.3	3 (3)	25	SMOFLipid
4	135.6	7 (6)	81	Lipofundn MCT/LCT
5	154.1	4 (4)	44	Lipofund MCT/LCT
6	147.4	7 (5)	86	SMOFLipid/ Omegaven
7	129.7	7 (5)	41	SMOFLipid
8	166.1	4 (4)	52	SMOFLipid
9	92.5	5 (4)	50	SMOFLipid
10	11.4	7 (5)	69	SMOFLipid
11	25.2	7 (5)	72	SMOFLipid
12	36.7	7 (5)	52	SMOFLipid/ Omegaven
13	12.8	7 (5)	91	SMOFLipid
14	135.3	7 (5)	61	SMOFLipid
15	50.9	7 (5)	89	SMOFLipid/ Omegaven
16	9.4	7 (5)	100	SMOFLipid
17	170.0	7 (5)	54	SMOFLipid/ Omegaven

PN = Parenteral nutrition; Mo = Months; SMOFLipid Fresenius Kabi; Lipofund MCT/LCT B.Braun; Omegaven Fresenius Kabi – given for restricted time of PN.

densitometer (General Electric Healthcare, Wisconsin, USA). A daily quality-assurance procedure was carried out. In addition, an anthropomorphic spine phantom was scanned at least twice a week. The BMD values were expressed as absolute values and the Z-scores were related to the norms for children above five years of age. Bone age was not assessed.

The nutritional values of the food intake, from oral feeding and PN, were calculated based on seven-day food records, and the percentage of energy from both sources was calculated. The PN regime was applied according to the ESPGHAN guidelines (16).

Laboratory tests

The Children's Memorial Health Institute is a certified participant in The European Research Network for Evaluation and Improvement of Screening, Diagnosis and Treatment of Inherited Disorders of Metabolism (ERNDIM) quantitative amino acids control programme. ERNDIM-certified reference materials were used for quality-assurance purposes. The plasma citrulline concentration was determined by an automatic amino acid analyser (JEOL Ltd, Musashino, Akishima, Tokyo, Japan) in 13 patients and the measurements were performed at least six hours after stopping PN administration and at least four hours after the last oral meal.

Liver function was assessed using the bilirubin concentration, namely total bilirubin and conjugated bilirubin and the international normalised ratio albumin concentration, which is a coagulation indicator. We also measured the liver enzyme levels: aspartate transaminase, alanine transaminase, gamma-glutamyl transpeptidase and alkaline phosphatase. A chemiluminescence immunoassay was used to estimate the concentration of 25-hydroxyvitamin (D 25 (OH)D). Vitamin A and E concentrations were determined by high-performance liquid chromatography.

Statistical analysis

The Polish version of Statistica 10 (StatSoft, Oklahoma, USA) was used. The Mann–Whitney *U* test and the Pearson coefficient of correlation were applied, with normal distribution assessed by the Shapiro–Wilk test.

RESULTS

All patients survived during the study period. Case number 12 (Tables 1, 2 and 3) had a serial transverse enteroplasty operation with a bowel prolongation of 22 cm 18 months before the study, despite the fact that the original bowel residual length was zero centimetres. After one year, it was estimated to be 15 cm long. Body mass deficit was found because the median SDS for body mass according to the chronological age in the research sample was −1.2 (range −2.96 to −0.49) and for body mass according to height age was −0.59 (range −1.5 to 0.6). SDS body mass according to chronological age did not correlate significantly with age or the duration of PN, but the duration of PN correlated with SDS body mass according to height for age ($r = 0.6468$, $p = 0.007$). This was consistent with the possible influence of PN on both height and weight, as the median SDS for body height was −1.72 (range −3.26 to −0.15). The duration of PN and age correlated negatively with body height in the percentiles $r = -0.57$ ($p < 0.03$) and $r = -0.57$, ($p < 0.02$), respectively, indicating a deficit in our patients. The duration of PN correlated with the SDS body mass index (BMI) according to height age $r = 0.62$ ($p = 0.01$), which might have reflected the simultaneous effect of PN on body mass and height when related to height for age. The number of PN days correlated negatively with the percentage of oral feeding in the mean daily energy requirements based on the ESPGHAN guidelines (16) ($r = -0.70$, $p = 0.002$). The contribution of oral feeding to the mean daily energy requirements was 39% (range 0–167%). The median energy intake from PN and oral feeding in relation to daily needs was 121% (range 86–223%) (Table 3). Case number three was weaned off home parenteral nutrition four months after the end of the study. In that case, the proportion of energy provided by PN was the lowest in the whole group, with a citrulline serum level of 12 μmol/L (Table 3). The median citrulline concentration in the research sample was 8.3 μmol/L (range 2.6–19.6), and in 11 of 13 subjects, the citrulline

