Research Article

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Long-term native liver fibrosis in biliary atresia: Development of a novel scoring system using histology and standard liver tests

Hirofumi Tomita[1], Yohei Masugi[2], Ken Hoshino[1], Yasushi Fuchimoto[3], Akihiro Fujino[1], Naoki Shimojima[1], Hirotoshi Ebinuma[4], Hidetsugu Saito[4], Michiie Sakamoto[2], Tatsuo Kuroda[1,*]

[1]*Department of Pediatric Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan;* [2]*Department of Pathology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan;* [3]*Division of Surgery, Department of Surgical Subspecialities, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan;* [4]*Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan*

Background & Aims: Although liver fibrosis is an important predictor of outcomes for biliary atresia (BA), postsurgical native liver histology has not been well reported. Here, we retrospectively evaluated postsurgical native liver histology, and developed and assessed a novel scoring system – the BA liver fibrosis (BALF) score for non-invasively predicting liver fibrosis grades.

Methods: We identified 259 native liver specimens from 91 BA patients. Of these, 180 specimens, obtained from 62 patients aged ⩾1 year at examination, were used to develop the BALF scoring system. The BALF score equation was determined according to the prediction of histological fibrosis grades by multivariate ordered logistic regression analysis. The diagnostic powers of the BALF score and several non-invasive markers were assessed by area under the receiver operating characteristic curve (AUROC) analyses.

Results: Natural logarithms of the serum total bilirubin, γ-glutamyltransferase, and albumin levels, and age were selected as significantly independent variables for the BALF score equation. The BALF score had a good diagnostic power (AUROCs = 0.86–0.94, p <0.001) and good diagnostic accuracy (79.4–93.3%) for each fibrosis grade. The BALF score revealed a strong correlation with fibrosis grade (r = 0.77, p <0.001), and was the preferable non-invasive marker for diagnosing fibrosis grades ⩾F2. In a serial liver histology subgroup analysis, 7/15 patients exhibited liver fibrosis improvement with BALF scores being equivalent to histological fibrosis grades of F0–1.

Conclusions: In postsurgical BA patients aged ⩾1 year, the BALF score is a potential non-invasive marker of native liver fibrosis.

Keywords: Biliary atresia; Hepatoportoenterostomy; Liver fibrosis; Liver biopsy; Non-invasive fibrosis marker.

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* Corresponding author. Tel.: +81 3 5363 3024; fax: +81 3 3356 8804.

E-mail address: kuroda-t@z8.keio.jp (T. Kuroda).

Abbreviations: BA, biliary atresia; LT, liver transplantation; LDLT, living donor liver transplantation; BALF, biliary atresia liver fibrosis; PELD, pediatric end-stage liver disease; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ChE, cholinesterase; PT-INR, prothrombin time-international normalized ratio; APRI, aspartate aminotransferase to platelet ratio index; PIIINP, procollagen type III amino-terminal peptide; AUROC, area under the receiver operating characteristic curve.

Introduction

Biliary atresia (BA) is a destructive, inflammatory, obliterative cholangiopathy that develops in 1/5,000 to 1/19,000 newborns [1]. The disease affects varying lengths of both the extra- and intra-hepatic bile ducts, and is classified according to the level of the most proximal part of the extra-hepatic biliary obstruction: atresia of the common bile duct (type 1), hepatic duct (type 2), or porta hepatis (type 3) [1,2]. To establish initial bile drainage, an anastomosis between the bile duct and the gastrointestinal tract can be created in certain cases ("correctable" BA, mostly type 1), but hepatoportoenterostomy is more often performed ("non-correctable" BA, mostly type 3) in such cases [2].

Hepatoportoenterostomy, first described by Kasai [3], can achieve initial bile drainage in 50–60% of cases [1]. However, liver fibrosis progresses rapidly before the bile drainage operation, and is an important predictor of outcome [4]. Even after successfully achieving bile drainage by portoenterostomy, progression of liver fibrosis may continue, leading to portal hypertension and cirrhosis [4]. Liver transplantation (LT) is performed when bile drainage is not achieved, or when complications of biliary cirrhosis occur [5]. Because of the progressive liver disease, long-term native liver survival is only achieved in approximately 20% of BA patients [4,5]. Thus, BA is the most common indication for LT in children; moreover, portoenterostomy is believed to be palliative, not curative [1].

