Table 2
Changes in microscopic intestinal morphology.

		n	Jejunum			Proximal ileum			Distal ileum		
			Villus height (μm)	Crypt depth (μm)	Absorptive mucosal surface per unit area ($cm^2/1 cm^2$)	Villus height (μm)	Crypt depth (μm)	Absorptive mucosal surface per unit area ($cm^2/1 cm^2$)	Villus height (μm)	Crypt depth (μm)	Absorptive mucosal surface per unit area ($cm^2/1 cm^2$)
Control		3	468.7 ± 35.0	167.3 ± 17.4	12.9 ± 1.9	338.2 ± 29.9	150.5 ± 12.0	9.2 ± 1.5	365.4 ± 29.9	158.2 ± 9.2	9.8 ± 1.6
80%SBR	Day 1	6	452.5 ± 18.7 †	180.2 ± 9.6 *	12.5 ± 0.8	382.8 ± 25.3 †	163.9 ± 6.3	10.8 ± 0.9	367.4 ± 18.2 ††	168.5 ± 9.5	9.9 ± 1.0
	Day 4	6	591.7 ± 39.6 *,†	220.2 ± 6.1 *,††	17.7 ± 1.2	463.4 ± 24.1 **,††	174.3 ± 6.9	14.0 ± 1.5 *,†	452.3 ± 24.7 **,††	176.5 ± 8.1	13.4 ± 0.8 *,†
	Day 7	6	553.6 ± 13.3 ††	220.8 ± 15.8 *,††	16.1 ± 0.9	513.6 ± 22.8 **,††	207.4 ± 13.2 **	14.6 ± 0.8 *,†	476.5 ± 28.1 **,††	191.5 ± 9.9 †	14.6 ± 1.1 **,††
	Day 11	6	639.7 ± 41.3 **,††	247.4 ± 18.4 **,††	21.9 ± 1.9 **,††	538.0 ± 25.1 **,††	212.3 ± 9.1 **	16.4 ± 1.0 **,†	519.4 ± 23.9 **,††	210.1 ± 17.6 *	15.9 ± 0.9 **,††
	Day 15	6	708.9 ± 24.1 **,††	250.7 ± 14.0 **,††	23.8 ± 1.1 **,††	615.7 ± 31.1 **,††	230.3 ± 8.4 **,†	19.0 ± 1.1 **,††	580.3 ± 17.3 **,††	246.0 ± 18.8 **	20.2 ± 0.7 **,††
Sham	Day 1	6	390.6 ± 10.1	152.5 ± 7.0	11.8 ± 0.6	305.6 ± 21.3	148.5 ± 7.4	8.0 ± 1.0	291.4 ± 9.5	146.3 ± 5.0	7.9 ± 0.3
	Day 4	6	444.0 ± 31.6	160.0 ± 8.2	14.0 ± 1.9	337.5 ± 8.2	168.8 ± 9.7	11.1 ± 1.4	328.6 ± 11.2	152.9 ± 12.1	9.7 ± 1.1
	Day 7	6	445.9 ± 14.9	160.8 ± 9.9	13.1 ± 1.0	355.2 ± 16.9	173.7 ± 8.3	10.4 ± 1.1	329.6 ± 14.0	152.1 ± 8.7	9.5 ± 0.7
	Day 11	6	479.2 ± 13.7	176.8 ± 8.6	14.1 ± 0.5	423.1 ± 14.6	201.7 ± 11.3 **	12.6 ± 0.8	386.8 ± 8.3	184.1 ± 7.0	11.4 ± 0.3
	Day 15	6	503.8 ± 16.0	198.4 ± 5.5	15.8 ± 0.9	425.2 ± 14.4	200.4 ± 5.4 **	13.6 ± 1.0	413.4 ± 12.3	208.2 ± 8.6 *	13.9 ± 0.8

Data are expressed as the means ± SE. Comparisons with controls were performed by Dunnett's test. Comparisons among the groups at similar time points were analyzed by Student's *t*-test.
* $P < 0.05$ versus controls.
** $P < 0.01$ versus controls.
† $P < 0.05$ versus the sham operation subjects.
†† $P < 0.01$ versus the sham operation subjects.
80% SBR, 80% small bowel resection.

(4.3 ± 0.8 ng/mL, $P = 0.009$). GLP-2 levels were maintained at significantly higher levels under short bowel conditions than in native small bowel length conditions ($P = 2.25 \times 10^{-6}$, Table 3).

4. Discussion

Ideally, the progression of intestinal adaptation in infants with short bowel syndrome would occur gradually over 1 to 2 years [32]. In the first 1 to 2 weeks after resection, ileus occurs in the remaining bowel. The next 1 to 6 months are characterized by hypersecretion. Fluid and electrolytes are lost owing to a large amount of watery stool excretion. Subsequently, morphological and functional adaptations occur, such as an increase in the absorptive mucosal surface area. Adaptation is known to result from an increase in villus height and in the rate of crypt cell proliferation [32]. After 1 to 2 years, the compensated absorptive mucosa could perform adequate nutrition and fluid absorption. However, we have encountered some cases in which ideal adaptation cannot be obtained. The clinical challenge is to induce intestinal adaptation early and effectively among children with short bowel syndrome. Postresection intestinal adaptation is supposed to occur only in response to feeding [32]. It was reported that adaptation was impaired in the absence of luminal nutrients in case of total parenteral nutrition [17]. Moreover, only 25% reduction in oral intake caused significantly lower enterocyte production in the crypts [6]. Here, we considered a management strategy to achieve both an orexigenic effect, which promotes food intake, and a trophic effect, which increases the absorptive mucosal surface. Among several gastrointestinal hormones, we focused on ghrelin and GLP-2, which are known to actively bring about these 2 effects [2,12,18,24]. They may provide a clue about how to solve the clinical problem of short bowel syndrome.

In short bowel environments, acyl ghrelin was maintained at an equivalent level compared with the native bowel length conditions. Acyl ghrelin levels increased immediately in the early postoperative period (Table 3). The timie when acyl ghrelin reached its peak on day 4 accorded with the time when the body weight and food intake recovered to the preoperative levels (Figs. 1 and 2). It also matched the start of the morphological adaptation of the remaining intestine. Among the multiple functions of acyl ghrelin [15], here we want to focus on the regulation of food intake. Numerous peptides secreted from the gastrointestinal tract decrease food intake; only one, acyl ghrelin has a promoting effect [35]. Luminal nutrients ingested orally can stimulate intestinal peristalsis, mucosal blood flow, and endogenous secretions of various hormones and growth factors [15,26,28]. The significant increase in endogenous acyl ghrelin levels in our 80% SBR animals within the first 4 postoperative days may suggest the necessity of ensuring the presence of luminal nutrients to initiate the adaptation of the residual intestine. Interestingly, a significant increase in endogenous des-acyl ghrelin level was seen on postoperative day 1, before a peak in the acyl ghrelin levels was reached on day 4. It was reported that the metabolic machinery that induces intestinal adaptation had already been turned on within the first 24 h in the 80% SBR model rats [37]; however, intestinal permeability, which may be detrimental to the organism, was also increasing at the same time [37]. Des-acyl ghrelin induces an anorexigenic effect by decreasing food intake and delaying gastric emptying [2,10]. Therfore, des-acyl ghrelin secretion may suppress the intake of luminal nutrients until the intestinal condition becomes well regulated. It is thus reasonable to say that the control of intake is an indispensable factor for intestinal compensation.

As was found in previous reports [18,19], significantly higher levels of GLP-2 were secreted under short bowel conditions compared with native bowel length conditions. GLP-2 levels increased immediately after the operation (Table 3). The peak GLP-2 level

Table 3
The secretion trends of endogenous acyl ghrelin, des-acyl ghrelin, and glucagon-like peptide-2 (GLP-2) following massive small bowel resection.

		n	Pre-prandial plasma acyl ghrelin (fmol/ml)	Pre-prandial plasma des-acyl ghrelin (fmol/ml)	Postprandial plasma glucagon-like peptide-2 (ng/ml)
Control		3	53.6 ± 9.2	583.6 ± 79.1	2.0 ± 0.2
80%SBR	Day 1	6	93.3 ± 22.7	1021.6 ± 93.1 **	3.6 ± 0.4
	Day 4	6	104.7 ± 14.1 *	709.1 ± 62.6	4.3 ± 0.8 **,†
	Day 7	6	65.4 ± 6.7	490.1 ± 41.8	3.1 ± 0.2 ††
	Day 11	6	72.1 ± 10.0	508.2 ± 54.7	3.3 ± 0.3 ††
	Day 15	6	73.4 ± 6.1	481.7 ± 46.0	2.8 ± 0.4
Sham	Day 1	6	93.7 ± 11.6	917.2 ± 108.2 *	2.9 ± 0.4
	Day 4	6	110.7 ± 24.1	694.8 ± 22.1	2.0 ± 0.2
	Day 7	6	105.4 ± 19.5	584.5 ± 83.9	2.1 ± 0.2
	Day 11	6	91.2 ± 11.8	565.0 ± 72.5	1.9 ± 0.1
	Day 15	6	95.2 ± 21.6	538.7 ± 102.9	2.2 ± 0.2

Data are expressed as means ± SE. The differences between the groups and the time courses were evaluated by a 2-factor factorial analysis of variance (ANOVA) followed by Tukey's multiple-comparison posttest. Comparisons with controls were performed by Dunnett's test, and comparisons between groups at similar time points were performed by Student's *t*-test. There were no significant differences between groups ($F = 2.94$, $P = 0.09$) and time courses ($F = 0.86$, $P = 0.49$) in the levels of acyl ghrelin. The time course difference was significant ($F = 13.73$, $P < 0.01$); however, there was no difference between groups ($F = 0.15$, $P = 0.70$) in the levels of des-acyl ghrelin. There were significant differences between groups ($F = 28.55$, $P < 0.01$) but not between the time course changes ($F = 1.97$, $P = 0.11$) in the levels of GLP-2.

* $P < 0.05$ versus controls.

** $P < 0.01$ versus controls.

† $P < 0.05$ versus the sham-operated subjects.

†† $P < 0.01$ versus the sham-operated subjects.

80% SBR, 80% small bowel resection.

in the 80% SBR animals was reached at the same time as the start of the expansion of the absorptive mucosal surface on day 4. Subsequent steady gain in body weight implied the production of functionally mature enterocytes [29]. Both in the preclinical and clinical models, GLP-2 is a well-studied intestinotrophic factor that enhances nutrient and fluid absorption in the context of massive small bowel resection [11,22,28]. Exogenous GLP-2 stimulates crypt cell proliferation and results in a significant increase in the absorptive mucosal area due to villus lengthening [8,20,31]. Additionally, it promotes nutrient transporter expression, intestinal blood flow [20,31], and intestinal barrier function [5]. The significant increase in endogenous GLP-2 in our 80% SBR animals within the first 4 postoperative days may suggest the necessity of ensuring enough stimulation to initiate the expansion of the absorptive mucosal surface. GLP-2 secretion is stimulated by luminal nutrients [12,19,25]. It was interesting that both acyl ghrelin and GLP-2 increased immediately at the same time and peaked at the time when morphological adaptation became evident.

From our laboratory findings, we could imagine a more effective method of inducing residual intestinal adaptation after massive small bowel resection. In a previous study, GLP-2 receptor expression was shown to have significantly increased by postoperative day 3 in 90% SBR model rats [13]. Moreover, continued intravenous administration of GLP-2 during the first postoperative week was required to maximize the adaptation of the remaining bowel in rats [12,13]. These findings suggest that early treatment with a continuous infusion of GLP-2 would be clinically beneficial for short bowel syndrome patients. However, it has been reported that exogenous GLP-2 suppresses ghrelin secretion by nearly 10% in humans [4]. In addition, GLP-2 administration led to a significant elevation of glucagon level [33]. Glucagon is a powerful inhibitor of ghrelin in humans [1]. In rats, intravenous glucagon has been reported to upregulate the synthesis and release of des-acyl ghrelin [14]. The regulation of food intake with exogenous GLP-2 is controversial. Both peripheral [3] and central [36] administration of GLP-2 inhibited food intake in rodents. In healthy humans, the physiologic [33] and pharmacologic [30] GLP-2 doses given intravenously for 3 to 4.5 h had no effect. Yet, the effects of the sustained administration of GLP-2 on food intake in humans are still unknown. These reports imply that a combined administration of acyl ghrelin and GLP-2 would be more useful. As an example of a possible clinical application of a combination that reinforces physiological hormone secretion patterns, the therapeutic schema may be as follows. Under total parenteral nutritional support, a continuous intravenous administration of GLP-2 should be initiated to induce augmentation of the absorptive mucosal area. Additionally, oral food intake should be started as early as possible, and GLP-2 supplementation should be continued in the postprandial period with administration of acyl ghrelin in the preprandial period to stimulate adequate compensation in the remaining small intestine.

