Long-term outcome, growth and digestive function in children 2 to 18 years after intestinal transplantation

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ABSTRACT

Objective: Small bowel (SB) transplantation (Tx), long considered a rescue therapy for patients with intestinal failure, is now a well recognised alternative treatment strategy to parental nutrition (PN). In this retrospective study, we analysed graft functions in 31 children after SBTx with a follow-up of 2–18 years (median 7 years).

Patients: Twelve children had isolated SBTx, 19 had combined liver–SBTx and 17 received an additional colon graft. Growth, nutritional markers, stool balance studies, endoscopy and graft histology were recorded every 2–3 years post-Tx.

Results: All children were weaned from PN after Tx and 26 children remained PN-free. Enteral nutrition was required for 14/31 (45%) patients at 2 years post-Tx. All children had high dietary energy intakes. The degree of steatorrhoea was fairly constant, with fat and energy absorption rates of 84–89%. Growth parameters revealed at transplantation a mean height Z-score of –1.17. After Tx, two-thirds of children had normal growth, whereas in one-third, Z-scores remained lower than –2, concomitant to a delayed puberty. Adult height was normal in 5/6. Endoscopy and histology analyses were normal in asymptomatic patients. Chronic rejection occurred only in non-compliant patients. Five intestinal grafts were removed 2.5–8 years post-Tx for acute or chronic rejection.

Conclusions: This series indicates that long-term intestinal autonomy for up to 18 years is possible in the majority of patients after SBTx. Subnormal energy absorption and moderate steatorrhoea were often compensated for by hyperphagia, allowing normal growth and attainment of adult height. Long-term compliance is an important pre-requisite for long-term graft function.

In the last 10 years intestinal transplantation (Tx) has become an accepted treatment for total and definitive intestinal failure.[1] However the established therapy for intestinal failure nowadays is home parenteral nutrition (PN), with excellent long-term results from experienced centres.[2 3] Intestinal Tx has to demonstrate its efficacy as an alternative therapy for intestinal failure beyond that of a rescue therapy for patients dying of PN-related complications. Short-term results of intestinal Tx have improved due to a better control of acute rejection and infections, and better patient selection. The 1-year patient and graft survival rates for isolated small bowel (SB) Tx and combined liver and small bowel transplantation (L–SBTx) are 77–65% and 60–59% respectively in the International Registry.[1] However, these statistics are for the patients a poor reflection of their everyday life and future. To enable consideration of Tx as an alternative treatment choice for intestinal failure, long-term markers of graft function are needed. The pattern of growth after intestinal Tx, one of the major signs of well-being and normal gastrointestinal functions in children, has been reported in several studies.[4–8] We assessed intestinal graft functions in further detail over a prolonged period at regular intervals after surgery, using stool balances, biological nutritional parameters, endoscopy and histology. Only children who could be completely weaned from PN for at least 2 years after intestinal Tx were enrolled in this study.

PATIENTS

In the period from 1988 to 1990, nine children received a SBTx in our institution; however, only one girl survived with her transplant, with a follow-up of more than 18 years post-Tx;[9] in one boy (patient 14) the graft was removed for rejection, and he received an L–SBTx 8 years later. In the period since 1994, 69 children underwent intestinal Tx, with six children undergoing a re-transplantation. In addition, from 1997 onwards, 17 children suffering from mucosal or motility disorders received a right colon graft together with the SB. From 1994, the overall patient survival rate was 70% (48/69), and the graft survival rate was 49% (17/35) for L–SBTx and 38% (15/39) for SBTx.

Thirty-one patients (eight girls, 23 boys) were free from PN for at least 2 years post-Tx. The clinical characteristics of these 31 patients at transplantation are reported in table 1. Their median age was 5 years (range 5 months to 13 years). The median follow-up was 7 years (range 2 years to 18 years). The indications for transplantation were: a SB syndrome in 12 children; a mucosal disease (microvillous atrophy, epithelial dysplasia or "tufting enteropathy") in ten patients; and a motility disorder (aganglionosis, chronic intestinal pseudo-obstruction syndrome) in nine patients. Twelve children received a SBTx and 19 an L–SBTx.