Because of the severe shortage of organs from deceased donors in Japan [6], determination of the optimal time for living donor LT (LDLT) is important for BA patients. To investigate the postsurgical state of the native liver, we have performed percutaneous liver biopsies as part of the patient's routine follow-up. Because native liver fibrosis in postsurgical BA patients has not been well reported, we retrospectively analyzed the histology findings from 259 native liver specimens, and their associated

data, in 91 BA patients. From this, we developed a novel scoring system – the BA liver fibrosis (BALF) score – which is a non-invasive, practical, and easily accessible potential marker of liver fibrosis that is based on standard liver tests; its accuracy was also evaluated by comparing with the pediatric end-stage liver disease (PELD) score, which is widely used for liver allocation determinations [7], and the levels of several non-invasive fibrosis markers. Furthermore, we evaluated serial native liver histology in a subgroup of 15 patients.

Patients and methods

Study population and ethical considerations

We retrospectively identified 91 BA patients from whom native liver specimens had been obtained between March 1993 and February 2013 at Keio (Japan) University School of Medicine. The patients had either visited our institution for an initial operation, were referred to us for follow-up after an initial operation (42 patients), or had been referred to us due the presence of LT indicators (49 patients) after an initial operation for bile drainage. From the 91 patients, 259 liver specimens were collected by wedge biopsy during laparotomy (34 specimens), percutaneous needle biopsy (161 specimens), or were obtained from explanted livers during LT (64 specimens). From these specimens, we excluded 1 explanted liver because of a hepatitis C virus infection, and 18 specimens because of liver histology findings (described below).

Development of the BALF score was conducted from 180 histology examinations obtained from 62 patients aged ⩾1 year, because liver biochemistry results were likely elevated before surgery, and for a certain period after surgery, regardless of the liver fibrosis grade. Of the 180 specimens, the median number of specimens obtained from individual patients was 1 (range, 1–11). Of the 62 patients, 28 (45.2%) were male and 34 (54.8%) were female. Type 1 BA was diagnosed in 9 patients (14.5%), type 2 in 2 (3.2%), and type 3 in 45 (72.6%); the diagnosis was unknown in 6 (9.7%). The initial surgery for bile drainage was hepaticoenterostomy in 6 patients (9.7%), hepatoportoenterostomy in 54 (87.1%), and an unknown procedure in 2 (3.2%); the median age at the time of the initial surgery was 64 days (range, 17–151 days). Selection of the study population is summarized in Fig. 1. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethical committee at Keio University School of Medicine (2012-173).

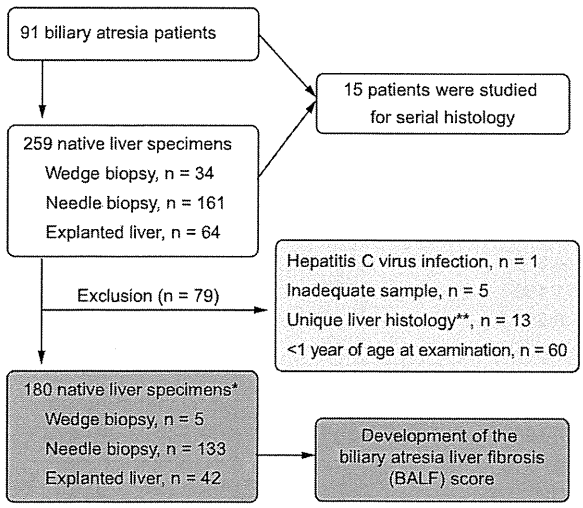

Fig. 1. Selection of the study population. *Obtained from 62 patients. **One patient revealed unique liver histology findings, indicating ductopenia, accompanied by little evidence of fibrosis in 13 serial percutaneous biopsies.

Data collection

The patients' clinical courses, documented pathological findings, and laboratory results around the time of liver specimen collection were collected from the patients' medical records. Collected standard biochemical test results included serum levels of total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), albumin, and cholinesterase (ChE). Collected hematological test results included prothrombin time-international normalized ratios (PT-INR) and platelet counts. These standard biochemical and hematological test results were obtained for all corresponding histological examinations. The PELD score [7] was calculated using the following equation:

$$\text{PELD score} = \{0.463 \times (\text{age} < 1\,\text{year}^{*}) - 0.687 \times \text{Log}_e[\text{albumin (g/dl)}] + 0.480 \times \text{Log}_e[\text{TB (mg/dl)}] + 1.857 \times \text{Log}_e(\text{PT-INR}) + 0.667 \times (\text{growth failure} < -2\ \text{standard deviation}^{**})\} \times 10$$

*Age was coded as 1 for children under 1 year; in other cases, it was coded as 0.

**Growth failure was coded as 1 for children, with height or weight <−2 standard deviations below age-specific normal values; in other cases, it was coded as 0.