Further studies on the relation between acyl ghrelin, des-acyl ghrelin and GLP-2 after massive small bowel resection are necessary to gain concrete information that may aid in developing a more effective method to induce remnant intestinal adaptation.

5. Conclusion

This is the first report to show the trends of endogenous preprandial plasma acyl ghrelin, des-acyl ghrelin and postprandial plasma GLP-2 in the context of massive small bowel loss. The expansion of the absorptive mucosal surface area became evident after postoperative day 4. All the 3 gastrointestinal hormones studied were elevated immediately after resection. The acyl ghrelin and GLP-2 levels were peaked at the same time as when body weight and food intake recovered to the preoperative levels and as when the remnant intestinal adaptation started. A management strategy that could achieve active orexigenic and trophic effects at the same time may provide a clue as to the development of a new therapy for inducing intestinal compensation in short bowel syndrome patients.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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References

[1] Arafat MA, Otto B, Rochlitz H, Tschöp M, Bähr V, Möhlig M, et al. Glucagon inhibits ghrelin secretion in humans. Eur J Endocrinol 2005;153:397–402.
[2] Asakawa A, Inui A, Fujimiya M, Sakamaki R, Shinfuku N, Ueta Y, et al. Stomach regulates energy balance via acylated ghrelin and desacyl ghrelin. Gut 2005;54:18–24.
[3] Baldassano S, Bellanca AL, Serio R, Mulè F. Food intake in lean and obese mice after peripheral administration of glucagon-like peptide 2. J Endocrinol 2012;213:277–84.
[4] Banasch M, Bulut K, Hagemann D, Schrader H, Holst JJ, Schmidt WE, et al. Glucagon-like peptide 2 inhibits ghrelin secretion in humans. Regul Pept 2006;137:173–8.
[5] Benjamin MA, McKay DM, Yang PC, Cameron H, Perdue MH. Glucagon-like peptide-2 enhances intestinal epithelial barrier function of both transcellular and paracellular pathways in the mouse. Gut 2000;47:112–9.
[6] Cronk DR, Ferguson DC, Thompson JS. Malnutrition impairs postresection intestinal adaptation. JPEN J Parenter Enteral Nutr 2000;24:76–80.
[7] de Segura IA, Vallejo-Cremades MT, Lomas J, Sánchez MF, Caballero MI, Largo C, et al. Exogenous ghrelin regulates proliferation and apoptosis in the hypotrophic gut mucosa of the rat. Exp Biol Med 2010;235:463–9.
[8] Drucker DJ, Erlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. Proc Natl Acad Sci USA 1996;93:7911–6.
[9] Hanson WR, Osborne JW, Sharp JG. Compensation by the residual intestine after intestinal resection in the rat. II. Influence of postoperative time interval. Gastroenterology 1977;72:701–5.
[10] Inhoff T, Mönnikes H, Noetzel S, Stengel A, Goebel M, Dinh QT, et al. Desacyl ghrelin inhibits the orexigenic effect of peripherally injected ghrelin in rats. Peptides 2008;29:2159–68.
[11] Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut 2011;60:902–14.
[12] Kaji T, Tanaka H, Holst JJ, Redstone H, Wallace L, de Heuval E, et al. The effects of variations in dose and method of administration on glucagon like peptide-2 activity in the rat. Eur J Pharmacol 2008;596:138–45.
[13] Kaji T, Tanaka H, Redstone H, Wallace LE, Holst JJ, Sigalet DL. Temporal changes in the intestinal growth promoting effects of glucagon-like peptide 2 following intestinal resection. J Surg Res 2009;152:271–80.
[14] Katayama T, Shimamoto S, Oda H, Nakahara K, Kangawa K, Murakami N. Glucagon receptor expression and glucagon stimulation of ghrelin secretion in rat stomach. Biochem Biophys Res Commun 2007;357:865–70.
[15] Korbonits M, Goldstone AP, Gueorguiev M, Grossman AB. Ghrelin – a hormone with multiple functions. Front Neuroendocrinol 2004;25:27–68.
[16] Kristenssson E, Sundqvist M, Astin M, Kjerling M, Mattsson H, Dornonville de la Cour C, et al. Acute psychological stress raises plasma ghrelin in the rat. Regul Pept 2006;134:114–7.
[17] Levine GM, Deren JJ, Yezdimir E. Small-bowel resection. Oral intake is the stimulus for hyperplasia. Am J Dig Dis 1976;21:542–6.
[18] Ljungmann K, Hartmann B, Kissmeyer-Nielsen P, Flyvbjerg A, Holst JJ, Laurberg S. Time-dependent intestinal adaptation and GLP-2 alterations after small bowel resection in rats. Am J Physiol Gastrointest Liver Physiol 2001;281:G779–85.
[19] Martin GR, Wallace LE, Hartmann B, Holst JJ, Demchyshyn L, Toney K, et al. Nutrient-stimulated GLP-2 release and crypt cell proliferation in experimental short bowel syndrome. Am J Physiol Gastrointest Liver Physiol 2005;288:G431–8.
[20] Martin GR, Wallace LE, Sigalet DL. Glucagon-like peptide-2 induces intestinal adaptation in parenterally fed rats with short bowel syndrome. Am J Physiol Gastrointest Liver Physiol 2004;286:G964–72.
[21] Martini AC, Fernández-Fernández R, Tovar S, Navarro VM, Vigo E, Vazquez MJ, et al. Comparative analysis of the effects of ghrelin and unacylated ghrelin on luteinizing hormone secretion in male rats. Endocrinology 2006;147:2374–82.
[22] McMellen ME, Wakeman D, Longshore SW, McDuffie LA, Warner BW. Growth factors: possible roles for clinical management of the short bowel syndrome. Semin Pediatr Surg 2010;19:35–43.
[23] Menge H, Hopert R, Alexopoulos T, Riecken EO. Three-dimensional structure and cell kinetics at different sites of rat intestinal remnants during the early adaptive response to resection. Res Exp Med 1982;181:77–94.
[24] Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, et al. A role for ghrelin in the central regulation of feeding. Nature 2001;409:194–8.
[25] Nelson DW, Murali SG, Liu X, Koopmann MC, Holst JJ, Ney DM. Insulin-like growth factor I and glucagon-like peptide-2 responses to fasting followed by controlled or ad libitum refeeding in rats. Am J Physiol Regul Integr Comp Physiol 2008;294:R1175–84.
[26] O'Brien DP, Nelson LA, Huang FS, Warner BW. Intestinal adaptation: structure, function, and regulation. Semin Pediatr Surg 2001;10:56–64.
[27] Park JM, Kakimoto T, Kuroki T, Shiraishi R, Fujise T, Iwakiri R, et al. Suppression of intestinal mucosal apoptosis by ghrelin in fasting rats. Exp Biol Med 2008;233:48–56.
[28] Pereira PM, Bines JE. New growth factor therapies aimed at improving intestinal adaptation in short bowel syndrome. J Gastroenterol Hepatol 2006;21:932–40.
[29] Pereira-Fantini PM, Thomas SL, Wilson G, Taylor RG, Sourial M, Bines JE. Short- and long-term effects of small bowel resection: a unique histological study in a piglet model of short bowel syndrome. Histochem Cell Biol 2011;135:195–202.
[30] Schmidt PT, Näslund E, Grybäck P, Jacobsson H, Hartmann B, Holst JJ, et al. Peripheral administration of GLP-2 to humans has no effect on gastric emptying or satiety. Regul Pept 2003;116:21–5.
[31] Scott RB, Kirk D, MacNaughton WK, Meddings JB. GLP-2 augments the adaptive response to massive intestinal resection in rat. Am J Physiol 1998;275:G911–21.
[32] Sigalet DL. Nonruminant Nutrition Symposium: the role of glucagon-like peptide-2 in controlling intestinal function in human infants: regulator or bystander. J Anim Sci 2012;90:1224–32.
[33] Sørensen LB, Flint A, Raben A, Hartmann B, Holst JJ, Astrup A. No effect of physiological concentrations of glucagon-like peptide-2 on appetite and energy intake in normal weight subjects. Int J Obes Relat Metab Disord 2003;27:450–6.
[34] Stengel A, Wang L, Taché Y. Stress-related alterations of acyl and desacyl ghrelin circulating levels: mechanisms and functional implications. Peptides 2011;32:2208–17.
[35] Strader AD, Woods SC. Gastrointestinal hormones and food intake. Gastroenterology 2005;128:175–91.
[36] Tang-Christensen M, Larsen PJ, Thulesen J, Rømer J, Vrang N. The proglucagon-derived peptide, glucagon-like peptide-2, is a neurotransmitter involved in the regulation of food intake. Nat Med 2000;6:802–7.
[37] Welters CF, Dejong CH, Deutz NE, Heineman E. Intestinal function and metabolism in the early adaptive phase after massive small bowel resection in the rat. J Pediatr Surg 2001;36:1746–51.

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●第39回日本小児栄養消化器肝臓学会　シンポジウム
小児の在宅栄養支援の問題点と今後の展開

小児腸管不全症例に対する在宅静脈栄養の現状と問題点

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*1大阪大学大学院医学系研究科外科学講座小児成育外科
*2同　小児科

曺　英樹*1・上原秀一郎*1・上野　豪久*1・和佐　勝史*1・奈良　啓悟*1
大植　孝治*1・臼井　規朗*1・野村　元成*1・正畠　和典*1・井深　奏司*1
銭谷　昌弘*1・中畠　賢吾*1・近藤　宏樹*2

Key Words：在宅静脈栄養，腸管不全，ヒルシュスプルング病類縁疾患，短腸症候群

要　旨

腸管不全患児において在宅静脈栄養（HPN）は社会・家庭復帰のために重要な役割を果たす。当科におけるHPNの現状と問題点について検討した。対象は1983年から2012年まで当科にてHPNを施行した40例。施行期間は8カ月～27年，疾患は腸管運動障害19例，難治性下痢10例，短腸症候群6例，その他5例であった。カテーテル（CVC）はカフ付きもしくは埋め込み型リザーバーを用いた。HPN施行においては院外薬局による無菌調剤とし，輸液ラインはクローズドシステムを用いた。微量元素，ビタミンは年齢に応じて一日必要量を毎日投与し，必要に応じてSeを投与した。転帰は離脱による終了が11例，原疾患による死亡が8例，転医が3例で，1例で小腸移植を行った。17例が現在も継続中である。1,000日あたりのCVC感染頻度は0.26であった。カテーテル関連合併症はカフ付きCVCで少なかった。適切なHPNの施行により合併症も少なく，多くの患児で成長発達を維持し，QOLの向上が可能となった。

緒　言

栄養療法においては消化管が機能している場合には経腸栄養が優先されるのが大原則である。しかし短腸症候群やヒルシュスプルング病類縁疾患をはじめとする腸管不全症例に対しては中心静脈栄養（Total Parenteral Nutirition：TPN）が長期にわたり必須となる。

在宅（中心）静脈栄養法（Home Parenteral Nutrition：HPN）とはTPNによるサポートを必要とする患児に家庭でTPNを行うことである。HPNにより患児は入院生活から解放され，成長していく上でかけがえのない大切な場所である家庭や学校への復帰を果たすことができるようになる。患児・家族ともquality of life（QOL）の向上がもたらされるだけでなく，その後の成長や発達に重要な機会を得ることができる。すなわち成長発達過程の小児においては，このHPNの成否が腸管不全の患児の予後とQOLを大きく左右するといっても過言ではない。

一方でHPNにも合併症が起こり得るのも事実である。カテーテル関連血流感染（Catheter Related Blood Stream Infection：CRBSI）をはじめとする感染性合併症，カテーテルの閉塞，破損などの機械的合併症，肝機能障害などの代謝性合併症が起こる危険があり，家庭においても入院時と同様に正しい知識によ

