The ATP-dependent uptake of [$^3$H]-taurocholate ([$^3$H]-TC) into membrane vesicles isolated from HA-BSEP$^{WT}$ and HA-BSEP$^{D404G}$ HEK293T cells was almost linear up to 5 min (data not shown). Its uptake value per minute was approximately 118- and 12.1-times higher in vesicles from HA-BSEP$^{WT}$ and HA-BSEP$^{D404G}$ HEK293T cells, respectively, than in vesicles from EV-HEK293T cells (Fig. 2e). Normalizing the BSEP expression levels in the membrane vesicles based on the results of the immunoblotting, which indicated that the expression of HA-BSEP$^{WT}$ was 6.7-times higher than that of HA-BSEP$^{D404G}$ (Fig. 2d), showed that the transport activity of [$^3$H]-TC mediated per unit mass of HA-BSEP$^{D404G}$ molecules did not differ significantly from that mediated by HA-BSEP$^{WT}$. Treatment for 24 h with 1 mM 4PB, a clinically relevant concentration in patients with OTCD,[17,18,20,24] increased the cell surface expression of HA-BSEP$^{WT}$ and HA-BSEP$^{D404G}$ by 2.6- and 2.1-times, respectively, in HEK293T cells (Fig. 3b), without significantly changing the expression level of either mRNA (Fig. 3a). These results suggest that 4PB treatment at a clinically relevant dose for humans could increase BSEP expression at the CM in BRIC2 patients with the c.1211A>G (p.D404G) mutation in *ABCB11* and, consequently, expand their capacity to secrete bile salts into bile. Therefore, the patient was enrolled in the intervention study to examine the therapeutic effect of 4PB on a BRIC2 patient.

Oral administration of 4PB (AMMONAPS; Swedish Orphan, Stockholm, Sweden) was started at a daily dose of 200 mg/kg per day divided into four doses. After 1 month, the dose was increased to 350 mg/kg per day and this was maintained for an additional month. Bilirubin absorption and endoscopic NBD were performed during treatment at the doses of 200 and 350 mg/kg per day, respectively. In bile specimens collected by NBD, concentrations of phosphatidylcholine and total cholesterol as well as of total bile acids in the BRIC2 patient was much lower than that of two control patients whose values were within or close to the reference range (Table 1),[8,25] supporting the diagnosis of BRIC2 in the patient enrolled in this study. Because neither any therapeutic effect on serum liver tests and the itching score nor any side-effects were observed, the dose was increased to 500 mg/kg per day, which is a clinically

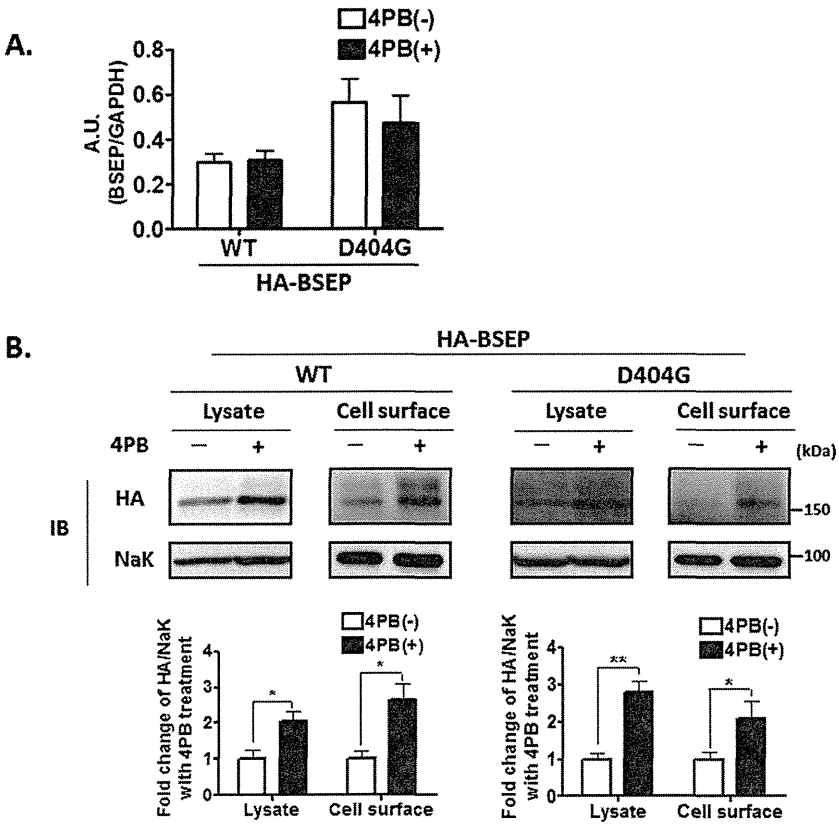


Figure 3 Effect of 4PB treatment on mRNA and protein expression levels of BSEP$^{D404G}$. HA-BSEP$^{WT}$ and HA-BSEP$^{D404G}$ HEK293T cells were treated with or without 1 mM 4PB for 24 h, subjected to (a) quantitative polymerase chain reaction and (b) cell surface biotinylation, and analyzed as described in Fig. 2(a,b). At the bottom of (b), the ratio of band intensities of HA-BSEP$^{WT}$ and HA-BSEP$^{D404G}$ relative to that of NaK was determined as described in Methods is shown. A representative result from two or three independent experiments is shown. Bars represent the mean ± SEM of triplicate determinations. $^*P < 0.05$; $^{**}P < 0.01$. 4PB, 4-phenylbutyrate; A.U., arbitrary units; BSEP, bile salt export pump; IB, immunoblotting; NaK, $Na^+$, $K^+$–ATPase α1 subunit; SEM, standard error of the mean; WT, wild type.

**Table 1** Biochemical analysis of bile specimens from NBD.

| | Disease | BA (mM) | PC (mM) | Ch (mM) | BA (mol%) | PC (mol%) | Ch (mol%) |
|---|---|---|---|---|---|---|---|
| Patient | BRIC2 | 0.18 | 0.01 | <0.04 | N.D. | N.D. | N.D. |
| Control 1 | Cholecystolithiasis | 15.8 | 3.8 | 2.1 | 72.7 | 17.6 | 9.7 |
| Control 2 | Choledochal Cyst | 20.6 | 4.4 | 1.8 | 76.8 | 16.5 | 6.7 |
| Reference values (8, 25) | | 21.3 ± 3.1 | 8.0 ± 1.8 | 1.1 ± 0.3 | 69 ± 2 | 22 ± 1 | 9 ± 1 |

BA, bile acids; BRIC2, benign recurrent intrahepatic cholestasis type 2; Ch, cholesterol, NBD, nasobiliary drainage; N.D., not determined (because PC and CH concentrations are close to and below limit of detection, respectively); PC, phosphatidylcholine.

relevant dose for OTCD, and this dose was maintained for the next 2 months. The serum levels of AST and ALT started to decline when the dose was increased to 500 mg/kg per day. These values finally reached close to the reference range (AST, <55 U/L; ALT, <40 U/L) (Fig.4 a, upper). Consistent with the decrease in AST and ALT levels, the concentrations of T-Bil and D-Bil decreased significantly after the start of 4PB treatment at 500 mg/kg per day. Two months after this dose was started, both parameters were almost normalized to within the reference range (T-Bil, <18 μM; D-Bil, <5 μM) (Fig. 4a, lower). In contrast, the concentration of serum bile acids (BA) also declined, but remained above the reference range (BA, <10 μM), probably because of the co-administration of UDCA (600 mg/day). The itching score decreased during 4PB treatment at 350 mg/kg per day (Fig. 4b). Almost complete and persistent relief of pruritus helped improve the patient's ability to sleep and thus increased his quality of life. However, the itching score did not correlate significantly with the serum levels of autotaxin (ATX) and BA (Fig. 4b), both of which have been proposed as potential pruritogens in cholestasis.[26]

The patient was followed up after the 4PB therapy. The liver tests and itching score remained unchanged for 1.5 months after the end of 4PB therapy but gradually returned to values almost equal to those before his enrollment in this intervention study. Four months after the cholestatic attack relapsed, the liver tests and pruritus spontaneously improved (Fig. 4). No severe side-effects were observed during or after 4PB therapy. The administration of the original drugs, UDCA and fat-soluble vitamins, was maintained during and after the course of 4PB treatment.