The surgical technique and immunosuppression protocol from 1994 have been reported elsewhere[10] (summarised in table 2). Within 1 year post-Tx the dosage of prednisone had been tapered to 0.15–0.2 mg/kg every other day. The dose of prednisone was shortly increased in ten patients (five due to liver rejection,[11] four due to autoimmune cytopenia,[12] one due to a suspected dysimmune enteritis). Three of them received daily prednisone (patients 10, 17, 20).

Patients were initially fed through a nasogastric tube or gastrostomy. Enteral nutrition was continued for months or years when necessary.

Table 1 Clinical characteristics of the 31 patients

	Sex	Diagnosis	Tx	Age at Tx	Follow-up
1	F	SBS	SB	5 months	18 years
2	F	Epithelial dysplasia	L–SB	3 years 10 months	12 years 1 month
3	M	Microvillous atrophy	L–SB	3 years 11 months	11 years 10 months
4	F	SBS	L–SB	10 years	10 years 5 months
5	M	SBS	L–SB+colon	4 years 4 months	9 years 9 months
6	M	Aganglionosis	L–SB+colon	4 years 6 months	9 years 7 months
7	F	Aganglionosis	L–SB+colon	5 years 3 months	9 years 3 months
8	M	Microvillous atrophy	SB	11 years 9 months	9 years 6 months
9	F	Epithelial dysplasia*	L–SB+colon	5 years 2 months	8 years 11 months
10	M	SBS	L–SB	2 years 9 months	8 years 10 months
11	M	Epithelial dysplasia	L–SB+colon	3 years 6 months	8 years
12	M	SBS	SB	3 years 1 months	8 years 9 months
13	M	SBS	L–SB	11 years 10 months	7 years 9 months
14	M	SBS	L–SB	12 years 10 months	7 years 7 months
15	M	Epithelial dysplasia	L–SB+colon	5 years 4 months	7 years 4 months
16	F	CIPO†	L–SB+colon ×2	4 years 10 months; 5 years 4 months	7 years 2 months
17	M	Aganglionosis	L–SB+colon	7 years 9 months	7 years 1 month
18	M	SBS	SB	6 years	7 years
19	M	Microvillous atrophy	SB+colon	2 years 11 months	2 years
20	M	Aganglionosis	L–SB+colon	3 years 1 months	6 years 4 months
21	F	Microvillous atrophy	L–SB+colon	3 years 6 months	2 years
22	M	SBS	L–SB	3 years 6 months	2 years 7 months
23	M	Microvillous atrophy	L–SB+colon	3 years 5 months	4 years 10 months
24	M	Aganglionosis	L–SB+colon	7 years 2 months	4 years 6 months
25	M	SBS	SB	5 years 3 months	4 years 2 months
26	M	Aganglionosis	SB+colon	5 years 10 months	4 years 2 months
27	M	Epithelial dysplasia*	SB+colon	6 years 10 months	3 years 7 months
28	M	Aganglionosis	SB+colon	4 years 9 months	2 years 10 months
29	F	Aganglionosis	SB+colon	4 years 4 months	2 years 6 months
30	M	SBS	SB	5 years 7 months	2 years 3 months
31	M	SBS	SB	3 years 7 months	2 years

CIPO, chronic intestinal pseudo-obstruction; F, female; M, male; SBS, short bowel syndrome; Tx, intestinal transplantation.
*Siblings.
†Two L–SBTx at 6-month interval (rejection).

Growth hormone was not used in this series. All children received each day vitamins D (600 to 900 IU), A (1500 IU) and E (5 mg) over a minimum of 2 years. Iron and magnesium were prescribed according to blood levels.

In all patients, the initial diverting ileostomy was closed within the first year after Tx. In four patients a new stoma was created between 4 and 7 years post-Tx due to colitis of the native or transplanted colon, or emergency surgery for occlusion. Otherwise, the enteric continuity was restored with the native colon or rectum.

METHODS

Growth parameters were measured at each visit. Two-thirds of the transplanted patients had a complete follow-up including scheduled blood controls, stool balance studies and digestive endoscopy according to the protocol. Once a year blood levels of magnesium, vitamins A, D and E, total proteins and albumin, clotting parameters, iron, transferrin saturation, ferritin, cholesterol, triacylglycerol, folates, vitamin B_{12}, pre-albumin and retinol-binding protein were recorded.