別刷請求先：〒565-0871　大阪府吹田市山田丘2－2
大阪大学大学院医学系研究科外科学講座小児成育外科（D6）
曺　英樹

表1 小児の在宅静脈栄養施行症例

基礎疾患	
腸管運動障害	19
難治性下痢	10
短腸症候群	6
その他	5
合計	40
性別	男児21 女児19
開始年齢	6カ月～15歳(平均3.2歳)
施行期間	244日～25.7年 (平均8.7年)

1983～2012年

る厳密な管理を要する。

当科では30年にわたり小児の腸管不全症例に対してHPNを行ってきた。これらの現状と問題点について後方視的に検討したので報告する。

対象・方法

1983年から2012年まで当科にてHPNを施行してきた小児40例を対象とした。男児21例，女児19例であり，対象となった疾患はHirschsprung病類縁疾患などの腸管運動障害19例，短腸症候群6例，難治性下痢10例，その他5例であった（表1）。

当科においてHPNは以下の手順で導入・維持した。症状が落ち着き家庭復帰を目指すにあたり，長期留置用のダクロンカフ付きカテーテル（Broviacカテーテル®）もしくは，皮下埋め込み型リザーバーを留置選択した（図1）。夜間を中心に間欠的TPNを行い，家族が十分にTPNの手技を習熟した段階でHPNに移行した。輸液は原則として院外薬局による無菌調剤とし，輸液ラインはクローズドシステムを用いた（図2）。微量元素，ビタミンは年齢に応じて一日必要量を毎日投与した。必要に応じて院内製剤によりSeを投与した。カテーテル刺入部の管理では刺入部の消毒はクロルヘキシジンまたはポピドンヨードを用い，患者の皮膚にあわせてフィルム型もしくはパッド型のドレッシングを選択した。

外来受診は安定期には月に1回程度とし，身長，体重を成長曲線にプロットして静的動的に成長を評価した。

カテーテルの種類による合併症の頻度を生存曲線にて評価した。またHPNの転帰，その他の合併症について後方視的に検討した。

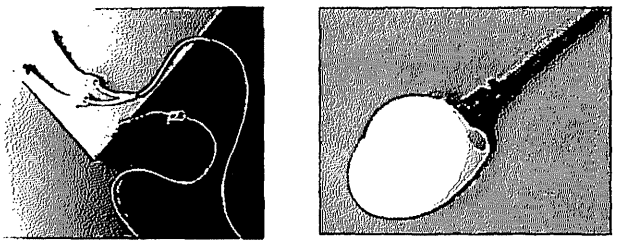

図1 HPNに用いるカテーテル

右：Broviacカテーテルと Hickmanカテーテル。ダクロンカフが皮下に癒着することにより長期間使用可能。シリコン製。破損すれば部位によっては修復可能である。
左：完全皮下埋込型ポート。これを皮下に留置する。中央の膜を特殊な針（Huber針）で穿刺して使用する。輸液をしていないときには体の外のデバイスがない状態を維持できる。

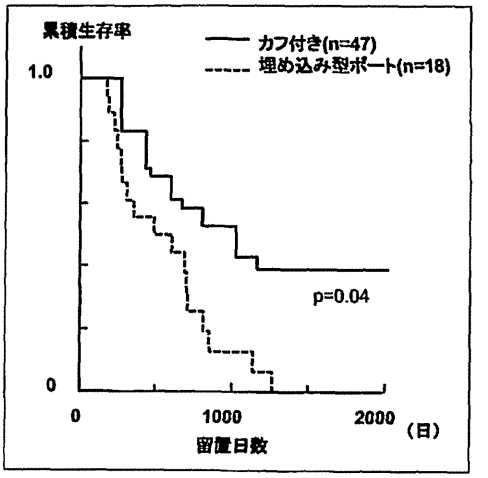

図2 カテーテルサバイバル分析

小児においてはカフ付きカテーテル（Broviacカテーテル）が合併症も少なく長持ちする傾向にあった。($p<0.05$)

結　果

開始時の年齢は6カ月～15歳（平均5.2歳），施行期間は継続中を含め，8カ月から27年（平均8.7年）であった。終了症例は離脱による終了が11例，死亡が8例，転医が3例，1例で長期の静脈栄養に伴う肝障害により，小腸移植を行った（表2）。死亡例のうち腸管不全およびHPNに関連する死亡は2例で腸炎による敗血症1例，肝不全1例であった。その他の4例は併存する消化管以外の疾患による死亡であった。

カテーテル1本当たりのCVCの使用期間は6カ月～7年（758±147日）で，1,000日あたりのCVC感染

表2　小児在宅静脈栄養の疾患別転帰

疾患名	症例数	継続	離脱	死亡	小腸移植	転医
腸管運動障害	19	10	2	5		2
難治性下痢	10	5	3	1	1	
短腸症候群	6	1	3	1		1
その他	5	1	3	1		
合計	40	17	11	8	1	3

表3　小児の在宅静脈栄養の合併症

合併症	症例数
成長障害	5例
肝障害	12例
血管閉塞	2例
その他	5例

※カテーテル関連の合併症をのぞく

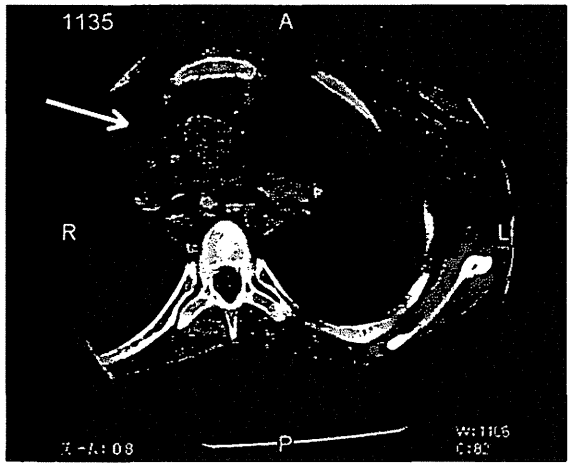

図3　長期HPNの合併症—SVC閉塞—

22歳女性。20年間HPNを継続していたが，上大静脈が完全閉塞した。現在大伏在静脈よりカテーテルを先端が下大静脈になるように留置している。カテーテルは腹部から体の外に出している。

頻度は0.26であった。カテーテル関連の合併症によるカテーテル使用期間は完全皮下埋め込み型ポートの方がカフ付きカテーテルよりも有意に高かった（図2）。

カテーテル関連以外の合併症では腸管運動障害の3例，難治性下痢の2例に成長障害を認め，GH補充療法を必要とした（表3）。肝障害は12例に認めた。その他に短腸症候群に伴うD-lactic acidosisを2例，性腺発育遅延2例，腎障害を1例に認めた。10年以上HPNを行った症例のうち，2例でSVCの完全閉塞を認めた（図3）。

考　　察

在宅静脈栄養とは入院中に行っている栄養療法を自宅にて行い，家庭生活への復帰や，就学などを目指すものである[1)~4)]。在宅栄養療法の導入によって患児は入院生活から解放され，家庭復帰，就学・社会復帰を果たすことができるようになりQOLの向上がもたらされる。

適応となる疾患は静脈栄養を要する疾患の全てである。主に小児では消化吸収障害もしくは運動機能障害を来す腸管不全症例が適応になる。消化吸収障害を来す疾患としては壊死性腸炎・小腸閉鎖・中腸軸捻転などの腸管大量切除後の短腸症候群，難治性下痢があげられる。腸管運動機能障害は小児領域ではヒルシュスプルング病類縁疾患と分類され，hypoganglionosis，慢性偽性腸閉塞症（CIPO：Chronic idiopathic intestinal pseudo-obstruction），MMIHS（Megacystis Microcolon Intestinal Hypoperistalsis Syndrome）がある。その他にも重症のクローン病などの経腸栄養を行うことが病態の増悪につながるような疾患や，ある程度の消化管機能は保たれているものの経口摂取および経腸栄養において十分な栄養を投与することができない病態で，原疾患の管理に入院を必要としない患者全てがHPNの適応となる[5)~11)]。

HPN施行の条件は，病状に急激な変化がない慢性期であること，継続的な栄養療法が必要であること，そして栄養療法により確実な治療効果が得られることである。特に小児においては自己による管理を期待することはほとんどできず，家族などの保護者が在宅静脈栄養療法における介護の中心的役割を果たすことになるので，介護者でもある家族がHPNに積極的であることや，HPNとその合併症対策について十分な理解があることが不可欠である[1)~4),12)]。施行する施設においても，HPNの専門的知識と技術を有する医師，薬剤師，看護師，管理栄養士により，入院中から退院

後も継続して家族に対する教育，サポートを行うことが必要である[12]。さらに，さまざまなトラブル，緊急事態に対応が可能であるというのが条件である。

小児の在宅中心静脈栄養では，特に成人に比べ，破損や感染などのカテーテルに関する合併症が多い[13)~15)]。したがって長期に使用できる，長期留置用カテーテルが優先される。特にダクロンカフ付きのBroviacカテーテル®は長期を目的として作成されたもの[16]で，HPNに適している。成人でよく用いられる完全皮下埋め込み式ポートは輸液をしていない時間は体外部分がないという利点がある[15),17)]。しかし輸液の度に皮膚を穿刺するため，小児ではその痛みに耐え難いこともしばしばみられる。自験例でも学童期には通学の利便性から埋め込み型ポートを選択する患児もみられたが，穿刺の痛みに耐えられず，多くの患児が次の入れ替え時にはBroviacカテーテルを選択する傾向があった。また，破損や感染などの合併症は小児ではポートよりもBroviacタイプの方で少ない傾向がみられた。いずれにせよ，それぞれのカテーテルの特徴を熟知し，疾患，年齢，投与方法および患児のライフスタイルに合わせて選択すべきである。

HPNにおける最も重要な注意点の一つは感染の予防である。HPNにおいてもCRBSI（カテーテル関連血流感染症）は重篤な合併症である。刺入部・輸液ラインの観察は怠ってはならないのはいうまでもなく，薬剤師による無菌調剤，クローズドシステムによる輸液ラインの管理，無菌的カテーテル管理が必要である[13]。当科ではTPN導入時期よりクローズドシステムによる管理の重要性を報告してきている[18]。これらの手技をHPNにおいても徹底することにより，低い感染率を保つことが可能となっている。近年，長期の在宅静脈栄養時のCRBSI予防のためのエタノールロックが注目されている[19]。その他にも抗生剤ロック，ウロキナーゼロック，NaOHロックなど，カテーテルの入れ替えがそう簡単ではない小児において，カテーテルを長持ちさせるための様々な工夫がされている。ただし，いたずらにカテーテルロックを繰り返してはならない。重篤な感染を来した場合，全身状態がよくない場合，保存的治療に抵抗する場合には躊躇なくカテーテルを抜去することも必要である。

その他，カテーテルに関連する合併症に血管閉塞がある。当科でも10年以上HPNを施行した2症例においてSVCの閉塞を来す結果となった。幸い，両症例ともTPNの依存度が低く，現時点では小腸移植の適応とはなっていないが，長期にわたるHPNを行う場合には十分注意を要する合併症の一つである。

HPNは消化管が使えない患児においては，QOLを保ちながら栄養状態を維持する有効な手段であるが，長期のTPNにおいては感染のみならず代謝上の合併症や成長障害を引き起こすため，可能な限り早くに経腸栄養，経口摂取に移行し，離脱を図るべきである。特に短腸症候群では多くの症例で離脱可能と考えられる[1),20)~22)]。ただし，これらの症例でも無理な離脱は受験などのストレスにより急速な栄養障害に陥る危険がありその場合は速やかに静脈栄養を再開すべきである。

一方で，とくにヒルシュスプルング病類縁疾患の患児においてはTPNの依存度が高く[9]，多くの場合で離脱の見込みも少ないと考えられる。長期に及ぶHPNにより，肝障害や成長障害を来す症例がしばしばみられる。また，腸炎を繰り返すことにより，敗血症や重篤な肝障害に陥り，命を落とすこともある。こういった症例には今後，小腸移植を視野に入れた検討を行うべきである。