## DISCUSSION

ALL OF THE treatments currently available for the cholestatic episodes in BRIC patients are symptomatic therapy because the mechanism responsible for the intrahepatic cholestasis during the attacks is poorly understood. Therefore, the development of a new mechanism-based medical therapy for this disease is highly desirable. Here, we provide the first direct clinical evidence that a patient with BRIC2, a subtype of BRIC caused by mutations in *ABCB11* that encodes BSEP, presented with impaired bile salt secretion into bile because of lessened expression of BSEP at the hepatocanalicular membrane (Fig. 1b, Table 1) and that 4PB therapy at 500 mg/kg per day, a clinically relevant dose used in OTCD patients, markedly improved liver function tests and relieved intractable itching refractory to bilirubin absorption and NBD (Fig. 4). *In vitro* analysis in the current and previous studies showed that the patient harbored two mutations, c.1211A>G (p.D404G) and c.1331T>C (p.V444A), both of which decreased the cell surface expression and transport function of BSEP (Fig. 2)[23] and that 4PB treatment partly relieved the effect of the p.D404G mutation on BSEP (Fig. 3b). Together, these suggest that 4PB is the first mechanism-based drug that may be effective against the cholestatic attacks in patients with BRIC2. All BRIC2-type *ABCB11* mutations that have been studied decrease BSEP expression at the CM, but have less impact on the transport activity of BSEP per se (Fig. 2).[21,22] Therefore, 4PB therapy should be effective for the cholestatic episodes in the majority of BRIC2 patients.

We cannot completely exclude the possibility that the symptomatic relief in the patient was due to spontaneous resolution rather than to the 4PB therapy. However, the fact that the liver tests and itching score exacerbated immediately after the end of the 4PB therapy and that, in general, asymptomatic periods in BRIC patients last from months to years[2] strongly suggests that 4PB therapy relieved the cholestatic episode in this patient with BRIC2, which was refractory to the medical and invasive therapy proposed by previous studies as optional treatments for BRIC.[4,7,9]

How the 4PB therapy improved the results of liver function tests in this study is not fully understood. We previously provided experimental evidences indicating that 4PB treatment decreased the ubiquitination of cell

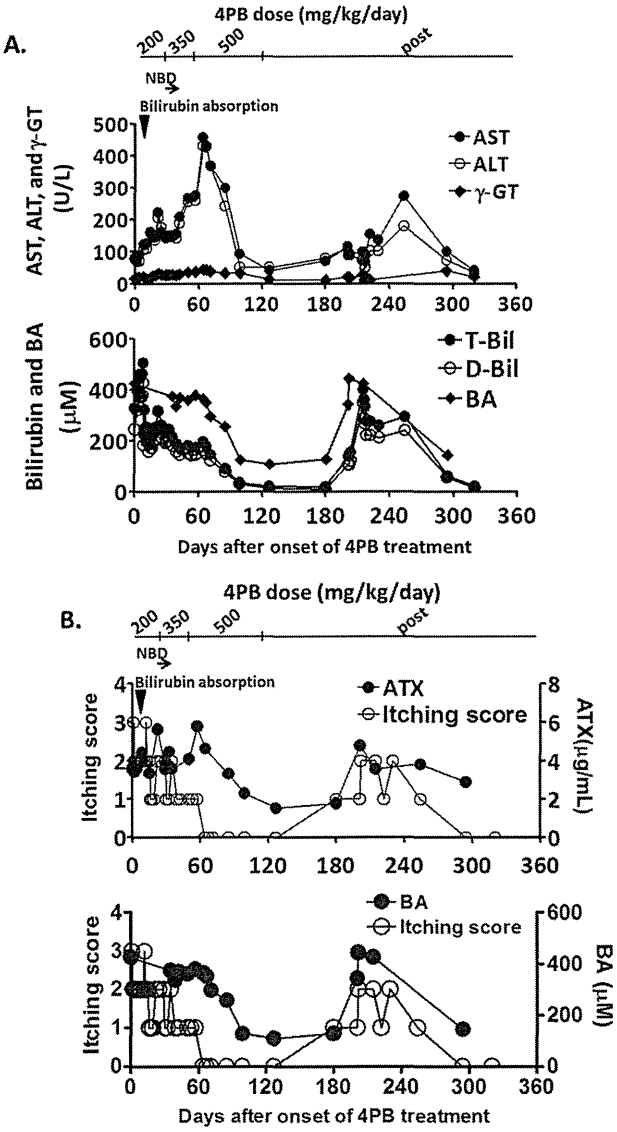


Figure 4 Liver function testing and itching intensity in a BRIC2 patient during and after the course of 4PB therapy. (a) Serum AST, ALT, γ-GT (upper), T-Bil, D-Bil, and BA (lower) levels were monitored during and after the period of 4PB therapy. (b) Correlation of itching scores for the BRIC2 patient with serum concentrations of ATX (upper) and BA (lower) in the patient during and after 4PB therapy. Pruritus severity was scored from 0 (no pruritus) to 4 (cutaneous mutilation, with bleeding and scarring) as described in Methods. The arrow and arrowhead indicate the time point and period when the patient underwent bilirubin absorption and NBD, respectively. γ-GT, γ-glutamyltransferase; 4PB, 4-phenylbutyrate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATX, autotaxin; BA, bile acids; BRIC2, benign recurrent intrahepatic cholestasis type 2; D-Bil, direct bilirubin; NBD, nasobiliary drainage; T-Bil, total bilirubin; WT, wild type.

surface-resident $BSEP^{WT}$ and $BSEP^{E297G}$, the form found most frequently in PFIC2 patients, and interrupted their internalization and degradation, resulting in induction of their expression at the plasma membrane.[16,27,28] Considering that p.D404G and p.V444A, the mutations found in this BRIC2 patient, have an impact on BSEP that is similar to, but milder than, the PFIC2-type mutation p.E297G (Fig. 2),[23,29] it is most likely that 4PB therapy increased the cell surface expression of BSEP in this BRIC2 patient through the same mechanism as in PFIC2 patients with the p.E297G mutation. This is consistent with the quantitative polymerase chain reaction analysis showing that transcriptional processing of $BSEP^{D404G}$ was unaffected by the treatment with 4PB (Fig. 3a).

NBD has been employed successfully for resolving cholestatic episodes in six of seven BRIC patients.[8] Immediate, complete and long-lasting symptomatic relief was elicited. In contrast, no apparent therapeutic effect of 1 week of NBD was observed for the BRIC2 patient in this study. NBD eliminates bile constituents including bile salts, bilirubin and pruritogens, and interrupts their enterohepatic circulation, thereby improving liver function and intractable pruritus. Therefore, it may be less effective in BRIC patients such as one in this study in whom biliary bile salt excretion and bile flow formation were severely disrupted. Medical therapy with 4PB that restores decreased hepatocanalicular expression of BSEP, biliary secretion of bile salts and bile flow formation is a reasonable and promising avenue for treatment of the cholestatic attacks in patients with this type of BRIC.

Treatment with 4PB may also have therapeutic potency for episodic intrahepatic cholestasis in specific BRIC1 patients, because an *in vitro* analysis has shown that treatment with 4PB partially restored the decreased expression of ATP8B1 caused by *ATP8B1* mutations naturally occurring in these patients.[30] Therefore, it is conceivable that 4PB therapy could relieve the cholestatic episodes in patients with BRIC1 who retain protein activity of ATP8B1 per se. Furthermore, even in the BRIC1 patients whose liver functions are barely improved by treatment with 4PB, intractable itching, the main complaint in the cholestatic attacks of patients with BRIC1, should disappear, because the antipruritic potency of 4PB on cholestatic itching was indicated in our previous study.[24] In PFIC1 patients, regardless of the lack of improvement in liver functions assessed by biochemical and histological analysis, therapy with 4PB significantly relieved sustained refractory pruritus, made it possible for the patients to sleep well, and thereby helped improve their quality of life and that of their families.[24] The relief of intractable itching by 4PB

therapy in the patient in this study might have been achieved by not only the improvement in liver function but also by its antipruritic effect, because the itching resolved prior to the improvement in liver function tests and to the decrease in the factors suspected to be causally associated with cholestatic pruritus. At present, the mechanism underlying the relief of cholestatic pruritus by 4PB therapy remains to be elucidated. Future studies will provide evidence regarding the clinical utility and safety of treatment with 4PB in BRIC1 patients and a better understanding of the mechanisms responsible for the effects of 4PB therapy on cholestatic pruritus.

Our study indicates that 4PB is the first mechanism-based drug against intrahepatic cholestasis in BRIC2 patients. Therapy with 4PB markedly improved liver function and relieved intractable itching during a cholestatic episode in a patient with BRIC2. Together with the fact that all the BRIC2-type mutations previously analyzed show a similar impact on BSEP to that of the p.D404G and p.V444A, mutations in this patient, this suggests that 4PB therapy should be effective in the majority of BRIC2 patients. Future clinical studies should be undertaken to validate the favorable outcome and safety of 4PB treatment in more patients than was possible in this study. If its usefulness is confirmed, 4PB therapy could become the preferred choice, instead of the existing medical and invasive therapy, for attenuating cholestatic episodes in BRIC2 patients. Clinical trials will be required to determine the utility and safety of 4PB as a therapy for BRIC1 and other diseases with cholestatic pruritus.