Table 2 Immunosuppressive regimen, 1988–2006

Time	Immunosuppressive regimen
1988–1990	Cyclosporine, prednisone, azathioprine
From 1994 onwards	Tacrolimus, prednisone
1994–2004	+ Azathioprine
From 2001 onwards	+ Induction with basiliximab
2002 only	+ Sirolimus for SBTx only

Balance studies were performed at 2- to 3-year-intervals during follow-up. For 3 days each meal was prepared in duplicate, in order to assess oral intake and net intestinal absorption. Before the first duplicated breakfast and after the last duplicated supper, carmine was administered orally to enable identification of the stool output that corresponded to the duplicated diet period. During these 3 days, duplicate meals, leftovers of served meals and stool output were collected daily and stored at +4°C. The 3-day samples were pooled and analyses were performed on homogenised samples. Fat, nitrogen, and total energy content were determined by the method of Van de Kamer,[13] nitrogen elemental analysis (Elemental Analyser FlashEA™ 1112; Thermo-Finnigan, San-Jose, CA, USA) and bomb calorimetry (PARR 1351 Bomb Calorimeter; Parr Instrument Company, Moline, IL, USA), respectively. Carbohydrate-derived energy was calculated by subtracting the energy associated with the nitrogen and fat components from the total energy in the sample. The energy conversion factors used were 23.6, 17.6 and 39.0 kJ/g for protein, carbohydrate and fat, respectively.[14] The conventional conversion factor 6.25 was used to express elemental nitrogen content as protein content. The oral metabolisable energy was calculated by subtracting the amount of energy excreted in stool output from that actually ingested (the difference between

duplicate meals and leftovers of served meals). The coefficient of net intestinal absorption expressed as a percentage of total energy ingested for the three main energy sources (nitrogen, carbohydrate and fat) and total energy represented the proportion of ingested energy not recovered in stool output. This was determined with alpha-1-antitrypsine clearance and measurements of faecal elastase.

An upper and lower digestive endoscopy was performed under general anaesthesia at the end of the balance study in order to collect biopsies of the transplanted intestine. The grading scheme followed the international criteria defined in 2003.[15]

RESULTS

In December 2006, 26 of 31 patients (84%) were free from PN after intestinal Tx. In five patients PN had to be re-instituted; these patients are included in this analysis for the post-Tx period until the re-introduction of PN.

Nutritional treatment

Oral and enteral nutrition

All children received continuous enteral nutrition in the first few post-Tx weeks. It was continued on a clinical basis, depending on the feeding behaviour, weight gain and pubertal stage. A protein hydrolysate was used in children younger than 3 years and a polymeric diet in older ones. Enteral feeding was required in 14/31 (45%) children at 2 years, 4/18 (22%) at 5 years, 2/10 at 7 years, 1/4 at 10 years. At final follow-up, ten patients had moderate or severe anorexia.

Parenteral nutrition

As an inclusion criterion, all patients at entry in this follow-up study were PN-free. PN had to be re-instituted in five children, 2.5- to 8-years post-Tx, before removal of the graft. This was the case for three patients, due to acute rejection following ischaemic or viral enteritis (patients 15, 19, 21). In two obviously non-compliant teenagers, the cause was chronic rejection, responsible for diarrhoea or acute obstruction (patients 8, 13).

Nutritional status

Growth

Z-scores for height at Tx and on follow-up are reported in table 3. A severe growth failure (Z-score < -2) was only present in a minority of patients (7/31, 23%) at Tx. The stature of all parents was within normal limits.