Table 3 Energy intake, vitamin D supplementation and serum citrulline levels

Case number	Daily energy needs (kcal/kg b.m.)*	Energy intake from PN in relation to daily needs (%)	Energy intake from PN and oral feeding in relation to daily needs (%)	Vitamin D supplementation per os (IU/kg b.m./day)	Vitamin D supplementation per os and with lipid emulsion in PN (IU/kg b.m./week)	Serum citrulline levels (μmol/L)
1	85	88	88	30	230	2.6
2	85	68	90	149	349	3.1
3	90	23	190	412	532	12
4	70	90	112	75	315	8.3
5	60	53	173	69	229	19.6
6	60	106	123	59	259	9.1
7	65	92	223	131	331	8.3
8	50	42	109	155	315	19.6
9	75	52	125	122	282	7
10	90	94	137	150	350	3.7
11	85	87	121	88	288	8.9
12	85	89	172	0	200	7.4
13	90	91	100	143	343	2.5
14	70	61	100	36	236	
15	85	92	104	33	233	
16	100	86	86	151	351	
17	50	82	151	82	282	

b.m. = Body mass; IU = International units; PN = Parenteral nutrition.
*Adapted from (16).

concentration was below 15 μmol/L (Table 3). All patients requiring seven-day PN had a citrulline concentration below 10 μmol/L. The contribution of enteral nutrition to the mean daily energy requirements correlated with the citrulline concentration ($r = 0.56$, $p < 0.05$). Increased citrulline concentration was observed in children with a higher contribution of oral feeding to the mean daily energy requirements. The citrulline concentration increased with the age ($r = 0.60$, $p = 0.03$) and duration of PN ($r = 0.60$, $p = 0.03$). The number of days of PN per week correlated negatively with citrulline concentration ($r = -0.75$, $p = 0.003$). There were two female patients over 12 years old – cases five and eight – in our cohort group with citrulline concentrations of 19.6 μmol/L and both received PN for four days per week (Table 2). In both cases, an almost total small bowel resection was performed during the neonatal period, with a partial resection of the colon. All patients requiring seven-day PN had citrulline concentrations below 10 μmol/L.

There was no statistically significant correlation between the citrulline concentration and the length of the residual intestine. The presence of an ileocecal valve had no influence on reducing PN and did not correlate with the number of PN days.

The median total bilirubin concentration in 15 patients was within normal values. The median conjugated bilirubin concentration in the whole group was normal in all patients. Two patients had an elevated total bilirubin concentration (>17 μmol/L) but no patients had an elevated conjugated bilirubin concentration >34.2 μmol/L. The results of the liver function are presented in Table 4.

Table 4 Liver function tests, albumin and INR.

	Median (range)	Patients with abnormal results
ALT (U/L)	35 (21–123)	9 (53%)
AST (U/L)	37 (23–120)	5 (29%)
GGT (U/L)	21 (13–80)	5 (29%)
ALP (U/L)	295 (180–417)	0
Total bilirubin (μmol/L)	11.37 (1.88–50.27)	2 (12%)
Conjugated bilirubin (μmol/L)	4.62 (1.88–17.61)	0
INR	1.17 (1.01–1.52)	8 (47%)
Albumin (g/L)	40.7 (37–43.5)	0

ALP = Alkaline phosphatase; ALT = Alanine transaminase; AST = Aspartate transaminase; GGT = Gamma-glutamyl transpeptidase; INR = International normalized ratio.

Decreased BMD, defined as a DXA total body Z-score of <−1.0 related to chronological age, was observed in 50% of the examined children. Abnormal bone mineralisation, defined as a DXA spine (L2–L4) Z-score of <−1.0 related to chronological age, was observed in seven of the eight patients examined. The DXA total body and spine Z-scores did not correlate with the body mass or body height SDS. Decreased BMD was also not dependent on age and PN length.

Vitamin E was not supplemented orally. One patient was vitamin A deficient and received oral supplements. There were no patients deficient in vitamin E. The mean concentration of vitamins A, E and 25-OHD were 339.2 ng/mL,

12.9 μg/mL and 20.1 ng/mL, respectively. Eight of the original 17 children had optimal vitamin 25(OH)D concentrations (≥20 ng/mL), according to new recommended levels (19). Nine of the 17 patients were deficient in vitamin D (25-(OH)D concentrations (<20 ng/mL). All but one of the 17 patients received additional oral supplements with vitamin D (Table 3). The median level of oral vitamin D supplements in the whole research sample was 2000 international units per day (88.5 international units per kg of body mass per day).

DISCUSSION

Children with USBS are susceptible to body mass and body height deficiencies. In our study, which, to the best of our knowledge, describes the biggest series of USBS patients, growth retardation increased with age and the length of PN. The duration of PN and age correlated negatively with body height in percentiles. The SDS body mass according to chronological age did not correlate with age and PN length. Body mass according to height age increased with age and the duration of PN. Body mass deficits were found for chronological age and for body mass according to height for age. These correlations were statistically significant. SDS BMI according to height for age also correlated with age and the duration of treatment. The total body BMD and spine BMD (L2-L4) Z-scores were impaired in our patients, and this corresponded to the findings of others studies, with an identical rate of 50% of patients' having a BMD Z-score that was <−1, with no improvement after increasing vitamin D supplements (20).