## ACKNOWLEDGMENTS

THIS STUDY WAS supported by a Grant-in-Aid for Scientific Research (C) (26460192) and Astellas Foundation for Research on Metabolic Disorders to H. H.

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Surg Today (2015) 45:813–818
DOI 10.1007/s00595-014-1024-z

REVIEW ARTICLE

# Effects of age at Kasai portoenterostomy on the surgical outcome: a review of the literature

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Received: 25 December 2013 / Accepted: 12 August 2014 / Published online: 12 September 2014


**Abstract** The efficacy of early Kasai portoenterostomy has been repeatedly reported. However, the optimal age for performing this procedure remains controversial. This article reviews the literature on the age of patients at the time of Kasai portoenterostomy and its utility as a prognostic indicator. The age at the time of surgery is a known predictor of outcome; however, its exact predictive value in this context is unclear. Multicenter studies involving large volumes of data have tended to show advantages of early Kasai portoenterostomy, and there is no clear evidence to recommend any delay in the timing of surgery. At present, a reasonable strategy would be to perform a Kasai portoenterostomy as early as possible. The stool color card system has recently been implemented in Japan as part of a nationwide screening program, and it is expected to work well based on the early reports. However, efforts to identify an optimal screening system for ensuring the earliest diagnosis of biliary atresia should continue. An early diagnosis of biliary atresia is difficult, and global efforts are required to improve the early diagnosis rates.

**Keywords** Biliary atresia · Kasai portoenterostomy · Early diagnosis · Liver transplantation

## Introduction

Kasai portoenterostomy was developed in the 1950s and was a significant milestone in the treatment of biliary atresia. The procedure has offered the chance of survival to patients with an uncorrectable type of biliary atresia that was previously considered to be fatal. Morio Kasai had expected to cure 80 % of patients with biliary atresia with this surgery. However, according to a recent report from the Japanese Biliary Atresia Registry (JBAR), the jaundice-free native liver survival rate unfortunately remains at approximately 60 % between six and 18 months after Kasai portoenterostomy.

Many studies have been performed to determine the factors that may influence the surgical outcomes, and much attention has been paid to the age at the time of the operation, which was reported as a significant risk factor by Kasai [1]. He reported a better surgical outcome in patients younger than 60 days old at the time of surgery. Since then, the efficacy of early surgery has been reported by numerous studies [2–8]. However, the optimal timing of Kasai portoenterostomy remains controversial [9–15]. Although the prognosis for patients aged ≥3 months is generally poor, there is no consensus whether 2 months is a critical age that can impact the prognosis. The role of neonatal surgery is also a matter of debate. This review discusses the literature on the significance of the age at Kasai portoenterostomy as a risk factor for a poor prognostic outcome.

## The age at Kasai portoenterostomy and the jaundice clearance rate

Many papers have supported the effectiveness of early surgery. In Japan, more than 2,600 cases of biliary atresia had been registered in the JBAR by 2012. The highest jaundice clearance rate (JCR) achieved among patients who underwent neonatal surgery and whose data were recorded in the JBAR was 71 %. The JCR worsened as the age at surgery

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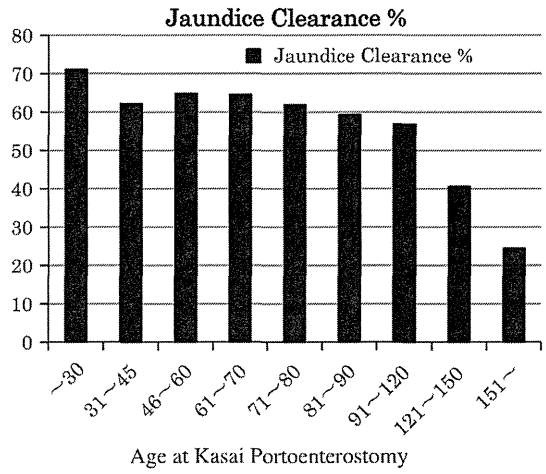


**Fig. 1** The age at Kasai portoenterostomy and the jaundice clearance rate among the patients in the Japanese Biliary Atresia Registry. The best jaundice clearance rate (JCR), 71 %, was achieved by patients who underwent neonatal surgery. The JCR was worse among patients with an age at the time of the procedure >3 months, but it was essentially the same among those aged between 1 and 3 months old

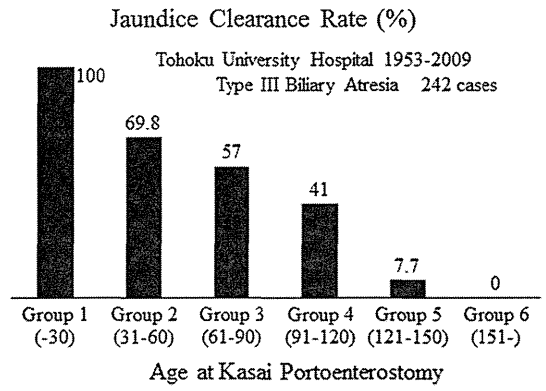


**Fig. 2** The age at Kasai portoenterostomy and the jaundice clearance rate among the patients at Tohoku University Hospital. A total of 242 patients with type III biliary atresia were assessed to identify the relationships between their age at Kasai portoenterostomy and the jaundice clearance rate (JCR). The patients were classified into six groups based on their age at Kasai portoenterostomy. The age at portoenterostomy and the JCR were significantly inversely correlated ($p < 0.0001$)

increased past 3 months old, but was essentially the same among patients aged 1–3 months old [16] (Fig. 1).

Among 242 patients with Type III biliary atresia (atresia at the porta hepatis, the most common type) at Tohoku University Hospital (TUH), the correlation between the age at portoenterostomy and the JCR was assessed using a Chi squared test. They were found to be significantly inversely correlated (Fig. 2).

Numerous multicenter studies have been performed in countries other than Japan. One Canadian group reported a 10-year native liver survival rate of 49 % among patients who underwent neonatal surgery, but the rate was 15 % among those with an age of >3 months old at the time of the operation [17]. Better outcomes following early surgery have also been reported from France [18], Switzerland [19] and Brazil [20] (Table 1).

On the other hand, some authors, including McKiernan [10], Wildhaber [12] and Shneider [14], have reported no significant relationship between the age at Kasai portoenterostomy and postoperative jaundice clearance. In the German registry, no significant advantage of early surgery was found [21]. Davenport et al. [22] reported the potential for reasonable medium-term survival in approximately one-third of infants aged ≥100 days undergoing portoenterostomy. At TUH, while some patients had an unfavorable postoperative course even after early portoenterostomy (before they were 2 months old), others achieved excellent bile drainage even after late surgery at ≥3 months of age. A 33-year-old female patient who underwent Kasai portoenterostomy at TUH at the age of 148 days is now a healthy mother of two children.

The reasons for these different outcomes among countries and institutions remain unclear. Although differences in surgical techniques and postoperative management may have some impact on the outcome, the severity of the pathological involvement of the hepatobiliary system, which is partly associated with the age at the operation, is believed to be a more important factor influencing the prognosis.

If the timing of disease onset varies greatly between cases due to various mostly unknown etiologies, then the age at the operation would be less significant as a predictive factor. On the other hand, if patients with similar disease characteristics, including the etiology and timing of disease onset, are treated using the same therapeutic strategy, including surgical techniques and postoperative management, then the age may be a significant risk factor.

The age at the operation is known to be an important predictive factor, but its predictive value is unclear at present. Therefore, the selection of Kasai portoenterostomy versus primary liver transplantation should not be decided based on a patient's age [15].

## The age at Kasai portoenterostomy and the long-term outcome

As the number of long-term survivors following Kasai portoenterostomy has grown, the relationship between the age at the operation and the long-term prognosis has also been studied; however, the relationship has not been fully elucidated. Lykavieris et al. reported that the 20-year native liver survival rate was significantly better in patients whose age was ≤90 days at the time of the operation, even though <18 %

**Table 1** The age at Kasai portoenterostomy and the native liver survival rate in various countries

| | | | | | | |
|---|---|---|---|---|---|---|
| Canada | Number of centers | 12 | Age at Kasai operation | <30 days | >91 days | |
| | Years of native liver survival | >10 years | Native liver survival % | 49 % | 15 % | |
| France | Number of centers | 45 | Age at Kasai operation | ≤45 days | >45 days | |
| | Years of native liver survival | 4 years | Native liver survival % | 51 % | 40 % | |
| Swiss | Number of centers | 7 | Age at Kasai operation | ≤45 days | 46–75 days | >75 days |
| | Years of native liver survival | 2 years | Native liver survival % | 75 % | 43.7 % | 11.3 % |
| Brazil | Number of centers | 6 | Age at Kasai operation | <60 days | 61–90 days | >90 days |
| | Years of native liver survival | 4 years | Native liver survival % | 54 % | 33.3 % | 26.6 % |
| Netherland | Number of centers | 6 | Age at Kasai operation | ≤60 days | >60 days | |
| | Years of native liver survival | 4 years | Native liver survival % | 56 % | 34 % | |

of patients in their long-term series who were treated with Kasai portoenterostomy avoided liver transplantation [23]. In contrast, Shinkai et al. [24] reported that the age at the operation had no significant effect on either the short-term or long-term prognosis following Kasai portoenterostomy.