Growth velocity was normal in 25/31 children up to puberty. A diminished velocity was observed in five children (three due to a high steroid dose, one due to chronic rejection, one transplanted just before puberty). Catch-up growth was

Table 3 Height at transplantation, expressed as Z-score for age

		Time post-Tx (years)						
	At Tx	2	5	7	10	15	Adult height (cm)	Target height (cm)
1	−2	0.5	0	−1	−1	0	160	163.5
2	−1.8	−2.5	−2.5	−3	−2.2		151	165.5
3	−2.6	−2.8	−2.4	−2.2	−3.3			171.5
4	−2	−3	−2.2	−1.1	−1.1		154	155.5
5	0	−0.5	−2.5	−2	−2.3			170.5
6	−2	−2.3	−3	−3	−3.2			172.5
7	0.5	1	1	1	1			157
8	−2.8	−3	−3.2	−2.5			159	*
9	−3	−3	−2.8	−3.5				157.5
10	−0.2	−1	−1.5	−2.7				172.5
11	−1.8	0.5	0.5	1				173
12	−0.7	−1.2	−0.3	−0.7				179
13	0.9	0.2	−0.4	−0.4			168	186.5
14	−2.4	−4.5	−2.3	−1.8			162	178
15	−3	−2.8	−2.8	−2.9				170
16	0	0	0	0				167.5
17	−1	−1.1	−1.2	−1.5				*
18	0.8	−0.8	0.4					*
19	−1.5	−2.2						*
20	−2.5	−2.5	−2.8					173
21	−4	−1.8						159.5
22	−0.8	0	0.5					170
23	−1	−2.5	−2					163.5
24	1	0.5	1					180
25	−1	−2						173
26	0	−1						170.5
27	−2	−1.3						170.5
28	0	0						163.5
29	1	0.5						166
30	−1.8	−1						171.5
31	−0.8	−0.5						175.5
Mean	−1.17	−1.21	−1.29	−1.55	−1.73			

Tx, intestinal transplantation. Target (genetic) height is calculated as: mean of (father's height + mother's height + 13) for a boy; and mean of (father's height + mother's height −13) for a girl.
* Parents' stature unknown.

observed only in the child with the most severe pre-Tx failure to thrive.

Weight was in all patients normal for height (Z-score between +1 and –1 for height). There were two different growth patterns identified: the majority of patients (21/31) growing with a Z-score greater than −2 (4/8 girls, 17/23 boys); the others, between −2 and −3. All but one of these patients with growth failure had received an L-SBTx. All of them had been transplanted more than 7 years ago. At Tx, one-half of them had a Z-score of –2 or lower. Only three of ten received long-term enteral feeding.

In these ten patients with growth failure, the peak of pubertal growth in the seven older ones was delayed at least 2 years from the median age. This delayed puberty is reflected in the decrease, from –1.29 to –1.73, in the mean Z-score between 5 and 10 years post-Tx. Endocrinological studies were normal in five of them.

In the six patients who completed their growth, five achieved adult height within normal limits, with a Z-score greater than –2. In three children with growth failure, a trial of pancreatic enzymes (despite a normal faecal elastase) was unsucessful.

Biological markers of nutritional status

For biological marker of nutritional status, see table 4. Albumin was within normal limits in all patients (data not shown). Prealbumin levels were normal in more than 90% of samples, whereas retinol binding protein levels were low in more than 50% of samples. Cholesterol levels were low in two-thirds of patients at all points, and in the lower range for all the others. Triacylglycerol levels were always normal. Vitamin B_{12} levels were normal in all patients, and folate levels in 90% of samples. Plasma vitamin A levels were low in one-half of the patients at 2 years, in one-third at 5 and 7 years, and was normal thereafter. Vitamins D and E levels were normal in most children. Prothrombin time was normal in all patients; none received vitamin K. Calcium and phosphorus levels were normal in all patients (data not shown). Iron and ferritin levels were mostly normal. Magnesium levels were low (between 0.5 and 0.7 mmol/l) in most patients despite supplementation (data not shown).

Digestive status

Bowel movements

In the three patients with an ileostomy, the daily stool output was 1500–2000 ml and was stable on follow-up. The other patients passed three to five stools per day. One-half of them used loperamide. All were continent day and night. The symptoms of chronic rejection in patient 8 were a progressively increasing diarrhoea.