このような長期静脈栄養を行う腸管不全患児に見られる胆汁鬱滞性肝障害（Intestinal Failure-Associated Liver Disease：IFALD）は，難治性であり，ときに肝不全に進行する場合もある[23]。原因として長期の静脈栄養による血漿アミノ酸パターンの変化や，細菌叢の増殖，腸炎，感染症などが考えられる。過栄養を回避し，経腸栄養を早期開始し，敗血症を予防することが，胆汁鬱滞の発生を抑制することにつながると考えられている[24)~26)]。また最近では，このIFALDに対しω-3系の多価不飽和脂肪酸を含んだ脂肪乳剤が，減黄効果と肝酵素の上昇を抑えることが報告されている[16]。本邦では薬事認可を受けていないが，一部の施設で試験的に使用され，その有効性が報告されており[27),28)]，その効果が期待されている。

このように非常に長期にわたるHPN症例ではSe欠乏が問題となる[29]。Seは現在市販されている静脈栄養剤にはSeは含まれていない。Seは微量元素のひとつであるが，欠乏により心筋症[30]を起こすことが言われている。当科ではSeの院内製剤を静脈内投与し，Seの血中濃度を維持している[31]。

結　論

成長・発達の過程にある小児にとって，毎日が貴重でかけがえのない日である。症状が安定していれば漫然と入院を長引かせることなく，一日も早い家庭・社会復帰を目指すべきであり，消化管に障害のある患児にとって在宅静脈栄養は家庭復帰のための強力なツー

ルとなる。適切なHPNの施行により合併症も少なく，多くの患児で成長発達を維持し，QOLの向上が可能であった。

文　献

1) Mughal M, Irving M: Home parenteral nutrition in the United Kingdom and Ireland. Lancet ; 16 ; 2 : 383-387, 1986
2) Colomb V: Home parenteral nutrition: the pediatric point of view. Nutrition; 15:72-73, 1999
3) 米倉竹夫：在宅栄養療法 小児での在宅栄養. 日本臨床 ；68 (増刊3) : 660-668, 2012
4) 吉田英生，高橋英世，大沼直拠，黒田浩明，田辺政裕，岩井潤：小児 home parenteral nutrition の問題点. 小児外科 24 : 1157-1165, 1992
5) Goulet OJ, Brousse N, Canioni D, Walker-Smith, JA, Schmitz, J, Phillips AD: Syndrome of intractable diarrhoea with persistent villous atrophy in early childhood: a clinicopathological survey of 47 cases. J Pediatr Gastroenterol Nutr ; 26 : 151-161, 1998
6) Andorsky DJ, Lund DP, Lillehei CW, Jaksic T, DiCanzio J, Richardson DS, Collier SB, Lo C, Duggan C: Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr ; 139 : 27-33, 2001
7) 吉田英生，照井慶太，佐藤嘉治，菱木知郎，齋藤武，光永哲也，照井エレナ，松浦玄，齋藤江里子，柴田涼平，三浦直子，横山由紀子：小児短腸症候群における栄養管理を中心とした治療戦略. 外科と代謝・栄養 ; 44 : 319-325, 2010
8) Ricour C, Gorski AM, Goulet O, Potter S, Corriol O, Postaire M, Nihoul-Fekete C, Jan D, Lortat-Jacob S, Pellerin D: Home parenteral nutrition in children: 8 years of experience with 112 patients. Clin Nutr ; 9 : 65-71, 1990
9) Bisset WM, Stapleford P, Long S, Chamberlain A, Sokel B, Milla PJ: Home parenteral nutrition in chronic intestinal failure. Arch Dis Child ; 67 : 109-114, 1992
10) Goulet O, Jobert-Giraud A, Michel JL, Jaubert F, Lortat-Jacob S, Colomb V, Cuenod-Jabri B, Jan D, Brousse N, Gaillard D, Nihoul-Fékéte C, Ricour C: Chronic intestinal pseudo-obstruction syndrome in pediatric patients. Eur J Pediatr Surg ; 9 : 83-89, 1999
11) Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R: Parenteral Nutrition Guidelines Working Group: Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology , Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR).11 Home Parenteral Nutrition in Children. J Pediatr Gastroenterol Nutr 41 ; Suppl 2 : S70-75, 2005
12) 高木洋治，岡田正：小児在宅栄養輸液のガイドライン. 小児科 ; 37 : 925-931, 1996
13) Colomb V, Fabeiro M, Dabbas M, et al: Central venous catheter-related infections in children on long-term home parenteral nutrition: incidence and risk factors. Clin Nutr 19 : 35535-9, 2000
14) 浅井俊哉，山東勤弥，李　都相，清水義之，曹　英樹，和佐勝史，高木洋治，岡田　正：在宅静脈栄養施行時のカテーテルトラブルの検討－Hickman-Broviac型カテーテルと完全皮下埋込式カテーテルの比較. 静脈経腸栄養 : 17 : 49-52, 2002
15) Knafelz D, Gambarara M, Diamanti A, Papadatou B, Ferretti F, Tarissi De Iacobis I, Castro M: Complications of home parenteral nutrition in a large pediatric series. Transplant Proc. ; 35 : 3050-3051, 2003
16) Broviac JW, Cole JJ, Scribner BH: A silicone rubber atrial catheter for prolonged parenteral allimentation. Surg Gynecol & Obstet ; 136 : 602-606, 1973
17) 井上善文，根津理一郎，中井澄雄，高木洋治，岡田正，川島康生：在宅静脈栄養における完全皮下埋込み式カテーテルの有用性に関する検討. 日消外会誌 ; 22 : 1839-1846, 1989
18) 井上善文，根津理一郎，川島康生，保木昌徳，藤井真，中井澄雄，和佐勝史，高木洋治，李鐘甲：カテーテル敗血症予防のための新しい輸液ライン接続システムの開発一実験的・臨床的検討一. 外科と代謝・栄養 ; 23 : 292-302, 1989
19) Wales PW, Kosar C, Carricato M, de Silva N, Lang K, Avitzur Y: Ethanol lock therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients with intestinal failure: preliminary experience. J Pediatr Surg ; 46 : 951-956, 2011
20) Georgeson KE, Breaux CW. Outcome and intestinal adaptation in neonatal short-bowel syndrome. J Pediatr Surg ; 27 : 344-348, 1992
21) Olieman JF, Poley MJ, Gischler SJ, Penning C, Escher JC, van den Hoonaard TL, van Goudoever JB, Bax NM, Tibboel D, IJsselstijn H: Interdisciplinary management of infantile short bowel syndrome: resource consumption, growth, and nutrition. J Pediatr Surg ; 45 : 490-498, 2010
22) Olieman JF, Penning C, Ijsselstijn H, Escher JC, Joosten KF, Hulst JM, Tibboel D: Enteral nutrition in children with short-bowel syndrome: current evidence and recommendations for the clinician. J Am Diet Assoc , 110 : 420-426, 2010
23) Diamond IR, de Silva NT, Tomlinson GA, Pencharz PB, Feldman BM, Moore AM, Ling SC, Wales PW: The role of parenteral lipids in the development of advanced intestinal failure-associated liver disease in infants: a multiple-variable analysis. JPEN ; 35 : 596-602, 2011
24) Teitelbaum DH, Han-Markey T, Drongowski RA, Coran AG, Bayar B, Geiger JD, Uitvlugt N, Schork MA: Use of cholecystokinin to prevent the development of parenteral nutrition-associated cholestasis. JPEN ; 20 : 100-103, 1997
25) Kubota A, Yonekura T, Hoki M, Oyanagi H, Kawahara

H, Yagi M, Imura K, Iiboshi Y, Wasa K, Kamata S, Okada A: Total parenteral nutrition-associated intrahepatic cholestasis in infants: 25 years' experience. J Pediatr Surg ; 35 : 1049-1051, 2000
26) Steinbach M, Clark RH, Kelleher AS, Flores C, White R, Chace DH, Spitzer AR: Pediatrix Amino-Acid Study Group: Demographic and nutritional factors associated with prolonged cholestatic jaundice in the premature infant. J Perinatol ; 28 : 129-135, 2008
27) Lilja HE, Finkel Y, Paulsson M, Lucas S: Prevention and reversal of intestinal failure-associated liver disease in premature infants with short bowel syndrome using intravenous fish oil in combination with omega-6/9 lipid emulsions. J Pediatr Surg ; 46 : 1361-1367, 2011
28) Venick RS, Calkins K. The impact of intravenous fish oil emulsions on pediatric intestinal failure-associated liver disease. Curr Opin Organ Transplant ; 16 : 306-311, 2011
29) 増本幸二, 甲斐裕樹, 岡陽一郎, 岩崎昭憲：中心静脈栄養法施行時の微量元素製剤使用の必要性と問題点. 栄養－評価と治療 26 (4) : 51-4, 2009
30) 祐野彰治, 橋都浩平, 仲西博子, 土屋恵司, 大川澄男: セレン欠乏症に起因する拡張型心筋症. 小児外科 ; 28 : 1236-1242, 1996
31) 上原秀一郎：小児の中心静脈栄養と微量元素. 静脈経腸栄養 ; 27 : 1223-1227, 2012

Long-term out come of pediatric patients receiving home parenteral nutrition

*1Department of pediatric surgery, Osaka University Graduate School of Medicine
*2Department of pediatric, Osaka University Graduate School of Medicine

Hideki Soh*1, Shuichiro Uehara*1, Takehisa Ueno*1, Masafumi Wasa*1, Keigo Nara*1, Takaharu Oue*1, Noriaki Usui*1, Motonari Nomura*1, Kazunori Masahata*1, Souji Ibuka*1, Masahiro Zenitani*1, Kengo Nakahata*1, Hiroki Kondo*2

Some pediatric patients who either cannot be fed enterally or are unable to tolerate sufficient enteral calories to provide their nutrition requirements, particularly those with short bowel syndrome or intestinal failure, will eventually require home parenteral nutrition (HPN). During the past 30 years, we have managed 40 patients on a HPN for periods ranging from 244 days to 27 years. Silastic Broviac catheters or catheters with subcutaneous implantable reservoirs were inserted into the superior vena cava. Solutions were infused using a closed line system and volumetric pump. All patients improved their nutritional status. Following HPN, bowel adaptation and initiation of full oral alimentation become possible in 14 patients. Administration of HPN is a safe, successful technique for maintaining an optimal nutritional status in children with severe digestive disorders, and permits resumption of a more normal daily lifestyle.

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ORIGINAL ARTICLE

Impact of pediatric intestinal transplantation on intestinal failure in Japan: findings based on the Japanese intestinal transplant registry

Takehisa Ueno · Motoshi Wada · Ken Hoshino · Shinji Uemoto · Tomoaki Taguchi · Hiroyuki Furukawa · Masahiro Fukuzawa

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Abstract
Introduction We assessed the impact of intestinal transplantation on Japanese pediatric patients with intestinal failure with data from the Japanese intestinal transplant registry.
Methods Standardized forms were sent to all known intestinal transplantation programs, requesting information on transplants performed between 1996 and June 30, 2012. Patients younger than 18 years were analyzed. Patient and graft survival estimates were obtained using the Kaplan–Meier method.
Results Of the 14 intestinal transplants, 4 were deceased and 10 were living donor transplants. The primary indications were: short gut syndrome ($n = 7$), intestinal functional disorder ($n = 6$), and re-transplantation ($n = 1$). The overall 1- and 5-year patient survival rates were 77 and 57 %, respectively. In transplants performed after 2006 ($n = 6$), the one-year patient survival rate was 83 %, and the 5-year survival rate was 83 %. Graft one- and 5-year survival rates were 83 and 83 %, respectively. The living-related transplant survival rate was 80 % at 1 year and 68 % at 2 years, compared to 67 and 67 % for cadaveric transplant recipients. There were no statistically significant differences in patient ($p = 0.88$) and graft ($p = 0.76$) survival rates between living donor and cadaveric transplant recipients. All current survivors discontinued PN.
Conclusion Intestinal transplantation has become an effective therapy for patients with intestinal failure who cannot tolerate PN.