According to findings from the TUH study of Type III biliary atresia patients who became jaundice-free following Kasai portoenterostomy, while the long-term outcome was influenced by the age at the time of the operation until the patients were 30 years old, the difference was smaller thereafter, and the native liver survival rate of each age group eventually tended to be concentrated at approximately 30 % [25]. The 40-year life expectancy may therefore be approximately 30 % even in patients who become jaundice-free following Kasai portoenterostomy, regardless of their age at the time of the procedure. This would be due to the existing liver pathology, which is determined very early in life in the majority of cases.

However, we still believe that better long-term results can be expected in more recent cases because the surgical outcomes improved remarkably during the 1970 s. Besides the age at the time of Kasai portoenterostomy, the time required for jaundice to disappear and an association between early cholangitis and portal hypertension have also been suggested as potential predictors of the prognosis after >20 years [26]. However, no reliable indicator for predicting very long-term prognosis (>30 years) has been identified so far. Further investigations are required to identify definitive factors that can determine the ultimate outcome of biliary atresia. Follow-up JBAR registration is ongoing, and the current status of 20-year survivors is gradually becoming apparent. After another 10 years, we should be able to determine 30-year outcomes using the JBAR data.

## Repeat Kasai portoenterostomy

After the initial Kasai portoenterostomy, a second Kasai portoenterostomy may be required in some cases. The main indications for the repeat procedure are insufficient bile drainage after the first surgery, or a cessation of bile drainage due to cholangitis or another cause. I hypothesize that the optimal timing of the initial and repeat Kasai portoenterostomy would be as follows: In the early phase of biliary atresia, the bile flow in the intrahepatic bile duct may be severely decreased due to the original pathology. If early surgery can be performed during this phase, good bile drainage cannot be achieved because there is insufficient bile reaching the porta hepatis, and thus, this area will rapidly be replaced by another fibrous mass before an enterobiliary anastomosis is established. In such cases, the drainage route of the bile in the liver may recover after a certain period due to the regeneration of the intrahepatic biliary network, and good bile drainage may be achieved after a timely repeat Kasai portoenterostomy.

If this hypothesis proves to be correct, then there is certainly an optimal time for Kasai portoenterostomy, and we should refrain from performing early surgery for this select subset of patients. However, neonatal surgery currently yields the best JCR, and it is difficult to confirm the above hypothesis clinically.

At TUH, jaundice was resolved in three quarters of the patients who achieved good bile drainage, but was not resolved at all in patients with poor or no bile drainage following initial Kasai portoenterostomy. Thus, the patients who develop sudden cessation of bile flow after achieving sufficient bile drainage following the initial Kasai portoenterostomy are currently the best candidates for repeat Kasai portoenterostomy, which should be employed only once for this select subset of patients. This is the widely accepted indication for repeat Kasai portoenterostomy [27].

The JBAR data indicate that the incidence of repeat Kasai portoenterostomy declined from 28 % between 1989 and 1999 to 15 % between 2000 and 2011 ($p < 0.0001$). The JCR after repeat surgery (34 vs. 36 %) and the jaundice-free native liver survival rates (57 vs. 55 %) were essentially the same between the two groups (Table 2).

**Table 2** Redo Kasai portoenterostomies recorded in the Japanese Biliary Atresia Registry

| Period | 1989–211 | 1989–1999 | 2000–2011 | *p* |
|---|---|---|---|---|
| *N* | 2,630 | 1,423 | 1,207 | |
| JCR % after the initial Kasai surgery | 61 | 63 | 61 | ns |
| Redo % | 21 | 28 | 15 | *<0.0001* |
| JCR % after Redo | 35 | 34 | 36 | ns |

*JCR* jaundice clearance rate

The incidence of repeat Kasai surgery was significantly reduced, but the overall survival rate was significantly higher in the later period (90 vs. 95 %, $p < 0.0001$). These results may be attributed to the improved availability of early liver transplantation and the limited number of patients selected for repeat surgery in the latter period [28].

Regarding the efficacy of repeat surgery among all patients, a further analysis of patients who have undergone repeat surgery may provide important information for determining more precise indications for repeat surgery. Even in the JBAR data, the number of neonatal cases remains limited, and the efficacy of repeat surgery for early neonatal cases is uncertain. Accumulated experience with repeat surgery for neonates would enable the elucidation of the disease process of biliary atresia and the optimal timing of Kasai portoenterostomy.

## Trends regarding the age at Kasai portoenterostomy

The relationship between the age at Kasai portoenterostomy and the surgical outcome is not straightforward. While the prognosis is poor in some patients even after early surgery, it is excellent in some patients who undergo late Kasai portoenterostomy at an age ≥4 months. Multicenter studies with a large volume of data have tended to show that early Kasai portoenterostomy is advantageous, and there is no clear evidence to recommend a delay in the timing of surgery as yet. At this stage, a reasonable strategy would be to make every effort to ensure that Kasai portoenterostomy is performed as early as possible, and to select patients for repeat Kasai surgery or liver transplantation on a case-by-case basis according to their condition and the extent of liver damage after a failed initial Kasai portoenterostomy.

Despite the importance of early Kasai portoenterostomy having been advocated for a long time, the age of the patients at the time of surgery has not significantly decreased since the JBAR was initiated. The age has also remained unchanged in the TUH series over the past 40 years.

The outcomes of medical treatment have improved markedly among small children in Japan, including those with biliary atresia. This is primarily due to a high standard of public health care, careful monitoring and management of expectant and nursing mothers, the development of new medical equipment, technical advances and free infant medical checks. However, earlier Kasai portoenterostomy has not been realized. The main reason for this may be that in Japan, the health checks of newborn babies are mainly performed by obstetricians who have no experience with biliary atresia. A prenatal diagnosis of biliary atresia remains difficult, because the condition does not present with any detectable signs during the prenatal period except for cystic structures at the porta hepatis in a minor subset of cystic types, such as Type I and Type IIId cysts according to Kasai's classification. Most patients develop no conspicuous symptoms except for jaundice, which is a common symptom in healthy neonates during the first month of life. The color of the meconium is normal in the majority of patients with biliary atresia. Whitish or clay-colored stools are passed early in life by only a quarter of patients, and direct bilirubin is rarely assessed for neonatal jaundice even by neonatologists. Thus, an early diagnosis of biliary atresia is very difficult.

## Approaches to the early diagnosis of biliary atresia

The need to establish a screening system has been remarked upon for a long time [29]. Currently, the stool color card is regarded as the most promising approach. The stool color card was originally developed by Matsui et al. and has been utilized in several areas of Japan since the early 1990s. Comparing the sample color shown in the card with the stool passed by the baby, the family member or another caregiver may be able to notice an abnormality of the stool color, and the baby can be taken to a specialist hospital for treatment [30]. In Taiwan, a similar card system was introduced nationwide early this century, and a successful outcome in terms of an early diagnosis was reported [31]. A pilot study of this system was introduced in Switzerland in 2009 [32].

In 2012, a nationwide stool color card system was introduced in Japan. The stool color card is inserted in the maternal and child health handbook, and the instructions indicate that it should be checked at least twice: once at the 1-month regular health check and again at a later date. The stool color card is based on a subjective color assessment, and it has the advantages of simplicity and low cost. On the other hand, color decisions made primarily by mothers may be incorrect, partly because mothers tend to have difficulties recognizing severe illness in their children due to the so-called normalcy bias.

It is important that mothers and caregivers are aware that patients with biliary atresia usually pass yellowish stools in the early neonatal period, and that the stool color then becomes pale yellow or whitish. The color card screening system was introduced to help increase the rate of early diagnosis of biliary atresia by double-checking the stool color, and more importantly, this system is expected to highlight the existence of biliary atresia, which is a very rare disease, and increase the awareness of the condition by mothers, physicians, and public health nurses.