Balance studies (table 5)

Twenty-two studies were performed in 15 children. The energy intake was high, well above the recommendation for age,[16] except in three cases (two of the patients studied at 10 years); the protein intake was also higher than recommended. The median energy absorption was less than 90%. The protein and carbohydrate absorption were always normal (>96–98%, data not shown). Fat losses in stools were significant: steatorrhoea was greater than 10 g/24 h on 14 occasions, and than 20 g on five occasions. The fat absorption was abnormal in nearly all the children, on three occasions (two children) as low as 60–62%. Five children with a steatorrhoea greater than 10 g/24 h, and all three children who were studied 10 years post-Tx, had an height Z-score lower than −2. In the five children who underwent

Table 4 Biological markers of nutrition

	Normal values	Time post-transplantation (years)				
		2	5	7	10	15
n		21	17	9	4	1
Prealbumin (g/l)	>0.11	0.18 (0.09–0.42)	0.17 (0.09–0.29)	0.16 (0.11–0.44)	0.22 (0.15–0.24)	0.2
RBP (mg/l)	30–60	26 (14–51)	41 (5–56)	25 (12–38)	35 (33–37)	18
Folates (mg/l)	5–12	10.3 (3.1–25)	8.6 (2.4–60)	4.4 (4.4–13)	11 (7.1–32)	
Vitamin B_{12} (mg/l)	>200	910 (400–1350)	841 (346–2400)	610 (312–1156)	643 (333–1495)	
Cholesterol (mmol/l)	3.2–6.95	2.4 (2.1–3.9)	2.75 (2.1–3.9)	2.95 (2.8–3.5)	3.4 (2.5–3.9)	3.74
Triacyglycerol (mmol/l)	0.35–1.5	0.7 (0.5–2.1)	0.95 (0.3–1.7)	0.8 (0.5–1.7)	0.8 (0.6–1.4)	0.64
Vitamin A (mg/l)	0.3–0.55	0.29 (0.06–0.45)	0.54 (0.1–0.89)	0.43 (0.14–1.63)	0.41 (0.2–0.48)	
Vitamin E (mg/l)	4.4–10	8.2 (4.4–17.9)	9 (6.8–18.6)	9.1 (6.5–12.8)	8.2 (5.8–14.2)	
Vitamin D						
25-Hydroxycholecalciferol (ng/ml)	13–40	15 (10–31)	26.5 (4–38)	24 (15–32)	19 (8–31)	15
1,25-Dihydroxycholecalciferol (pg/ml)	20–80	25 (16–82)	42 (23–91)	49 (29–83)	42 (36–56)	
Iron (mmol/l)	>11	8.5 (3–34)	13.5 (2.3–22)	14 (6.4–18.3)	24.5 (12.9–26.4)	15.2
Ferritin (mg/l)	>18	44 (2–443)	47 (4–156)	47 (20–79)	17 (17–68)	23

Values are medians and ranges.

Table 5 Balance studies

	Time post-transplantation (years)				
	2	5	7	10	18
n	8	7	3	3	1
Daily energy intake (% recommendation for age)*	138 (24) (112–171)	130 (45) (69–192)	149 (24) (108–150)	116 (32) (63–121)	108
Daily protein intake (g/kg)*	4.5	3.15	3.05	2.07	2
Total energy absorption (%)*	88 (1.2) (64–95)	89 (4.2) (83–89)	84 (7) (82–95)	86 (5) (82–91)	95
Fat absorption (%)*	86 (5) (73–93)	84 (11) (61–90)	68 (16) (60–91)	84 (13) (62–85)	92

*Values are medians (SD) with ranges shown in parentheses.
†Normal >92%.

serial stool collections, up to 10 years, the absorption of fat and energy remained stable. No difference was significant between SBTx and L–SBTx. Alpha-1-antitrypsin clearance and faecal elastase were always normal.

Endoscopy

Endoscopy was performed in 15/31 children at 2 years, 13/18 at 5 years, 7/10 at 7 years, 2/4 at 10 years, one at 15 and 18 years. In 10/39 cases (26%) the indication for endoscopic evaluation were acute symptoms: diarrhoea, colitis, bleeding, suspected lymphoproliferative disease.

Small bowel was normal in all asymptomatic patients. In children with acute symptoms, ulcerations were seen in half the cases. The colon graft was abnormal only once (patient 15), showing a severe colitis.