The basic problem for patients with USBS seemed to be growth deficiencies, which were related to inadequate uptake of energy and food components in relation to the patient's individual needs. We did not use enteral nutrition and relied on oral feeding up to the tolerance limits.

It seemed essential that the provision of a sufficient nutritional substrate was mandatory for achieving satisfactory growth in children and therefore a nutrition rehabilitation programme could be of importance in nutritional management. It was difficult to answer the question about whether relying on oral feeding was our best choice. Feeding disorders are of great significance for children who are predominantly fed parenterally, which might be the reason why only one child could be weaned off PN. It was promising that the children with USBS whose enteral intake was higher than 100% of their daily energy requirements were able to achieve a reduction in the number of days of PN. The negative correlation between the percentage of oral feeding and the number of PN days was statistically significant.

The use of trophic factors for enhancing mucosal hyperplasia seems to be promising. Studies with glucagon-like peptide 1 (GLP2) analogue (teduglutide) in adults with SBS showed enhanced intestinal adaptation, a diminished need for parenteral support, an increased absorptive capacity of the remnant intestine and increased plasma concentrations of citrulline, which is a biomarker of mucosal mass (21). The safety and usefulness of teduglutide therapy in children with SBS were assessed, and the results showed that the PN requirement was reduced and increased enteral feeding was observed (22). The citrulline concentration seemed to be a good marker for monitoring during intestinal rehabilitation treatment, but its role in USBS was not fully elucidated. We found that the concentration of plasma citrulline in patients with a bigger contribution of enteral intake in the daily energy requirements was also higher. The former studies also reported low plasma citrulline concentrations in SBS patients, which correlated with the residual bowel length and the weak association of citrulline level >10 μmol/L with bowel adaptation (23). A positive correlation between plasma citrulline concentrations and absorptive intestinal mass in adult SBS patients with a higher absorption of fat was found by one study, with an identified cut-off value of 20 μmol/L of plasma citrulline concentration to distinguish transient from permanent intestinal failure in their SBS cohort (12). In our study, we found no correlation between citrulline concentration and small-intestine length, probably because the differences between the residual lengths of the small bowels were too small, despite the large age range. However, we found that the plasma citrulline concentration was higher in older patients and patients fed parenterally for a longer time. This means that time could be a good prognostic factor for these patients. We found that children with higher citrulline concentrations required fewer days of PN weekly. The only patient (case number three) who was weaned off parenteral nutrition, who had a serum citrulline concentration of 12 μmol/L, casts doubt over the validity of the threshold of 15 μmol/L for independence from PNs. In this case, only 25% of his daily energy intake was delivered by the parenteral route. The patients with a higher percentage of enteral intake had reduced PN days per week. It was possible that a higher oral energy intake in our patients could have resulted in a better nutritional state, but feeding difficulties are well recognised in children with a history of long-term PN.

USBS can be complicated by liver disease that is associated with intestinal failure with fatal outcomes (15). In approximately half of our patients, we observed elevated alanine transaminase (Table 3), but none of the patients had elevated conjugated bilirubin (>34.2 μmol/L) and all had normal albumin levels. It is important that almost all of our patients received novel lipid emulsions containing omega-3 fatty acids from fish oil (Table 2). The 25-OHD deficiency observed in the majority of our patients was also observed in the healthy population. One important finding was that the parenteral supplementation of vitamin D was not effective in eliminating these deficits, despite the fact that 40 international units per kilogram of body mass was provided with lipid emulsions, which complied with the dose recommended by ESPGHAN of 30 international units/kg per day intravenously. (16). When we compared the 25(OH)D serum levels with the published reference values (19), nearly half of our patients had optimal vitamin 25(OH)D. A study of BMD and vitamin D status found that the majority of the patients with intestinal failure had low

BMD Z-scores and were deficient in vitamin D (24). Deficiencies in other vitamins were not relevant.

Our results showed that a number of factors could significantly improve the prognosis of patients with USBS. These were the close monitoring of nutritional status, the steady and early introduction of enteral nutrition and the aggressive prevention, diagnosis and treatment of infections such as central venous catheter sepsis and bacterial overgrowth.

CONCLUSION

The children with USBS that we investigated were growth deficient according to chronological age, but their body mass and height were proportional. Vitamin D deficiency was often present, irrespective of supplementation, with frequent abnormal bone mineralisation. Citrulline concentrations below 10 μmol/L were found in patients requiring seven-day PN. Cholestasis was not observed, despite long-term PN.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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