In some areas in Japan, urinary sulfated bile acid (USBA) is used for the early diagnosis of biliary atresia [33]. Compared with the stool color card system, this method is quantitative, and thus, more objective. The method may be promising, but it has numerous disadvantages related to cost effectiveness, the proper handling of urine samples, and control of the false-positive rate, which all need to be resolved before it can be adopted as a nationwide screening system. An appropriate combination of USBA and the stool color card system may be a practical solution for overcoming the disadvantages of using each method individually.

Direct bilirubin [34] and serum bile acid [35, 36] measurements have previously been evaluated for screening for biliary atresia. However, these approaches were associated with problems related to the timing of sampling and the setting of appropriate cut-off levels that could not be resolved. Thus, no screening system was established. A trial of a new protein biomarker has also been reported [37].

The stool color card system has just begun nationally in Japan, and the system is expected to work well based on the initial results and the findings in other countries. However, we should continue to pursue an optimal screening system for ensuring the earliest possible diagnosis of biliary atresia.

## Future prospects

Every effort has been made to achieve better outcomes following Kasai portoenterostomy since its development half a century ago. Currently, the 1- and 10-year native liver survival rates are approximately 60 and 50 %, respectively (Fig. 3). However, 30–40 % of patients require a liver transplantation several years after a Kasai portoenterostomy. Some patients have undergone a liver transplantation after surviving >40 years due to advanced liver cirrhosis or severe complications.

Several reports have been published regarding hepatic regeneration using iPS cells, and this is a promising area for future therapies [38]. Biliary atresia may be treated using this technology in the near future.

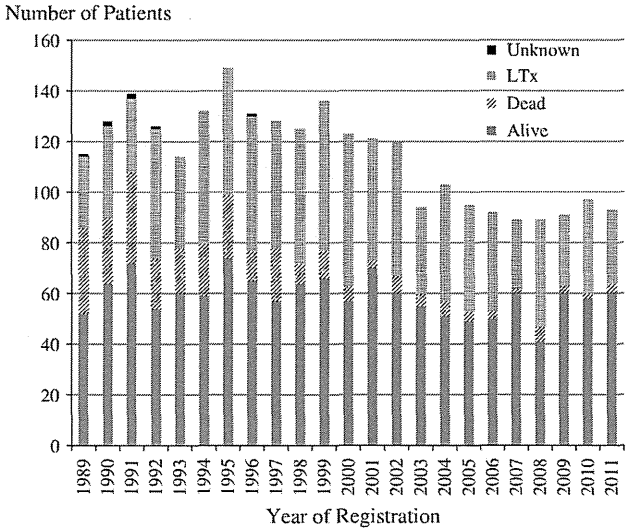


**Fig. 3** The current status of the patients in the Japanese Biliary Atresia Registry. The current status has been recorded for most patients included in the registry. While the short-term native liver survival rate is approximately 60 %, approximately 40 % of patients have required a liver transplantation within several years of a Kasai portoenterostomy

Great advances in the treatment of biliary atresia can be achieved by elucidating its etiology. Our ultimate goal is the prevention of biliary atresia. Until such a time, everything possible should be done to improve the outcomes following Kasai portoenterostomy, including finding ways to ensure an earlier diagnosis and the implementation of appropriate surgical techniques and postoperative care, including the management of long-term survivors.

Difficulties related to the early diagnosis of biliary atresia are not a problem limited to Japan [39], and efforts must be focused on improving the rates of the early diagnosis of biliary atresia worldwide.

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■ 原 著

# 生体肝移植後の学童後期・思春期の小児の療養生活の実態と生活の満足度

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# Daily-life situations and subjective-life satisfaction of living liver-transplanted adolescent children

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**【Summary】**

**【Objective】** This study examines the daily-life situation and the subjective-life satisfaction of living liver-transplanted preadolescent and adolescent children.
**【Design】** Cross-sectional survey
**【Methods】** Our study sample consists of 9 preadolescent and adolescent children who had undergone liver transplantation. Data were collected through semistructured interviews and questionnaires about their daily-life experiences. Descriptive statistics and qualitative descriptive research methods were used for the data analyse.
**【Results】** Our survey showed how elementary school children (fourth to sixth grades) could manage their health by themselves with parental support. They did know that they experienced an operation in their childhood period, but did not sufficiently understand the "transplantation" itself. Self-management of high-school children differs according to their transplantation period or their perception about the transplantation. In regard to subjective-life satisfaction, all the elementary school children had scores higher than the standard value; however, half of the high school children showed scores lower than that value. In particular, the subjective-life satisfaction did not always correspond with their physical situations.
**【Conclusion】** Preadolescent children could manage their health with parental support. Their satisfaction score was higher than the standard value. However, they did not sufficiently understand the "transplantation" itself. Self-management of adolescent children differs according to their transplantation period or their perception about the transplantation. The satisfaction score did not necessarily correspond to their physical situation. Medical staffs should support children with due consideration of their past experiences and understanding of the disease, the treatment, and the transplantation itself.

**Keywords:** liver transplantation , children, quality of life

## I. 緒 言

小児に対する肝移植の生存率は，成人の肝移植に比して良好である[1]。小児の肝移植患者は，成人の肝炎や肝癌のような移植後に再発する可能性のある疾患は少なく，長期生存が期待される。

末期肝不全患者に対する有効な根治的治療は，肝移植であるが，移植医療を受けた患者家族の術後の長期的な見通しは，情報が少なく，不確定な部分が多い。肝移植を必要とする小児は，移植を受けるまでの間，対症療法をしながら慢性疾患患者としての生活が続

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(2013・9・24受領；2014・2・25受理)

く[2]。移植後は，免疫抑制剤の内服や感染予防のための自己管理，移植後長期において起こりうる合併症への不安等，種々の問題を抱えながら生活していかなければならない。

小児肝移植後の長期的問題は，医学的見地から各移植施設において調査されているが[3-6]，心理社会的問題に関しては，明らかになっていない部分が多い。学童から思春期の小児は，生活の主体が家庭から学校へと移行し，家族中心の健康管理から小児主体の健康管理に移行する重要な時期にある。特に，慢性疾患をもつ思春期の小児は，自己同一性の確立という発達課題の中，病気をもつ自分を見つめなおし新たな自己像を形成していく段階にある。また，思春期は，思春期特有の思考や，疾患・治療に対する否認などの情緒面の問題，友達など周囲との関係性の影響を受けやすく，不適切なセルフケア行動といったセルフケアの逸脱が生じやすい時期である[7]。そのため，医療者は，思春期の小児の病気とともに生活していく自分としてのアイデンティティを確立していく過程で経験する葛藤や混乱に一緒に向き合い，小児のもつ力を最大限に引き出し，困難に対処できるように支援する必要がある。しかし，個々の病状によって移植時期は異なり，成長発達過程で身体・精神・社会面において，患児・家族がどのような問題に直面し，どのように対処しているのかは明らかにされていない。そこで，本研究では，学童後期・思春期の小児への支援を検討するために，肝移植後の学童後期・思春期の小児の療養生活の実態および生活の満足度を明らかにすることを目的とした。

## II. 方　法

### 1. 対　象

現在A病院に外来通院中の10～18歳の肝移植後の小児で，本人の承認および保護者の同意が得られ，病名・病気についての説明を受けている者とした。また，質問紙調査および面接を行うため，識字可能で自分の体験を自由に語ることのできる者とした。

### 2. 調査期間

調査期間は，2011年10月～2012年3月であった。

### 3. 調査方法

対象者への依頼は，担当医が基準を満たすことを確認した者に対し，外来受診時に行った。面接は，診察室で対象者と研究者の1対1（本人が希望する場合，親の同伴も可とした）で行った。面接内容は，同意を得た上でICレコーダーに録音した。基本的属性および療養生活，病気に対する捉えや体験については，質問紙（自作）調査および半構造化面接を行い，生活の満足度については，既存の質問紙を用いた。質問紙は，診察の待合中に記載してもらい，面接の際に回収した。面接は，質問紙の結果を基に行った。また，外来診察時は診察に同席するとともに，検査データの情報を得た。

### 4. 調査内容

基本的属性として，性別，現在の年齢，就学状況，原疾患，移植時期，移植時年齢，身長・体重，家族構成について尋ねた。原疾患・移植時期等，子どもが分からない場合は，保護者に確認した。また，肝機能データについては，診察時に確認した。

療養生活については，日常生活（起床・就寝時間，食事，活動等），療養行動（日常注意していること，免疫抑制剤の内服，困っていること等），学校生活（出席状況，体育やクラブ活動・行事への参加，学校生活をどう感じているか，放課後の活動，友達関係，周囲の人の理解等），病気に対する捉えや体験について尋ねた。