Histological examination

Intestinal villi were normal in length and shape in all 26 children who remained PN-free (fig. 1). The mucosa was normal in most cases. A mild inflammatory infiltrate was seen in one-fifth of biopsies. Only one episode of acute rejection was diagnosed (patient 26) 2 years post-Tx, with a good evolution.

In the five patients who lost their graft, two episodes of acute rejection were diagnosed with ulcerations, severe inflammatory infiltration, and focal crypt loss. In two other patients, chronic rejection was evidenced by villous atrophy, a severe infiltration with mononuclear and plasma cells, fibrosis under the epithelium and around the large vessels of the submucosa (fig. 2). In the two patients with suspected lymphoproliferative disease, there was a severe and diffuse mononuclear infiltrate associated with plasma cells.

Lymphangiectasias were common in the first post-Tx months, but were rarely seen in the biopsies later on.

Biopsies of the transplanted colon showed a mild to moderate inflammation of the lamina propria in one-half of the patients, without any other sign of rejection (fig. 3). There was acute rejection in the colon of only one child (patient 15), who underwent later on a colectomy.

In our first two patients who suffered from a mucosal disease and did not receive a colon graft, colitis developed after takedown of the initial ileostomy. It required the recreation of an ileostomy in both patients and this resolved the symptoms.

DISCUSSION

In this long-term study of intestinal transplantation, late graft loss was uncommon and occurred in only 16% of the intestinal grafts after the first post-Tx year. This single-centre experience is clearly contrasting to the recent results of the international registry showing a continuous decline of graft survival rate curve with time post-Tx.[1] These differing results may be related to our systematic follow-up policies, long-term and long-

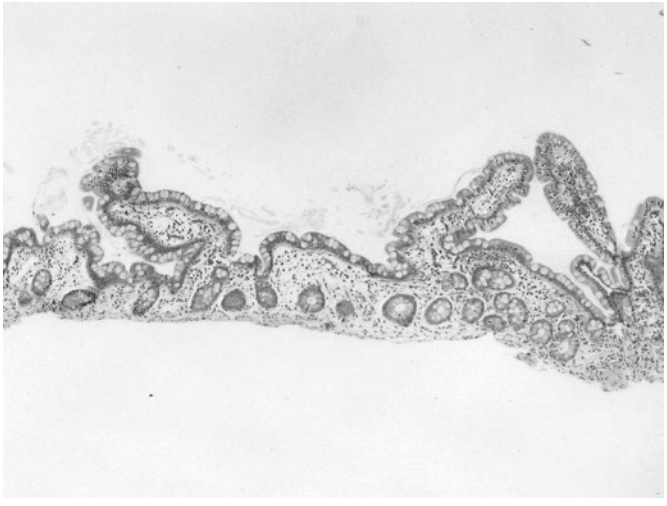

Figure 1 Ileal biopsy 10 years after combined liver and small bowel transplantation. Villi are normal and there is no inflammation (patient 2) (haematoxylin and eosin staining, magnification ×10).

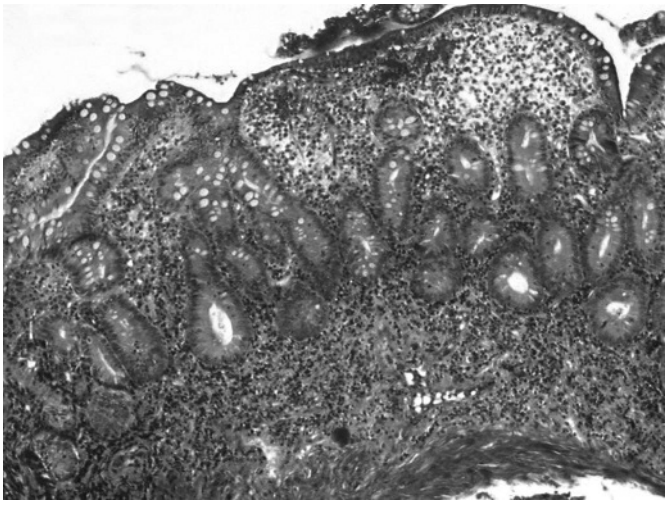

Figure 2 Ileal biopsy 8 years after small bowel transplantation. Chronic rejection: villous atrophy, severe infiltration with mononuclear and plasma cells, fibrosis under the epithelium and around the large vessels of the submucosa (patient 8) (Masson trichrome staining, magnification ×40).