Keywords Intestinal transplant · Pediatric transplant · Japanese registry

T. Ueno (✉)
Department of Pediatric Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: ueno@pedsurg.med.osaka-u.ac.jp

M. Wada
Department of Pediatric Surgery, Tohoku University School of Medicine, Sendai, Japan

K. Hoshino
Department of Surgery, Keio University Graduate School of Medicine, Tokyo, Japan

S. Uemoto
Department of HBP Surgery and Transplantation, Kyoto University, Kyoto, Japan

T. Taguchi
Department of Pediatric Surgery, Kyusyu University School of Medicine, Fukuoka, Japan

H. Furukawa
Department of Gastroenterologic and General Surgery, Asahikawa Medical University, Asahikawa, Japan

M. Fukuzawa
Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan

Introduction

Intestinal failure is caused by a critical reduction of functional gut mass to below the minimal amount necessary for adequate digestion and absorption to satisfy nutrient and fluid requirements for maintenance in adults and growth in children [1]. The most common type of intestinal failure is short bowel syndrome with an estimated incidence of 3–5 cases per 100 000 births per year

[2]. Advances in neonatal intensive care, anesthesia, nutritional support, and surgical techniques have improved the survival of children, so the prevalence of common causes of short bowel syndrome, including gastroschisis, necrotizing enterocolitis, and intestinal atresia has likely increased in recent years [3]. Some survivors, however, develop irreversible intestinal failure. The prognosis for intestinal failure related to short gut syndrome and intestinal motility disorders has improved dramatically owing to the development of parenteral nutrition (PN). Some children achieve long-term survival with PN at home with a relatively good quality of life, but others develop serious side effects that can eventually lead to death. However, PN-related complications, such as loss of venous access and intestinal failure-associated liver disease (IFALD), are still major problems for patients with intestinal failure [4]. Intestinal transplantation can significantly improve their prognosis and quality of life. Early efforts to transplant the small bowel have failed due to refractory graft rejection and sepsis. Outcomes improved during the early 1990s, but survival rates were still inferior to those for other organ transplants. Over the past 5 years, individual centers have reported improved outcomes with better long-term intestinal engraftment.

The first intestinal transplant in Japan was performed in 1996. The total number of intestinal transplants in Japan has increased to 24 as of June 2011. We assessed the impact of intestinal transplantation on Japanese pediatric patients with intestinal failure based on data from the Japanese intestinal transplant registry.

Methods

Standardized forms were sent to all known intestinal transplantation programs, requesting information on intestinal transplants performed between 1996 and June 30, 2012. The data included age, sex, date of birth, date of transplant, type of donor (deceased or living), pre-transplant status (home or hospital), underlying disease, procedure, ABO blood type, immunosuppression regimen (induction and maintenance therapy), and post-transplant status (PN requirement, intravenous (IV) fluid requirement, and daily life restrictions). Patients under 18 years of age were analyzed. The data were entered into a Microsoft Excel spreadsheet and analyzed with JMP version 10.0 (SAS Institute Inc, USA). Patient and graft survival estimates were obtained using the Kaplan–Meier method. For survival analysis, failure was defined as occurring on the date of graft removal or death. A p value <0.05 was considered statistically significant. This study was approved by the institutional review board.

Results

Four programs provided data on 14 grafts in 13 patients who were received transplants between 1 April 1996, and 30 June 2012 in Japan. The participation rate was 100 %. All intestinal transplants performed in Japan are captured in the registry database. All patients were followed, unless the patient has passed way. Ten grafts were obtained from living donors, and four cases involved deceased donors. The annual number of intestinal transplants, according to organ donation type, is shown in Fig. 1. Prior to 2005, 25 % of patients who underwent transplantation were called in from home, as compared with 66 % in the last 5 years (Fig. 2).

There were nine male and five female recipients. The age distribution of the recipients is shown in Fig. 3. Two-thirds of the patients were over 6 years old. The youngest recipient was 8 months. The causes of intestinal failure requiring intestinal transplantation are shown in Fig. 4. Approximately half of the patients had conditions that result in short gut syndrome.

Most patients ($n = 13$) received isolated intestinal transplants. There was only one case of simultaneous liver-intestinal transplantation from two living-related donors. Twelve patients received grafts from donors with an identical ABO blood type. Two patients received grafts from ABO compatible donors. There were no transplants involving ABO incompatibility. All patients were on tacrolimus maintenance therapy. The types of induction therapy used are shown in Fig. 5. Antibody-based induction therapy and tacrolimus-based maintenance immunosuppression were used even if the medication was not commercially available in Japan.

Graft and patient overall survival as of June 2011 are shown in Kaplan–Meier plots (Fig. 6a, b, respectively). The one-year and 5-year patient survival rates were 77 and 57 %, respectively, comparable with rates from the international intestinal transplant registry. Five recipients died.

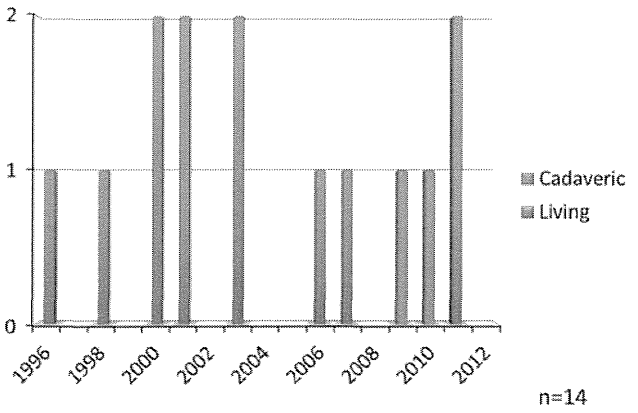

Fig. 1 Number of intestinal transplants by year

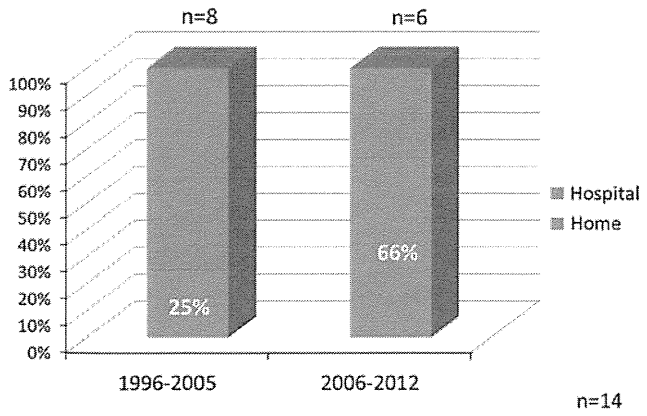

Fig. 2 Pre-transplant patient status

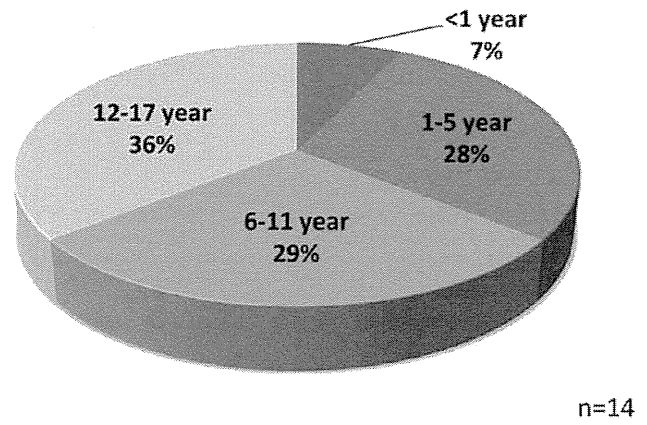

Fig. 3 Recipient age at transplant

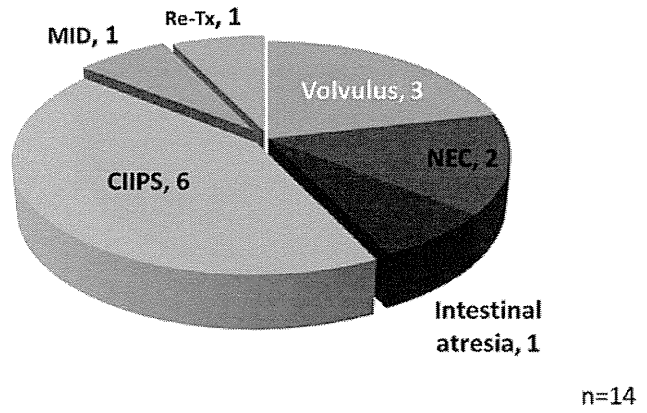

Fig. 4 Cause of intestinal failure *NEC* necrotizing enterocolitis, *CIIPS* chronic idiopathic intestinal pseudo-obstruction syndrome, *MID* microvillus inclusion disease, *Re-Tx* Re-transplant

The causes of death included sepsis ($n = 3$), post-transplant lymphoma ($n = 1$) and intra cranial hemorrhage ($n = 1$).

The 1-year overall graft survival rate was 80 % for cadaveric grafts versus 50 % for living donor grafts ($p = 0.76$), as shown in Fig. 7a. The 1-year overall patient survival rate was 80 % for cadaveric grafts versus 67 % for living donor grafts ($p = 0.88$), as shown in Fig. 7b.

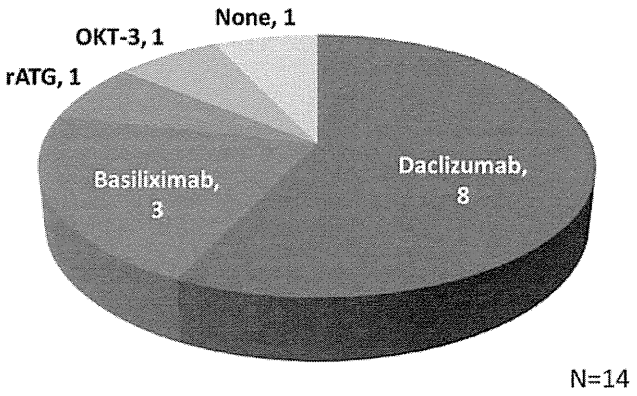

Fig. 5 Induction immunosuppression therapy *rATG* rabbit anti-thymus globulin, *OKT-3* anti-CD3 monoclonal antibody

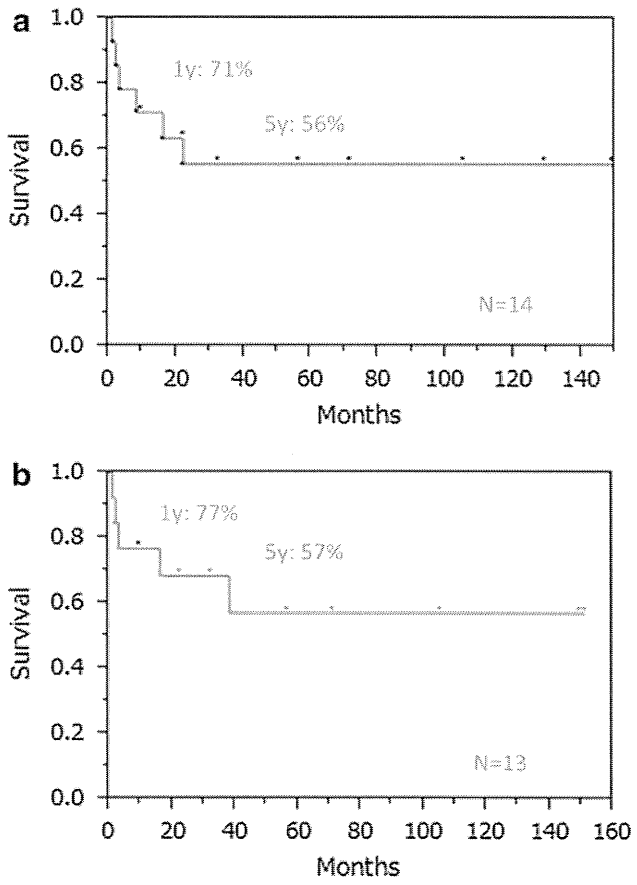

Fig. 6 Overall graft (**a**) and patient (**b**) survival

Graft survival improved over the last 5 years. The one- and five-year graft survival rates were 83 and 83 % for 2006–2011 versus 63 and 38 % for 1996–2005 ($p = 0.14$), as shown in Fig. 8a. The 1- and 5-year patient survival rates were 83 and 83 % for 2006–2011 versus 71 and 43 % for 1996–2005 ($p = 0.27$), as shown in Fig. 8b.