生活の満足度は，中村ら[8,9]の開発した，疾患とは直接関係のない一般の日常生活に関する満足度（包括的なQOL）を調べる調査票（小学校高学年から中学生用と，高校生以上用の2種類）を用いた。小・中学生用は，「不安や悩み」「家と家族の満足」「友達の満足」「学校と先生の満足」「全体的な健康の満足」「体力と勤勉性，自尊感情」の6因子・37項目（総得点：185点），高校生用は，「友達の満足」「学校生活の満足」「精神面の満足」「親と経済の満足」「異性との関係性・自尊感情」「身体的活力」「進学や就職の悩み」「きょうだい関係の満足」の8因子・40項目（総得点：200点）から構成される。得点が高いほど，生活の満足度が高い。各質問紙は，信頼性・妥当性が確認されている。

### 5. 分析方法

1）事例ごとの個別分析

療養生活に関しては，質問紙の結果より実態を整理した。面接内容は，得られた録音データから逐語録を作成し，療養生活における子どもの認識や実際，子どもの体験や直面した困難・問題とそれに対する対処に

ついて，類似性のある内容を整理し，まとまりの意味を表す簡潔な一文で表した。生活の満足度質問紙は，点数を小学生の男子/女子，高校生の男子/女子の標準値における標準偏差よりデータを基準化（基準値平均を0，標準偏差を1）し，基準値と比較した。

2）全体分析

個別の質問紙と面接結果より，療養生活の実態について類似性のある内容を整理し，意味内容が損なわれないよう抽象度を高め，カテゴリーを抽出した。分析は，小児看護学の研究者2名のスーパーバイズを受けながら行い，分析結果の真実性を確保した。

### 6. 倫理的配慮

対象者およびその保護者に対して，研究参加の自由，途中中断の権利，プライバシーの保護，研究結果の公表などについて口頭・書面にて説明し，同意を得て実施した。なお，本研究は，研究者所属機関の倫理審査委員会の承認（承認番号：23-51）を得て実施した。

### 7. 用語の定義

療養行動：肝移植後の子どもに必要な内服管理や感染予防，情報獲得などの疾患管理に伴う行動

## III. 結　果

### 1. 対象者属性

対象者は，男子3名，女子6名だった。現在の年齢は，平均年齢14.2±3.0（SD）［10～17］歳で，小学生3名，高校生6名であった。移植時の平均年齢は，8.2±5.4［2～17］歳で，移植後経過期間は，7カ月から12年1カ月［平均5.7±3.6年］だった。すべての症例は，免疫抑制剤の内服治療中であったが，うち1名のみ脳死肝移植登録中で，外来でアルブミン製剤の点滴治療を要していた。身長のSDスコア平均は，−1.11±0.9［−2.46−−0.07］SDで，−2SD以下は，1名のみだった。肥満度の平均は，10.2±0.22［−9.5−61.5］%で，軽度肥満が1名，高度肥満が1名でいずれも女子であった（**表1**）。

### 2. 肝移植後の学童後期・思春期の小児の療養生活の実態

全症例結果より，療養生活の実態は，小学生3名と高校生6名では発達段階を反映した相違がみられたため，小学生と高校生に分けて，日常生活・学校生活・疾患管理に対する認識と実際，病気に対する捉えや体験および生活の満足度（QOL）の特徴を示す。療養

**表1　対象者の概要**

| 症例 | 年齢（歳）/性別/学校 | 移植後経過期間 | 原疾患 | 家族構成 | 肝機能（U）AST/ALT/γGTP | 身長SD/肥満度（%） |
|---|---|---|---|---|---|---|
| A | 10/男/小学校 | 5年9カ月 | 先天性門脈欠損症<br>高ガラクトース血症 | 2人（母） | 33/14/15 | −0.4/−6.8 |
| B | 10/女/小学校 | 7年3カ月 | 先天性門脈欠損症<br>高ガラクトース血症<br>声門下狭窄 | 5人<br>（母，兄，祖母，伯母） | 29/20/18 | −1.2/−7.9 |
| C | 11/女/小学校 | 8年2カ月 | 胆道閉鎖症 | 4人<br>（母，姉，兄） | 21/15/16 | 0.4/15.7 |
| D | 15/男/高校 | 2年11カ月 | 胆道閉鎖症 | 5人<br>（両親，兄，妹） | 24/21/19 | −1.7/−9.5 |
| E | 17/女/高校 | 7カ月 | 胆道閉鎖症 | 4人（両親，妹） | 14/10/14 | 2.46/28.1 |
| F | 15/女/高校 | 1年11カ月 | 胆道閉鎖症<br>肝肺症候群 | 7人<br>（両親，弟4人） | 34/36/77 | 1.6/61.5 |
| G | 17/女/高校 | 7年 | 劇症肝炎 | 3人（母，姉） | 27/24/62 | 2.1/7.1 |
| H | 17/男/高校 | 7年4カ月 | 胆道閉鎖症<br>（脳死肝移植登録中） | 7人<br>（両親，妹3人，弟1人） | 177/164/21 | 0.07/1.5 |
| I | 16/女/高校 | 12年1カ月 | 胆道閉鎖症 | 3人（母，弟） | 24/14/22 | 0.1/2.1 |

生活の認識と実際，病気に対する捉えや体験については，カテゴリー《　》を示した。

1）小学生の療養生活の実態

日常生活では，《生活で困っていることはない》と捉えており，制限のない日々を過ごしていた。免疫抑制剤への影響から，禁止されている食品の制限を守ることも認識しており，決められたことは守っていた。また，《清潔や食事，生活習慣に気をつけている》というように普段の衛生行動を実践していた。学校生活については，《学校生活は楽しい》と捉えており，《毎日通学していた》。《友人との関係はうまくいっている》と捉えており，下校後は友人と遊んで過ごすなど，通常の小学生と変わらない学校生活を送っていた。疾患管理では，管理の中心は免疫抑制剤の内服であり，《薬を毎日飲むことは体のために必要である》と捉えていた。しかし，《薬は自分で飲むが，うっかりして忘れることがある》《薬は家の人に言われて飲むが，うっかりして忘れたことがある》というように，時々内服忘れがあった。外来受診については，《受診のために学校に遅刻したり休むことは気にしていない》《受診のために学校に遅刻することは体のために必要である》と捉えていた。対象の小学生は3名ともに移植時期は幼児期であり，うち1例は移植のことを≪学校の課題を通して知った≫状況であり，≪移植をいつしたかはよくわからない≫≪肝臓をもらったことはよくわからない≫≪手術したことしかしらない≫≪移植のことはわからない≫という認識だった。他の症例からは，移植や病気に対する認識の要素は上がらなかった（**表2**）。

2）高校生の療養生活の実態

日常生活では，小学生と同様に《生活で困っていることはない》と捉えていたが，脳死肝移植登録中の症

**表2　小学生の療養生活に対する認識と実際に関する要素**

| | 認識 | 実際 |
|---|---|---|
| 日常生活 | 《生活で困っていることはない》<br>《日常生活での制限はない》<br>《日常生活で注意していることはない》<br>《食べ物の制限を守ることは体のために必要である》<br>《食べ物の制限を守ることはなんともない》<br>《お腹を守るようしている》<br>《体調が悪いと勉強に集中できない》 | 《水泳や運動の制限は守っている》<br>《制限のない生活》<br>《禁止されている食べ物に対して決められたことを守っている》<br>《清潔や食事，生活習慣に気をつけている》<br>《体調が悪い時は寝る》 |
| 学校生活 | 《学校生活は楽しい》<br>《傷が恥ずかしい》<br>《友人との関係はうまくいっている》<br>《移植のことを話した友人は，病気のことを理解してくれている》 | 《友人に傷のことを言われたら移植のことを話す》<br>《クラス全員あるいは仲の良い友人に移植のことを話している》<br>《熱がなかったら学校にいく》《毎日通学している》<br>《運動制限はない》《クラブ活動に参加している》<br>《体育の参加は自分または親が決定している》<br>《体育の参加は親が決めている》<br>《下校後は友人と遊んだり習い事に通っている》 |
| 疾患管理 | 《薬を飲むことに気をつけている》<br>《薬を毎日飲むことは体のために必要である》<br>《薬をのむことは普通のことである》<br>《薬を飲まないと死んでしまう》<br>《薬は今後は自分で管理したい》<br>《受診のために学校に遅刻したり休むことは気にしていない》<br>《受診のために学校に遅刻することは体のために必要である》<br>《外来受診は友達と会える》 | 《薬は自分で飲むが，うっかりして忘れることがある》<br>《薬は家の人に言われて飲むが，うっかりして忘れたことがある》 |
| 病気に対する捉え・体験 | ≪学校の課題を通して知った≫<br>≪移植をいつしたかはよくわからない≫<br>≪手術したことしかしらない≫<br>≪移植のことはわからない≫<br>≪肝臓をもらったことはよくわからない≫ | |