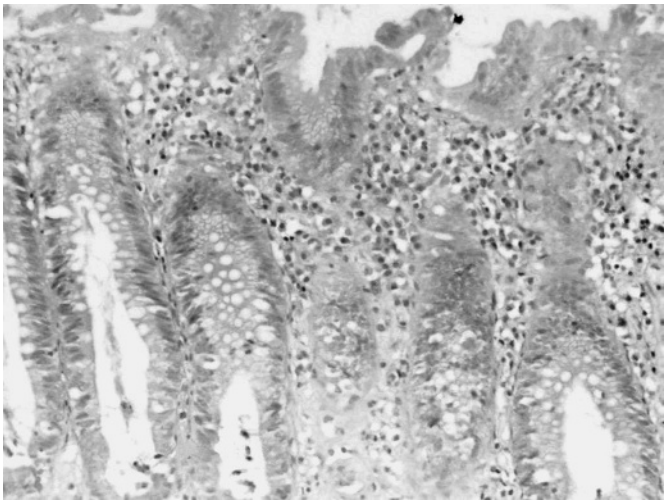

Figure 3 Colon biopsy 7 years after combined liver and small bowel transplantation. Mild to moderate inflammation of the lamina propria (patient 9) (haematoxylin and eosin staining, magnification ×10).

distance, and the early transfer to our unit for severe acute events. Late acute rejection was a rare, but severe, problem.[4] As expected, poor compliance was a concern and responsible for graft loss in two teenagers. It must be emphasised, however, that in compliant patients no occult chronic rejection was diagnosed either on clinical or histological findings.

The proportion of patients requiring long-term enteral nutrition points to eating disorders as an important concern. Early prevention with oral feeding of neonates with intestinal failure and later multidisciplinary care are crucial.

A functional intestinal graft should support a normal growth pattern. Except in children on high-dose steroids, the growth velocity was normal from the second post-Tx year and up to puberty. In one-third of the children, however, stature remained below the normal limits. As they may have delayed puberty these children may finally reach a normal height, although later than their peers. Indeed, most of the older patients attained an adult height within normal limits although shorter than their genetic target height. We did not generally observe a catch-up growth and others have found the same.[4 5 8] However, only one-quarter of our patients were very short at the time of transplantation, whereas in the only study that reports catch-up growth[7] the 23 patients were younger and more stunted (median age 1.1 year, height −3.36 SD at Tx). The improbability of a catch-up growth is important in the timing of transplantation as the height "lost" before transplantation will probably be lost forever.

Extra-digestive causes were not evident in the subgroup of children with growth failure. Hormone levels were normal. A genetic origin was improbable as the original diseases were different, the pair of siblings followed different growth patterns and no patient had parents of short stature. Chronic inflammation was not found in the majority of intestinal biopsies. Most of these patients had received an L–SBTx, but a difference between the two types of transplantation was not significant in the whole group in the present study or in other studies.[4–8] All children received low-dose steroids: the pharmacokinetics of the drug could have induced more side effects on growth in some children.[17]

The absorptive function of the intestine was evaluated by the method of balance studies. Steatorrhoea was important in the majority of patients, resulting in an energy absorption rate nearly always lower than normal. A previous study reported also a coefficient of lipid absorption of 86% only in a group of 22 children.[18] The fat loss was not due to pancreatic insufficiency as the faecal elastase was normal and treatment with pancreatic enzymes ineffective. Early after transplantation lymphatic dilations were common on systematic biopsies, although less frequent thereafter. The transplant surgeon does not reconnect the lymphatic system where chylomicrons circulate after release by the enterocytes. Fat malabsorption is thus probably due to an insufficient re-establishment of a functional lymphatic circulation. The stability of the absorption rates in those children who underwent serial studies suggests the absence of occult chronic rejection, but also of any late functional adaptation.