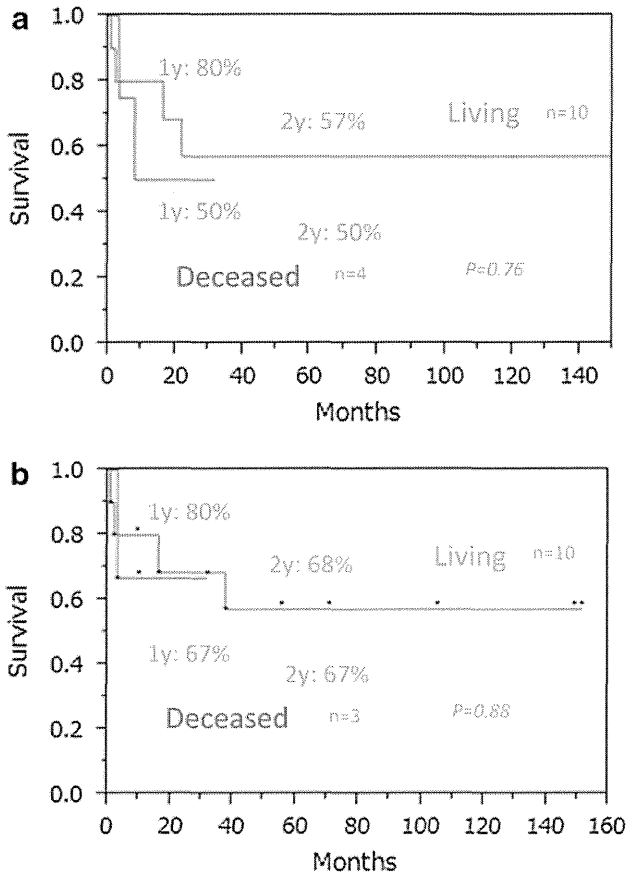

Fig. 7 Graft (**a**) and patient (**b**) survival according to graft type

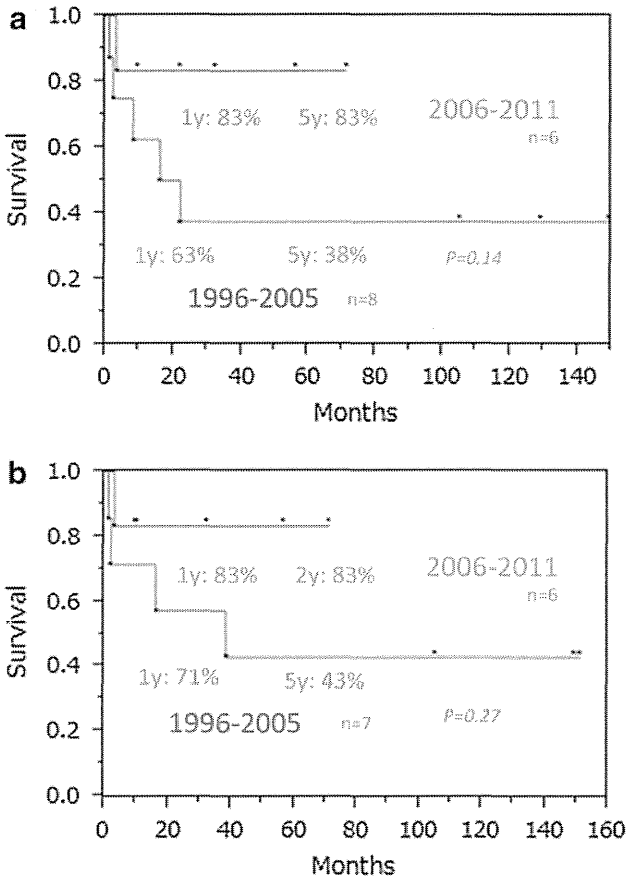

Fig. 8 Graft (**a**) and patient (**b**) survival by era

Graft function in terms of PN dependence was excellent. All patients became PN-free after intestinal transplantation, although two-thirds of patients require continuous or intermittent intravenous fluid support. Of the eight patients who were alive at the time of data collection, all patients were off parenteral nutrition, with three patients requiring intravenous fluids daily, two patients requiring intravenous fluids occasionally (Fig. 9). Most recipients stopped parenteral supplementation, eat, and have resumed normal activities. Of the seven surviving patients 1 year after transplant, six lead a full life.

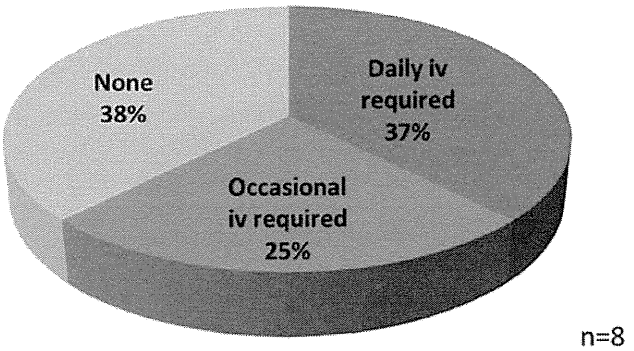

Fig. 9 Intravenous (IV) fluid requirement after intestinal transplantation

Discussion

Children with intestinal failure are at risk for numerous complications, especially PN-related complications. For example, loss of venous access and IFALD are still major problems for patients with intestinal failure because they are potentially life-threatening [4].

Catheter-related bloodstream infections were common in patients with intestinal failure [5]. Survival of children with chronic intestinal failure has increased as result of home PN. Adequate central venous accesses crucial for the successful management of home PN, but venous access can be complicated by episodes of catheter-associated infection, repeated procedures to replace catheters, and catheter-related thrombosis. Management and prevention of catheter-related thrombosis are of vital importance. [6].

IFALD can be a progressive and fatal entity in children with short gut syndrome. Parenteral fish oil-based fat emulsions are safe and may be effective in the treatment of PN-associated liver disease [7]. A lipid reduction protocol may prevent cholestasis [8]. Despite all efforts to prevent

complications, some children develop end-stage intestinal failure.

As outcomes of intestinal transplantation have improved, it has become the definitive treatment for patients with intestinal failure who cannot tolerate PN. Over the past decade, intestinal transplantation has become accepted as standard therapy for patients with life-threatening complications of PN in many countries [9, 10].

Currently, evaluation for transplant is recommended for pediatric patients with intestinal failure who are doing poorly on PN due to loss of more than 50 % of the major intravenous access sites (two out of four sites include both internal jugular veins and subclavian veins); recurrent severe catheter-related sepsis; progressive liver dysfunction; or impaired renal function due to massive gastrointestinal fluid loss.

Timely referral to an intestinal transplant program is important for children with intestinal failure because intestinal transplantation is easier and safer with adequate central venous access and normal liver function [11]. For patients who undergo intestinal transplantation, patient survival is similar to remaining on PN. The inclination is therefore to move towards earlier transplantation and avoiding the need for concomitant liver transplantation [12].

The 2011 report of the intestinal transplant registry confirmed that intestinal transplantation has become a definitive therapeutic option for patients with intestinal failure. By 2011, 2,611 intestinal transplants had been performed throughout the world with 79 participating centers worldwide. Three types of intestinal transplantation are performed: (1) isolated intestinal transplantation (1,184 cases); (2) liver and intestine transplantation (845 cases); and (3) multivisceral transplantation (619 cases). In pediatric patients, two-thirds acquired short gut syndrome as a result of congenital disease, including gastroschisis, intestinal atresia, and necrotizing enterocolitis [10].

On the other hand, only 14 intestinal transplants have been performed in patients under 18 years of age in Japan. The number is relatively small, although it is estimated that 40 pediatric patients require intestinal transplants nationwide [13]. In the Japanese experience, the 1- and 5-year overall patient survival rates are 77 and 57 %. The one-year survival rate was 83 % for the last 5 years. These are considered acceptable results for the treatment of intestinal failure. Our results in Japan are comparable with results worldwide, even though there are only one or two cases per year performed in Japan compared to over 100 intestinal transplants yearly performed in the world. In our opinion, children with intestinal failure should be treated with intestinal transplantation in Japan as well as in other countries when feasible.

There were two major reasons for the low number of intestinal transplants in Japan. One reason is the lack of available organs. For a long time, relatively few donations from deceased donors were obtainable in Japan. As with other solid organs, most intestinal transplants in Japan are performed with living-related donors. Although the situation has changed due to the new Act on Organ Transplantation, which went into effect in 2010, the number of deceased donations has not increased dramatically, especially among pediatric donors.

The financial barrier is the other, more profound reason preventing the greater use of intestinal transplantation in Japan. Since the procedure is not covered by health insurance, either the patient or the transplant center must pay the considerable costs out of pocket.

Some patients develop liver failure with short gut syndrome. These patients need simultaneous liver-intestinal transplants. A combined liver-intestine transplant has less risk of acute rejection than an isolated intestinal transplant because the liver may have protective effects on the intestine [10]. Combined liver and intestine transplants are the most frequent procedure in infants and children, accounting for half of the cases. Current organ allocation guidelines have not allowed for simultaneous combined liver–intestine organ retrieval until the law was revised in 2010; thus, simultaneous liver–intestine transplantation with a deceased donor graft had been impossible. Isolated intestinal transplantation, the preferred procedure, was offered to patients with limited IV access or recurrent line infections. Combined liver–intestine transplants are performed for treatment of irreversible liver disease caused by PN. Isolated intestinal transplantation from deceased donors following living-related liver transplantation, referred to as sequential combined liver-intestine transplantation, has been attempted.

Previously, the law on organ transplantation banned donors below 15 years of age. This is the main reason why there were relatively few pediatric transplant recipients. Intestinal transplant for infants was previously not possible because of donor-recipient size mismatch. Only a small number of pediatric transplants have been performed. Pediatric patients still await the opportunity to benefit from intestinal transplantation. Moreover, younger patients sometimes develop liver failure [3]. Multivisceral transplants are recommended for the treatment of severe gastrointestinal motility disorders [14]. However organ allocation guidelines do not allow for multivisceral organ retrieval. Further reform of allocation guidelines is needed.

This analysis found that improved induction immunosuppression is strongly associated with higher survival rates. The use of antibody induction therapy appears to be particularly important for the success of intestinal transplantation, possibly due to the large lymphoid mass of this type of graft [15]. Induction with rabbit anti-thymus globulin (rATG) minimized the amount of tacrolimus needed for

maintenance immunosuppression, facilitated the long-term control of rejection, and decreased the incidence of opportunistic infections, resulting in a high rate of patient and graft survival [16]. The combination of rATG and rituximab was an effective induction therapy according to our preliminary data. The number and severity of rejection episodes increased when the liver was not included as part of the graft. An immunosuppression regimen including rATG, rituximab, and steroids may have a protective effect against post-transplant lympho proliferative disease (PTLD) and chronic rejection [17]. Sirolimus is a safe rescue therapy in children with intestinal transplants when tacrolimus is not well tolerated. Renal function and hematologic disorders seem to improve, although other simultaneous strategies could be involved [18]. However, those medications are not commercially available with insurance coverage in Japan. Children after intestinal transplant should be managed with limited immunosuppression.

Preemptive assessments are recommended, even for patients doing well on PN, and for infants and adults with an ultra-short gut or for infants with total intestinal aganglionosis or microvillus inclusion disease, since patients with these findings have very poor survival rates on PN [15].

Early referral and listing are important for successful outcomes. Presently, because of the risks involved as well as financial reasons, transplants are rarely offered to pediatric patients in Japan. However, this treatment will undoubtedly become more common over time as the results of intestinal transplantation continue to improve.

Conclusion

Intestinal transplantation has become the definitive treatment for patients with chronic intestinal failure. Since intestinal transplantation in Japan has yielded satisfactory results, indications for the procedure should be expanded. The national health insurance should cover intestinal transplants to reduce the incidence of PN-related complications. Systems facilitating combined simultaneous liver–intestine and multi-organ transplants should be developed. We continue to work on reforming national health insurance coverage and realizing multi-organ transplantation in Japan.