**表3　高校生の療養生活に対する認識と実際に関する要素**

| | 認識 | 実際 |
|---|---|---|
| 日常生活 | 《薬以外は普通の生活である》<br>《生活で困っていることはない》<br>《決められていることを守ることは体のために必要である》<br>《決められていることを守ることは仕方ない》<br>《決められていることを守ることは簡単でありなんともない》<br>《活動制限はない》《食べ物や活動に制限がある》<br>《特に気をつけていない》<br>《傷が気になる》《手術後のほうが体が動きやすい》<br>《悪くなる前は普通の生活だったが今の状況は良くない》<br>《自分の思いを医療者に伝えるのは難しい》<br>《ときどき体調が悪いことがある》 | 《食べ物の制限は守っている》<br>《制限のある食べ物は母親が外す》<br>《自分なりに感染予防行動をとっている》<br>《活動制限を守っている》<br>《活動制限を守れていない》<br>《体調が悪い時は無理をしない》 |
| 学校生活 | 《学校生活は楽しい》《学校生活は普通である》<br>《学校生活は面倒くさいが進級のことがあり休めない》<br>《学校生活の制限は体育である》<br>《親しい友人には移植や病気のことを話し，理解してくれている》<br>《親しい友人に移植のことを説明している》<br>《友人関係はうまくいっている》<br>《友人関係はまあまあである》 | 《学校には毎日行っている》<br>《自分の体調にあわせて無理しない学校生活を送る》<br>《体育の参加は自分で決める》<br>《体育の参加は医師が決めており制限されている》<br>《運動制限は特にない》<br>《クラブ活動に参加している》<br>《クラブ活動に参加していない》<br>《担任に移植のことを説明している》<br>《移植後に友人とのコミュニケーションが図れなかったが，今は新たに友人を作った》 |
| 疾患管理 | 《肝臓は問題ない》《薬を飲むことは体のために必要である》<br>《毎日薬をのむことは面倒くさい》<br>《薬を飲むことや点滴は面倒くさいが仕方ない》<br>《薬による副作用がある》《薬の必要性がわからない》<br>《薬を飲むことは友達と違うので嫌である》<br>《薬をのむことは移植前も後も変わらないし何ともない》<br>《薬は飲みたくないが悪くなったり病気になるのは困る》<br>《自分なりに管理している》《外来受診は面倒くさい》<br>《外来受診や検査は体のために必要である》 | 《薬は親や家族に任せている》<br>《内服は自分で管理している》<br>《薬を飲み忘れることがある》<br>《薬の飲み忘れがないよう自分なりに対策をとっている》<br>《薬を飲み忘れた時は自分なりに対処する》<br>《体調が悪い時は親に言ったり友達に確認してもらう》<br>《感染に気をつけている》<br>《特に気をつけていない》 |
| 病気に対する捉え・体験 | 《移植の必要性を小学生・中学生の時に聞いた》<br>《移植のことを中学生で理解した》<br>《手術の時に移植のことは分かった》<br>《移植を受けたあとに移植について聞いた》<br>《移植については親に任せていた》<br>《肝臓は親がくれるものである》<br>《移植のことを聞いたがどうでもよかった》<br>《知らないうちに移植が終わっていた》<br>《親に聞く前から漠然と移植について知っていた》<br>《手術のことは覚えていないのでなかったものと一緒である》<br>《移植前は疲れやすかったが，移植後は身体が楽になった》<br>《もらった肝臓は元気である》<br>《自分の病気は重い病気である》<br>《黄疸はやばい》《肝臓をもらったことは感謝している》 | |

例のみ《悪くなる前は普通の生活だったが今の状況は良くない》と捉えていた。また，活動については，一部制限のある症例もあったが，体調が良いと《活動制限を守れていない》状況であった。しかし，《体調が悪い時は無理をしない》というように，自分なりの対処法を身に付けていた。学校生活については，《学校生活は楽しい》《学校生活は普通である》《学校生活は面倒くさいが進級のことがあり休めない》と捉えてい

た。《体育の参加は医師が決めており制限されている》症例以外は，《体育の参加は自分で決める》状況であり，《自分の体調にあわせて無理しない学校生活を送る》ようにしていた。学童後期に移植を受けた症例では，《移植後に友人とのコミュニケーションが図れなかったが，今は新たに友人を作った》状況があった。しかし，現在は全例，子どもなりに友人関係を築いていた。疾患管理では，《薬を飲むことは体のために必要である》と捉えていながらも，《毎日薬をのむことは面倒くさい》《薬を飲むことや点滴は面倒くさいが仕方ない》と捉えていた。また，《薬による副作用がある》《薬を飲むことは友達と違うので嫌である》《薬の必要性がわからない》と否定的な捉えのある者もいた。免疫抑制剤の管理では，服薬忘れの経験が全例にあり，《薬の飲み忘れがないよう自分なりに対策をとっている》者や《薬を飲み忘れた時は自分なりに対処する》者があった。病気に対する捉えや体験では，移植について知った時期は，《移植の必要性を小学生・中学生の時に聞いた》《移植のことを中学生で理解した》《手術の時に移植のことは分かった》と自分なりに捉えていた者，《移植を受けたあとに移植について聞いた》者があった。移植に対しては，高校生時に移植を受けた者は，《肝臓は親がくれるものである》と捉えていた。劇症肝炎で小学生時に移植を受けた者は，《知らないうちに移植が終わっていた》と捉えていた。幼児期に移植を受けた者は，《親に聞く前から漠然と移植について知っていた》ものの，《手術のことは覚えていないのでなかったものと一緒である》と移植のことを捉えていた。中学生の時に移植を受け，《移植のことを聞いたがどうでもよかった》と捉えていた者は，移植を受ける前は，移植は受けなくてよいと思っていた。また移植後は，ストーマ造設など当初のイメージとは異なる生活を送っていた。自分の病気に対しては，学童後期以降に移植を受けた者では《移植前は疲れやすかったが，移植後は身体が楽になった》と移植後の変化を捉えていた。また，自分の体調が良いことを《もらった肝臓は元気である》と捉えている者や，反対に《黄疸はやばい》と黄疸を体調悪化の指標として捉えている者もいた。脳死肝移植登録中の者は，《自分の病気は重い病気である》と現在の自分の状況を認識していた（**表3**）。

### 3. 肝移植後の学童後期・思春期の小児の生活の満足度

男女別の一般小中学生，高校生の基準値と個別に比較した結果を示す。

1）小学生の生活の満足度

総得点は，3例ともに基準値より高かった。家と家族の満足が低いケースA/Bは，ともに片親の家族構成だった。「体力と勤勉性，自尊感情」が低い症例Bは，幼児期に開けた気管切開孔が数mm開存しており，学校の体育で一部制限があった（**図1**）。

2）高校生の生活の満足度

総得点は，6例のうち3例（D/G/I）は基準値より低い結果であった。身体的活力（第6因子）の低い症例は，4例（D/E/F/G）で最も多かった。脳死肝移植登録中の症例の総得点は，基準値よりも高く，また身

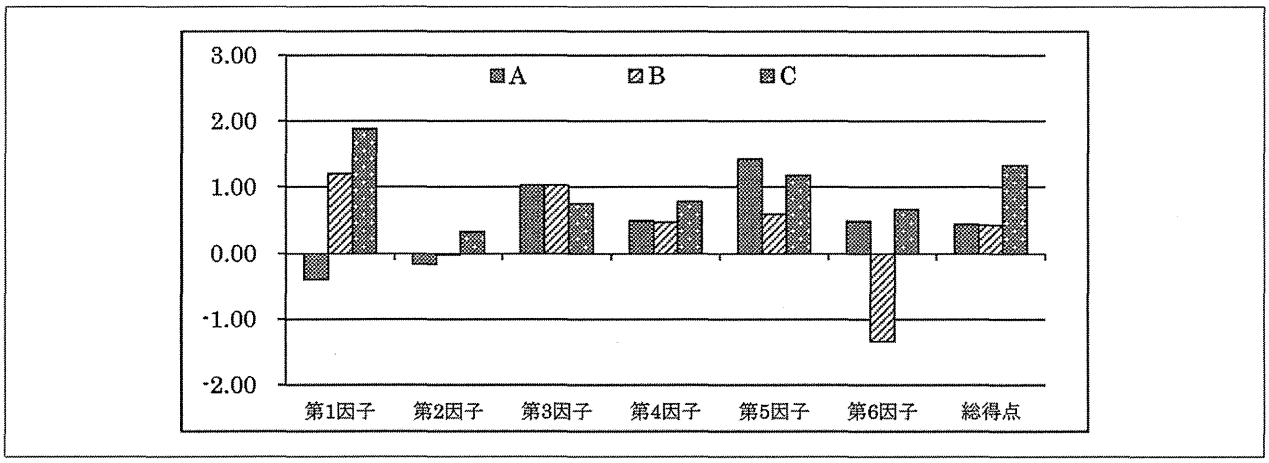


**図1　小学生3例（A，B，C）の生活の満足度（0：基準値）**

第1因子：「不安や悩み」，第2因子：「家と家族の満足」，第3因子：「友達の満足」，第4因子：「学校と先生の満足」，第5因子：「全体的な健康の満足」，第6因子：「体力と勤勉性，自尊感情」