Fat malabsorption is usually compensated by hyperphagia and should not be a cause of growth failure. The patients included in this study were indeed hyperphagic, most of them receiving theoretically more energy than the recommended intakes. However, the dietary reports might have been falsely optimistic due to the variability of the spontaneous food intakes. Protein intakes were also reported as high, with the same possible bias. Indeed, it is most probable that the growth retardation in a significant proportion of children was due to the faecal energy loss and that the importance of closely controlling the energy intake was not recognised early on: all these patients were transplanted at the beginning of our experience, when PN-dependent children were more stunted and when after transplantation more attention was directed on survival and rejection than on nutrition and growth. Weaning of all nutritional support, including enteral nutrition, was a goal: this is retrospectively debatable considering the reduced absorptive function and the frequent anorexia. The three children who underwent a balance study at 10 years post-transplant are an example: their energy intake was insufficient or borderline, especially as one of them had the most important (albeit stable) steatorrhoea of the whole group. Considering the proportion of children depending on enteral nutrition years post-Tx, and the normal growth curve of the patients more recently transplanted, we assume now that an intensive nutritional approach is a major key for growth.[5]

Nutritional parameters in blood were evaluated as markers of graft function. Mostly normal folate and vitamin B_{12} levels suggested a generally efficient absorption. Low retinol-binding protein levels could have been due to the frequent vitamin A deficiency.[19] Low cholesterol level was a reflection of steatorrhoea, and might be protective against late post-transplant cardiovascular risks. Malabsorption of fat-soluble vitamins was also a consequence of steatorrhoea but less significant than in cholestasis, as the clotting parameters were normal. The vitamin supplementation explains probably why we did not observe the early hypovitaminosis E reported in another study.[18] The compliance with supplementation may have been low later on. However, plasma levels evaluate stores imprecisely: the ratio to blood lipids for vitamin E[20] and conjunctival smears or measurement in the liver for vitamin A[19] are deemed more adequate. Levels of iron and magnesium were recorded, but were not considered here as good markers of absorption as they are dependent on intake, and magnesium levels are decreased during treatment with tacrolimus.[21] IGF-1 levels could have been used for evaluation of the nutritional status;[22] however, they were reported in one study as low before transplantation and normal thereafter, despite a decreased growth velocity.[5]

Endoscopic and histological findings gave further important information for the long-term: it must be emphasised that no

sign suggestive of chronic rejection, such as cellular infiltration or fibrosis, was incidentally discovered. When the patient was asymptomatic the histology was normal. The only exception may be the non-compliant patient in whom chronic rejection was diagnosed after emergency surgery for obstruction; however, previous symptoms had most probably been neglected. The relationship between rejection and the acute occlusion is also unclear in this multi-operated patient.

Simultaneous transplantation of the right colon in patients with mucosal and motility disorders is controversial.[23] However, complications were observed only once. In the majority, the reabsorptive function of the colon reduced the number of stools and helped to maintain night and day continence. Biopsies of the transplanted colon often showed a mild lymphocytic infiltration, with no signs suggestive of rejection. We suggest that these lymphocytes might be regulatory T cells, necessary to maintain acceptance of the graft.[24] It is noteworthy that two patients, with mucosal disease without a colon graft, developed serious complications when the enteric continuity was restored with the native colon or rectum; symptoms resolved only after ileostomy. In our opinion, this is a strong reason to transplant the colon when needed.

In conclusion, intestinal transplantation allows the majority of patients to have intestinal autonomy with subnormal to normal digestive function, assuring a normal growth and pubertal development. Due to fat malabsorption and frequent eating disorders, a high energy intake, either oral or enteral, is necessary. Chronic rejection does not appear to develop insidiously in compliant patients. Although rare, late acute rejection may complicate an infectious diarrhoea. Long-term follow-up by an experienced centre remains critical to minimise this late severe complication. Specific studies regarding quality of life will have to be performed, especially in comparison with long-term home PN.[25] Further functional, histological and immunological studies are needed to understand better the long-term bilateral adaptation of the transplanted intestine and of the recipient.

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Long-term outcome, growth and digestive function in children 2 to 18 years after intestinal transplantation

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