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References

1. Goulet O, Ruemmele F (2006) Causes and management of intestinal failure in children. Gastroenterology 130(2 Suppl 1): S16–S28
2. DeLegge M, Alsolaiman MM, Barbour E et al (2007) Short bowel syndrome: parenteral nutrition versus intestinal transplantation. Where are we today? Dig Dis Sci 52(4):876–892
3. Wales PW, de Silva N, Kim J et al (2004) Neonatal short bowel syndrome: population-based estimates of incidence and mortality rates. J Pediatr Surg 39(5):690–695
4. Maroulis J, Kalfarentzos F (2000) Complications of parenteral nutrition at the end of the century. Clin Nutr 19(5):295–304
5. Cole CR, Frem JC, Schmotzer B et al (2010) The rate of bloodstream infection is high in infants with short bowel syndrome: relationship with small bowel bacterial overgrowth, enteral feeding, and inflammatory and immune responses. J Pediatr 156(6):941–947 947. e1
6. van Ommen CH, Tabbers MM (2010) Catheter-related thrombosis in children with intestinal failure and long-term parenteral nutrition: how to treat and to prevent? Thromb Res 126(6):465–470
7. Gura KM, Lee S, Valim C et al (2008) Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics 121(3):e678–e686
8. Cober MP, Teitelbaum DH (2010) Prevention of parenteral nutrition-associated liver disease: lipid minimization. Curr Opin Organ Transpl 15(3):330–333
9. Magee JC, Krishnan SM, Benfield MR et al (2008) Pediatric transplantation in the US, 1997–2006. Am J Transpl 8(4 Pt 2):935–945
10. Grant D (2011) Small bowel transplant Registry. In: 12th International Small Bowel Transplant Symposium. Washington DC
11. Rodrigues AF, van Mourik ID, Sharif K et al (2006) Management of end-stage central venous access in children referred for possible small bowel transplantation. J Pediatr Gastroenterol Nutr 42(4):427–433
12. Sudan D (2010) Long-term outcomes and quality of life after intestinal transplantation. Curr Opin Organ Transpl 15(3):357–360
13. Ueno TW, Hoshino M, Sakamoto K, Furukawa S, Fukuzawa H, M. (2013) A national survey of patients with intestinal motility disorder who are potential candidate for intestinal transplantation in Japan. Transpl Proc 45(5):2029–2031
14. Tzakis AG, Kato T, Levi DM et al (2005) 100 multivisceral transplants at a single center. Ann Surg 242(4):480–490 discussion 491–3
15. Grant D, Abu-Elmagd K, Reyes J et al (2005) 2003 report of the intestinal transplant registry: a new era has dawned. Ann Surg 241(4):607–613
16. Reyes J, Mazariegos GV, Abu-Elmagd K et al (2005) Intestinal transplantation under tacrolimus monotherapy after perioperative lymphoid depletion with rabbit anti-thymocyte globulin (thymoglobulin). Am J Transpl 5(6):1430–1436
17. Vianna RM, Mangus RS, Fridell JA et al (2008) Induction immunosuppression with thymoglobulin and rituximab in intestinal and multivisceral transplantation. Transplantation 85(9): 1290–1293
18. Andres AM, Lopez Santamaria M, Ramos E et al (2010) The use of sirolimus as a rescue therapy in pediatric intestinal transplant recipients. Pediatr Transpl 14(7):931–935

クロライドチャネルを介した便秘治療

Treatment for Chronic Constipation with Chloride Channel-2 Activator

福土 審

東北大学医学系研究科行動医学

福土　審（ふくど　しん）
1983年東北大学医学部医学科卒業，医学博士。'87年東北大学医学部附属病院心療内科助手，デューク大学医学部研究員などを経て，'98年東北大学心療内科助教授，'99年東北大学大学院医学系研究科行動医学分野教授（現職）。2011年東北大学病院心療内科長（現職）。研究テーマ：脳腸相関，過敏性腸症候群

Key Words: 慢性便秘，機能性便秘，過敏性腸症候群，大腸運動

Abstract

便秘をきたす最も頻度が高い疾患群は，機能性消化管障害である。その代表が機能性便秘と便秘型過敏性腸症候群である。便秘の治療は単に糞便を出すだけでは不十分であり，消化管機能生理学と消化管機能薬理学に沿い，恒常性を守る方向にて行うことが重要である。Cl- channel-2を賦活化する薬物lubiprostoneは，小腸における水分泌を促して便通を改善する薬物であり，機能性便秘と便秘型過敏性腸症候群に有効である。

■はじめに

便秘はありふれた現象である[1]。ここでは，下部消化管機能が軽度に障害される最もありふれた便秘に対する最新の治療について論述する。重度の便秘の場合には専門的な配慮が必要である。また，大腸癌などの器質的疾患に基づく便秘，麻薬などによる薬剤性便秘，甲状腺機能低下症などによる二次性の便秘に関しても本稿では扱わない。

■便秘をきたす機能性消化管障害

便秘をきたす最も頻度が高い疾患群は，機能性消化管障害（functional gastrointestinal disorders）である[1]。国際的に使用される診断基準であるRome III基準[2, 3]に基づく便秘である機能性便秘（functional constipation）[2, 3]のわが国における正確な有病率は公刊されていない。一方，その約1/4-1/3が便秘型である過敏性腸症候群（Irritable Bowel Syndrome: IBS）の有病率は人口の14.2%，1年間の罹患率は1-2%，内科外来患者の31%と高頻度である[1]。IBSに関しては，わが国では，厚生労働省研究委託費によって診断・治療ガイドラインが公表され，これが普及してきたが[4]，それを更に精緻精密に進歩させた日本消化器病学会による診断・治療ガイドラインが2014年に公表される予定である。その中でIBS便秘型に関しても論述されることになっている。

■便秘型過敏性腸症候群

患者が便秘を訴える場合に，排便頻度が最も臨床現場で使われている指標であろう。しかし，症例によっては，1日4行の排便があり，従来の便秘の印象とは異なる場合も少なからず経験される。この場合，腹痛，腹部不快感，腹部膨満感という内臓感覚の症状の有無が重要である。Rome III基準においては，IBSを「腹痛あるいは腹部不快感が，最近3ヶ月の中の1ヶ月につき少なくとも3日以上は生じ，その腹痛あるいは腹部不快感が，①排便によって軽快する，②排便頻度の変化で始まる，③

■Shin Fukudo, MD, PhD, Professor
Department of Behavioral Medicine Tohoku University Graduate School of Medicine

便形状（外観）の変化で始まる，の３つの便通異常の２つ以上の症状を伴うもの」と定義している（表1）[3]。

Rome III基準においては，下部消化管の機能性障害において，糞便の形状（外観）を重視し，その割合で亜型を分類する（表2）。便秘型(IBS-C)は硬便／兎糞状便が25%以上かつ軟便／水様便が25%未満，下痢型(IBS-D)は軟便／水様便が25%以上かつ硬便／兎糞状便が25%未満，混合型(IBS-M)は硬便／兎糞状便が25%以上かつ軟便／水様便が25%以上，分類不能型(IBS-U)は便秘型，下痢型，混合型のいずれでもないものである（表3）[3]。

■機能性便秘

Rome III基準では，「腹痛のない便秘」である機能性便秘を分類している（表4）[3]。排便頻度減少の他に，硬便あるいは兎糞状便，残便感，排便困難による力み，直腸肛門の閉塞感，排便時の用手努力がその症状の構成要素である。機能性便秘はIBS-Cに準じて診断・治療されることが多く，IBS-Cの病態生理と治療を把握しておくことがその効率的なマネジメントの鍵となる。

■便秘の病態

機能性消化管障害とは，通常の臨床検査によっては，異常が検出されない程度の消化管機能の異常によって症状が生じる症候群である[2]。「通常の臨床検査によっては」という限定条件を付けたのは，最先端の科学的手法を使えば異常が検出されるからである。重度の便秘の場合には，通常の臨床検査によって異常が認められる場合が多く，その大多数は機能性消化管障害の範疇を越えた消化管運動異常症(gastrointestinal motility disorders)である[4]。慢性特発性偽性腸閉塞症(chronic idiopathic intestinal pseudo-obstruction)は立位腹部X線写真で鏡面像が見られることが多い。巨大結腸症(megacolon)は腹部X線写真で顕著な大腸ガス，大腸造影検査，大腸内視鏡検査あるいは腹部CTで拡張した大腸が見られる。

IBS-Cあるいは機能性便秘の場合，症例によっては，下部消化管内視鏡検査による大腸黒皮症が見られる。これは，市販あるいは処方薬のセンナ常用による病変である。大腸粘膜生検像の軽度非特異炎症像はIBSでしばしば見られる病像である。これは，上皮下の膠原線維が増生するmicroscopic colitisとは異なる。消化管機能検査を行うと，X線不透過マーカー法では消化管通過時間が遅延して

表1　IBSのRome III診断基準（引用:文献[3]）

■腹痛あるいは腹部不快感が
■最近３ヶ月の中の１ヶ月につき少なくとも３日以上を占め
■下記の２項目以上の特徴を示す
　(1) 排便によって改善する
　(2) 排便頻度の変化で始まる
　(3) 便形状（外観）の変化で始まる

*少なくとも診断の６ヶ月以上前に症状が出現し、最近３ヶ月間は基準を満たす必要がある。
**腹部不快感とは、腹痛とはいえない不愉快な感覚をさす。
病態生理研究や臨床研究では、腹痛あるいは腹部不快感が１週間につき少なくとも２日以上を占める者が対象として望ましい。

表2　Bristol便形状尺度（引用:文献[3]）

型	説明
1	分離した硬い木の実のような便（排便困難を伴う）
2	硬便が集合したソーセージ状の便
3	表面にひび割れがあるソーセージ状の便
4	平滑で柔らかいソーセージ状あるいは蛇状の便
5	柔らかく割面が鋭い小塊状の便（排便が容易）
6	ふわふわした不定形の小片便、泥状便
7	固形物を含まない水様便

表3　IBSの分類 (Rome III)（引用:文献[3]）

1. 便秘型 IBS (IBS-C)：
　硬便 or 兎糞状便[a]が便形状が 25%以上、かつ、
　軟便 or 水様便[b]が便形状の 25%未満[c]
2. 下痢型 IBS (IBS-D)：
　軟便 or 水様便[b]が便形状の 25%以上、かつ、
　硬便 or 兎糞状便[a]が便形状の 25%未満[c]
3. 混合型 IBS (IBS-M)：
　硬便 or 兎糞状便[a]が便形状の 25%以上、かつ、
　軟便 or 水様便[b]が便形状の 25%以上[c]
4. 分類不能型 IBS (IBS-U)：
　便形状の異常が不十分であって、
　IBS-C、IBS-D、IBS-M のいずれでもない[c]

[a]Bristol 便形状尺度１型２型
[b]Bristol 便形状尺度６型７型
[c]止瀉薬、下剤を用いない時の糞便で評価する

表4　機能性便秘のRome III診断基準（引用:文献[3]）

■下記の2項目以上の特徴を示す		
a. 排便困難による力み	≧	排便の25%
b. 硬便 or 兎糞状便	≧	排便の25%
c. 残便感	≧	排便の25%
d. 直腸肛門の閉塞感	≧	排便の25%
e. 排便時の用手努力	≧	排便の25%
f. 排便回数	<	3回/週
■下剤を使わない限り軟便は稀である		
■IBSの診断基準を満たさない		

*少なくとも診断の6ヶ月以上前に症状が出現し、最近3ヶ月間は基準を満たす必要がある。

いる例があるが，これが正常であることも稀ではない。圧トランスデューサ法による大腸内圧所見では，IBSの大腸運動は刺激反応性の亢進で特徴づけられる。neostigmine負荷刺激と伸展刺激の両刺激に対する顕著な大腸内圧での分節運動亢進が見られる。その一方で，IBS-Cでは，排便を促す推進運動が低下していることが多い。バロスタットという薄いポリエチレンバッグをコンピュータ制御下に伸展刺激に用いる内臓感覚検査を行うことにより，IBSでは内臓知覚過敏を認める[4]。

この他に，機能性直腸肛門障害による便秘の病態がある。これは，直腸肛門の排泄機能の異常によって排便機能が障害されるものであり，正確な診断のためには専門的な直腸肛門機能検査が必要である。