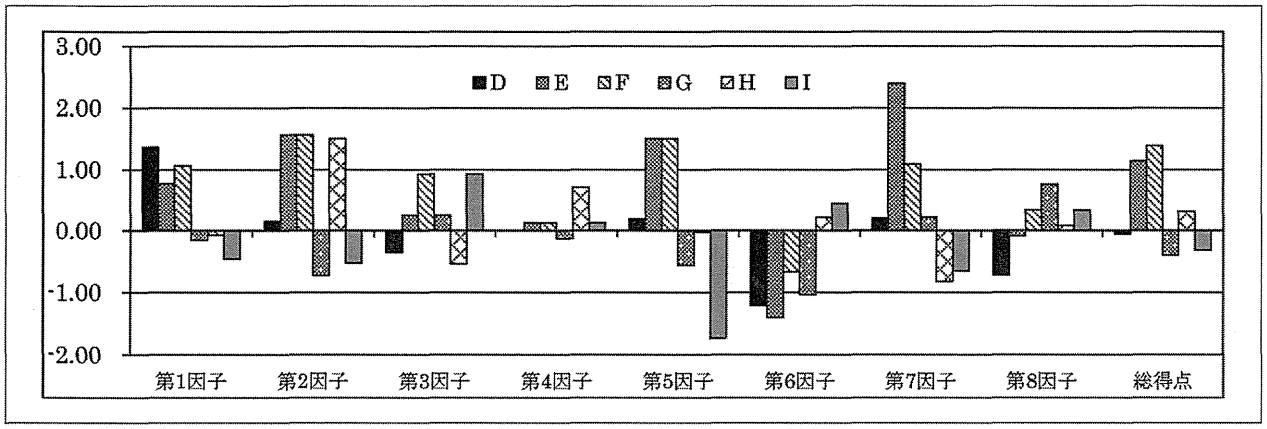


図2　高校生6例（D，E，F，G，H，I）の生活の満足度（0：基準値）
第1因子：「友達の満足」，第2因子：「学校生活の満足」，第3因子：「精神面の満足」，第4因子：「親と経済の満足」，第5因子：「異性との関係性・自尊感情」，第6因子：「身体的活力」，第7因子：「進学や就職の悩み」，第8因子：「きょうだい関係の満足」

体的活力（第6因子）も高かった。症例Iは，免疫抑制剤の内服が隔週であり，通常の高校生と変わらない生活を過ごしているにもかかわらず，総得点が基準値より低かった。因子ごとの得点では，異性との関係性・自尊感情（第5因子）が，基準値より－1.74と特に低かった（図2）。

## IV. 考　察

療養生活の実態は，発達段階を反映した相違がみられたため，小学生と高校生に分けて療養生活の実態と生活の満足度について考察する。

### 1. 肝移植後の小学生の療養生活の実態と生活の満足度

肝移植後の小学生は，日常生活・学校生活は特に困っていることはなく，決められていることは守る生活を送っていた。また，疾患管理の中心は免疫抑制剤の内服であり，症例は薬の必要性を理解し，うっかり忘れはあるものの親のかかわりで適切に実施していた。小児の自分の疾患の捉え方は，自覚症状や制限，内服薬の有無や母親の説明，友達や先生のかかわりだけではなく，自分の知識や体験などの影響も受ける[10]。対象の症例は，いずれも移植時期は幼児期であり，移植そのものへの認識は低かった。しかし，免疫抑制剤を毎日飲むことや特定の食品の制限は，過去の体験から自分なりに体のために必要であることを受け止めていた。また，制限があることを負担に感じていないことが，療養生活での制限はないこと，免疫抑制剤の内服の必要性といった認識につながっていたと考える。

生活の満足度は，総得点においては基準値より高かったが，症例によっては「不安や悩み」，「家と家族の満足」，「体力と勤勉性，自尊感情」の下位尺度において基準値より低かった。移植後の小児にとって，普通の生活を送ることや友人や家族，医療者等，親しい人からの支援を得ることが生活の満足につながる[11]。一方，小児のQOL低下には家族機能の低下と関連がある[12]ことから，生活の満足度には，家族の状況や周囲の人との関係性も影響すると考える。「体力と勤勉性，自尊感情」が低い症例は，学校生活における運動制限など，友達と違う自分という捉えから，体力や自尊感情の低下につながっていたと考える。

### 2. 肝移植後の高校生の療養生活の実態と生活の満足度

肝移植後の高校生の療養生活では，移植後1年未満の症例，脳死肝移植登録中の症例以外は，日常生活は困っていないと捉えており，免疫抑制剤の内服があること以外は，通常の高校生と変わらない生活を過ごしていた。しかし，すべての例で内服の飲み忘れの経験があり，移植時期により内服の必要性の捉え方や移植の経験は異なっていた。内服薬の必要性を理解していなくても親への思いや親のサポートがあることによって内服を継続している[13]ように，思春期においても，親のかかわりもあり療養行動が維持されていたと考える。

学童後期以降に肝移植を受けた症例は，移植後の体調改善の変化を捉えていたが，幼児期に移植を受けた

症例は，移植を受けたことは分かっていてもそれによる変化を実感していなかった。小児腎移植後患者では，適切な療養行動遵守の動機付けとして，患者にとってちょうどよい加減の配慮や心遣いを周囲から得られること，移植腎機能の低下とそれによって起こる状況を恐れる患者の心情が影響していた[14]。移植をしたことの実感が低くまた経過が良い場合は，不適切な療養行動の一因となりうるため，子どもの過去の体験や疾患や治療，移植そのものへの小児の認識を理解した医療者のかかわりが求められる。

生活の満足度では，一般の高校生平均に比べ身体的活力が低い症例は，運動制限のある者や体調が時々悪い者，日常生活に制限のない者であった。しかし，脳死肝移植登録中で日常生活の制限もある症例は，むしろ身体的活力の得点は高く，満足度が高かった。日常生活の制限がないにもかかわらず，異性との関係性・自尊感情の満足度が特に低い症例は，総得点の生活の満足度も低かった。肝移植後の思春期の生活体験は，発達段階だけではなく移植時期や原疾患によっても体験が異なり，QOL に影響していた[15]ことから，生活の満足度は，病状と必ずしも一致するわけではなく，周囲との関係や自尊感情など他の要因も複雑に絡みあっていることが示唆された。

### 3. 肝移植後の学童後期・思春期の小児への実践への示唆

本研究で明らかとなった肝移植後の学童後期・思春期の小児の療養生活の実態と生活の満足度は，この時期にある子どもの療養生活や発達過程の中で，子ども自身がどのような問題に直面しながら過ごしているかのアセスメントのための視点として活用できる。医療者には，発達過程で逐次変化していく学童・思春期の小児の望む生活や治療・療養行動の間の葛藤を受け止め，解決方法をともに考えること，周囲からの適切なサポートが得られるような支援が求められると考える。

### 4. 本研究の限界と課題

本研究は，対象者が 9 名と限られていること，対象者の年代が小学生と高校生に限定していること，またデータ収集が 1 施設であるため，研究結果の一般化には限界がある。今後，対象施設や対象者数を増やし，より信頼性のある研究結果としていく必要がある。

## V. 結　論

本研究により，肝移植後の学童後期・思春期の小児の療養生活の実態と生活の満足度について明らかとなった。学童後期は，親のかかわりもあり療養行動は保たれていた。しかし，移植を受けたことに対しては，手術を受けたことは理解しているものの，いずれも移植を受けた時期が幼児期であり，移植そのものの理解は低かった。生活の満足度は，総得点は基準値より高かったが，因子によっては，子どもの背景により低い項目があった。思春期の小児は，身体状況と生活の満足度は必ずしも一致しなかった。また，移植を受けた時期や移植に対する捉えによって療養行動に対する認識が異なった。子どもの過去の体験や疾患や治療，移植そのものへの捉えを理解した医療者のかかわりが求められる。

**謝　辞**

本研究にご協力いただいた対象者の皆様，本稿作成にあたり，ご助言を下さいました先生方に感謝申し上げます。

本研究は，公益財団法人ファイザーヘルスリサーチ振興財団の助成を受けた。

第 49 回日本移植学会総会（2013 年，京都）において内容の一部を発表した。

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