■便秘治療の概要

IBS-Cあるいは機能性便秘の場合，薬物としては，まず，消化管腔内環境調整を行う戦略が勧められる。機能性便秘の中の表現形が明確な一群を慢性特発性便秘として，小腸粘膜上皮にあるCl-channel-2 (ClC-2)を賦活化する薬物lubiprostone[5]が日本の臨床で使用可能になっている。これは，日本人の研究者上野隆司博士が開発したプロストン化合物である。プロスタグランジンの分解産物に何等かの機能があるに違いないという発想から発見された機能性脂肪酸であり，その多くが細胞膜のチャネルに対する作用がある。ClC-2は，小腸粘膜上皮の管腔側に発現している[5]。その開口は塩素イオンの管腔内への移動とともに水分子の移動を促す。LubiprostoneはClC-2を活性化することにより，下部消化管内腔の水分量を増大させて便秘を改善するものである（図1）。日本の臨床データにおいて，用量依存的な便通の改善が見られ，慢性特発性便秘にもIBS-Cにも有効である（図2）[6]。適応症は慢性便秘症となっている。その関連薬として，消化管上皮でcyclic guanosine monophosphateを誘導し，水分分泌を促進する薬物linaclotide[7]が米国で開発された。これも，慢性特発性便秘と

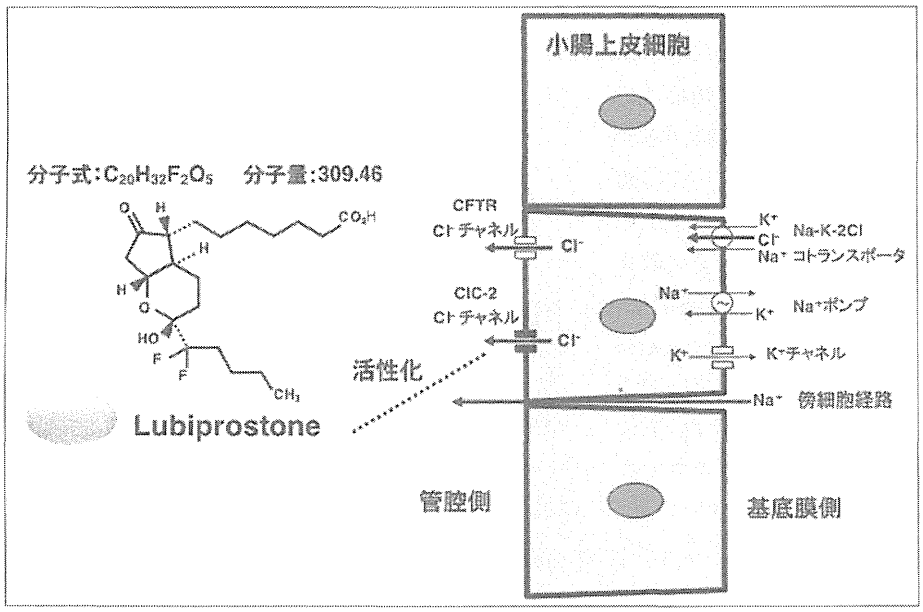

図1　クロライドチャネルとルビプロストン
ルビプロストンの構造式（左）とそのCl- channel-2 (ClC-2)への作用。小腸粘膜上皮にはCystic Fibrosis Transmembrane conductance Regulator (CFTR) Cl- channelもあるがルビプロストンはClC-2に特異的に作用する。

IBS-Cの双方に薬効を示す。消化管腔内環境調整には，この他にも高分子重合体，乳酸菌製剤などの手段があり，適宜組み合わせることが可能である。

しかし，これらで効果不十分であれば，下剤を追加する。これには，少量の酸化magnesiumが有益である[1]。しかし，高齢者，腎障害を持つ患者では時々高Mg血症を見るので，時々は血清Mg濃度を点検する。それでも効果不十分であれば，刺激性下剤ではあるが効果がより緩徐なpicosulfateを頓用で用いる。picosulfate水溶液の1日回10滴を標準用量とし，便通に応じて患者に自己調節させる。効果不十分ならば増量，便形状が水様便，泥状便になるようであれば減量する。下剤作用のあるlactulose投与でも良い。

下剤の使用法で最も重要なことは，アントラキノン系下剤を長期投与しないことである[1]。アントラキノン系下剤の長期投与は，大腸黒皮症，大腸運動のさらなる異常，下剤への依存などを招きやすいので，IBS-C患者には行うべきでない。IBS-C患者に限らず，アントラキノン系下剤は連続投与せずに，使用頻度の低い頓用を基本とするべきである。その代わり，可能な限り生理的大腸運動に結びつく処方内容にする。

推進運動が低下していると考えられる便秘に対しては，5-HT$_4$刺激薬mosapride[8]，D$_2$拮抗薬兼cholinesterase阻害薬itoprideを用いることがあるが，便秘そのものへの保険適応はないため，使用に際しては慢性胃炎を診断する必要がある。理論的にはcholinesterase阻害薬acotiamide[9]の下部消化管運動への作用もあり得るが，機能性ディスペプシアにおける便秘に対する臨床知見の蓄積が待たれるところである。

■おわりに

機能性消化管障害においては，治療目標を症状の消失に置くよりも，むしろ症状の自己制御に置くほうが結果として満足が得られることが多い。医療従事者が患者の苦痛を傾聴し，受容することが治療の基本になる。通常の臨床検査では異常がなくとも，専門的検査を行えば異常が検出されることを念頭に置く。医療従事者が患者の症状に関心を示せば，治療効果にも好影響を及ぼす。その上で，使用薬物の薬理作用を患者が理解しやすい言葉で説明する。偏食，食事量のアンバランス，夜食，睡眠不足，心理社会的ストレスは便秘の増悪因子であり，除去・調整を勧める。便秘の治療は，ただ便を出せば良いという訳ではなく，あくまでも，消化管の生理に沿い，これを助ける薬物療法を行うのが基本である。

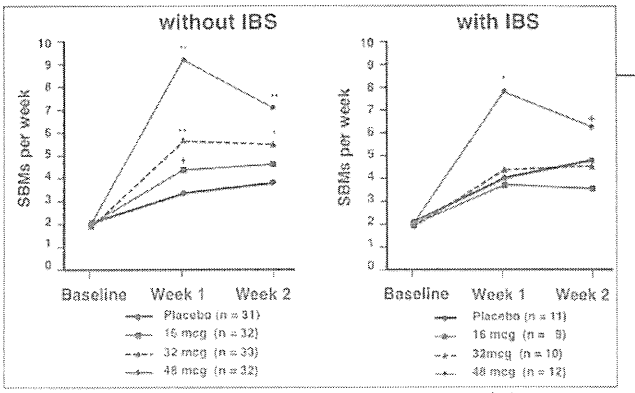

図2　慢性便秘症に対するルビプロストンの臨床効果
文献[6]より許可を得て引用。SBM: 自発排便回数。左が腹痛のない慢性特発性便秘症，右が便秘型過敏性腸症候群。

文　献

1) Toner BB, Chang L, Fukudo S, *et al.* Gender, age, society, culture, and the patient's perspective. In: Drossman DA, Corazziari E, Delvaux M, Spiller RC, Talley NJ, Thompson WG, Whitehead WE, edts. Rome III: the Functional Gastrointestinal Disorders, Third Edition. Degnon Associates, McLean, Virginia, pp231-294, 2006.
2) Drossman DA, Corazziari E, Delvaux M, *et al.*: Rome III: The Functional Gastrointestinal Disorders: Third Edition. Degnon Associates, McLean, 2006.
3) Longstreth GF, Thompson W G, Chey WD, *et al.* Functional bowel disorders. Gastroenterology 130: 1480-1491, 2006.
4) 福土審，金澤素，篠崎雅江，遠藤由香，庄司知隆，相模泰宏，森下城，本郷道夫．過敏性腸症候群．小牧元，久保千春，福土審編集：心身症診断治療ガイドライン2006．協和企画，東京，2006, pp 11-40.
5) Cuppoletti J, Malinowska DH, Tewari KP, *et al.* SPI-0211 activates T84 cell chloride transport and recombinant human CIC-2 chloride currents. Am J Physiol Cell Physiol 287: C1173-1183, 2004.
6) Fukudo S, Hongo M, Kaneko H, *et al.* Efficacy and safety of oral lubiprostone in constipated patients with or without irritable bowel syndrome: a randomized, placebo-controlled and dose-finding study. Neurogastroenterol Motil 23: 544-e205, 2011.
7) Johnston JM, Kurtz CB, Macdougall JE, *et al.* Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology 139: 1877-1886, 2010.
8) Kanazawa M, Watanabe S, Tana C, *et al.* Effect of 5-HT4 receptor agonist mosapride citrate on rectosigmoid sensorimotor function in patients with irritable bowel syndrome. Neurogastroenterol Motil 23: 754-e332, 2011.
9) Matsueda K, Hongo M, Tack J, *et al.* A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. Gut 61: 821-828, 2012.

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GASTROENTEROLOGY

Risk of subsequent biliary malignancy in patients undergoing cyst excision for congenital choledochal cysts

Taku Ohashi,* Toshifumi Wakai,* Masayuki Kubota,† Yasunobu Matsuda,§ Yuhki Arai,† Toshiyuki Ohyama,† Kengo Nakaya,† Naoki Okuyama,† Jun Sakata,* Yoshio Shirai* and Yoichi Ajioka‡

Divisions of *Digestive and General Surgery, †Pediatric Surgery, §Gastroenterology and Hepatology and ‡Molecular and Diagnostic Pathology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

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Correspondence
Dr Toshifumi Wakai, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan. Email: wakait@med.niigata-u.ac.jp

Conflict of interest
The authors have no conflicts of interest to disclose.

Abstract

Background and Aim: The aim of this study was to elucidate the risk of subsequent biliary malignancy in patients undergoing cyst excision for congenital choledochal cysts.
Methods: A retrospective analysis of 94 patients who had undergone cyst excision for congenital choledochal cysts was conducted. The median age at the time of cyst excision and median follow-up time after cyst excision were 7 years and 181 months, respectively.
Results: Biliary tract cancer developed in four patients at 13, 15, 23, and 32 years after cyst excision. The cumulative incidences of biliary tract cancer at 15, 20, and 25 years after cyst excision were 1.6%, 3.9%, and 11.3%, respectively. The sites of biliary tract cancer were the intrahepatic ($n = 2$), hilar ($n = 1$), and intrapancreatic ($n = 1$) bile ducts. Of the four patients with biliary tract cancer after cyst excision, three patients underwent surgical resection and one patient received chemo-radiotherapy. The overall cumulative survival rates after treatment in the four patients with biliary tract cancer were 50% at 2 years and 25% at 3 years, with a median survival time of 15 months.
Conclusions: The risk of subsequent biliary malignancy in patients undergoing cyst excision for congenital choledochal cysts seems to be relatively high in the long-term. The risk of biliary malignancy in the remnant bile duct increases more than 15 years after cyst excision. Despite an aggressive treatment approach for this condition, subsequent biliary malignancy following cyst excision for congenital choledochal cysts shows an unfavorable outcome.

Introduction

A condition that predisposes to extrahepatic cholangiocarcinoma is congenital cystic dilatation or choledochal cyst.[1–3] Although these cysts are relatively rare, coexisting carcinoma as a complication has been well documented.[4] A mixture of bile and pancreatic secretions may promote the development of carcinoma because 90% of choledochal cysts are associated with anomalous pancreaticobiliary ductal junction (APBDJ).[5] Carcinoma can develop anywhere along the biliary tract in addition to originating in the choledochal cyst.

Cyst excision is the treatment of choice for congenital choledochal cysts because of the risk of subsequent biliary malignancy.[6,7] A number of authors have reported biliary tract cancer after cyst excision for congenital choledochal cysts;[8–30] however, most previous reports were single cases[8–17] or studies with a limited number of patients.[18–30] The aim of this study was to elucidate the risk of subsequent biliary malignancy in patients undergoing cyst excision for congenital choledochal cysts.

Methods

Patients. A total of 114 consecutive Japanese patients with congenital choledochal cysts were identified from a database at Niigata University Medical and Dental Sciences from January 1971 through December 2006. Of the 114 patients, 20 patients who had a coexisting biliary tract cancer including gallbladder cancer ($n = 19$) and extrahepatic cholangiocarcinoma ($n = 1$) were excluded from this study. The remaining 94 patients who underwent cyst excision constituted the final group of patients for this retrospective study. The group comprised 73 females and 21 males with a median age of 7 years (range, 0–63 years) at the time of cyst excision. The protocol of the present study was approved by the Institutional Review Board of Niigata University Medical and Dental Hospital.

Of the 94 patients who underwent cyst excision, 85 patients (90%) had choledochal cysts with APBDJ. According to Todani's classification,[31] 49 were classified as type I cysts and 45 as type IV-A cysts. Excision of the choledochal cyst was performed as the

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