As a non-invasive fibrosis marker, the AST to platelet ratio index (APRI) [8] was also calculated; a serum AST level of 35 IU/L was used as the upper normal limit:

$$\text{APRI} = \{(\text{AST/upper normal limit})/[\text{platelet counts } (10^9/\text{L})]\} \times 100$$

The APRIs in patients having a history of splenectomy, partial splenic embolization, or with biliary atresia splenic malformation syndrome were excluded from further analyses. Direct serum fibrosis markers, including serum levels of hyaluronic acid, type IV collagen 7S domain, and procollagen type III amino-terminal peptide (PIIINP) [9], were collected for most of the corresponding histological examinations. The normal ranges are ⩽50.0 ng/ml for hyaluronic acid, ⩽6.0 ng/ml for type IV collagen 7S domain, and 0.30–0.80 U/ml for PIIINP.

Evaluation of liver histology

Wedge biopsy specimens, ⩾5 mm in size, were obtained by surgical resection from the edge of the liver during laparotomy. Percutaneous liver biopsies, ⩾1.0 cm in length, were performed with an 18-gauge suction needle under ultrasonographic guidance. All of the biopsies and operations were performed after obtaining written informed consent. The biopsy specimens and explanted livers were fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin-eosin, Azan-Mallory, and Elastica van Gieson stains. Liver fibrosis was evaluated based on the documented pathological findings that had been reported at the time of examination by experienced pathologists, according to the METAVIR scoring system [10] or the new Inuyama classification [11] as follows: F0, no portal fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa or lobular distortion without cirrhosis; and F4, cirrhosis. Five specimens, containing no or few portal tracts, were indeterminate for fibrosis grade. One patient revealed unique liver histology findings, indicating ductopenia, accompanied by little evidence of fibrosis in 13 serial percutaneous biopsies. When compared to the other subjects, the blood test results for this patient did not correspond to the histological fibrosis grade; therefore, these 13 specimens were excluded from the analysis.

Development of the BALF score by ordered logistic regression analysis

To predict the histological fibrosis grade, ordered logistic regression analyses were performed, using the histological fibrosis grades as ordinal data (F0, F1, F2, F3, and F4) for the dependent variable; the independent variables included logarithmic transformations of the collected standard biochemical and hematological test results, and age at the time of the corresponding histological examination. For multivariate logistic regression analysis, independent variables showing strong correlations ($|r| > 0.7$) to each other were avoided because of multicollinearity concerns. The equation comprising the BALF score was developed by adding a minus sign to the regression equation for the logit of F0 probability in the multivariate analysis.

Table 1. Baseline data, stratified by histological fibrosis grade, for the development of the biliary atresia liver fibrosis (BALF) score.

	F0 (n = 15)	F1 (n = 53)	F2 (n = 44)	F3 (n = 34)	F4 (n = 34)
TB (mg/dl)	0.5 (0.2-0.9)	0.7 (0.3-10.1)	0.8 (0.3-11.5)	1.9 (0.4-24.5)	7.2 (0.3-30.1)
AST (IU/L)	33 (25-83)	36 (18-550)	75 (22-251)	108 (35-1065)	181 (94-472)
ALT (IU/L)	22 (14-79)	35 (9-676)	64 (13-457)	86 (21-411)	133 (37-587)
GGT (IU/L)	44 (10-102)	68 (7-1108)	142 (8-1384)	204 (66-1456)	317 (32-1817)
Albumin (g/dl)	4.4 (3.7-4.7)	4.1 (3.1-5.1)	4.0 (3.0-5.1)	3.7 (2.4-4.6)	3.2 (1.5-4.5)
ChE (IU/L)	326 (220-598)	342 (97-567)	278 (122-581)	185 (46-335)	141 (43-323)
PT-INR	1.07 (1.00-1.21)	1.07 (0.91-1.47)	1.03 (0.86-1.25)	1.04 (0.86-2.01)	1.14 (0.89-1.48)
Platelet count (× 10^9/L)	141 (70-356)	165 (52-372)	127 (45-392)	113 (56-446)	152 (42-524)
Age (yr)	9.7 (1.1-18.8)	7.0 (1.2-19.9)	5.3 (1.2-19.2)	7.4 (1.1-25.4)	2.4 (1.0-33.6)

Data are presented as median (range).
TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ChE, cholinesterase; PT-INR, prothrombin time-international normalized ratio.

Assessment of the BALF score

After developing the BALF score equation, the score at the time of each histological examination was calculated. The BALF score and other non-invasive markers were assessed in the same population that was used for development of the BALF score equation. We also calculated and evaluated the BALF score results in patients aged <1 year before and after bile drainage surgery.

Analysis of serial liver histology and the BALF score in each patient

Among the 91 patients involved in this study, 31 underwent histological examinations at the time of their initial operation during the study period. Of these, 15 had repeated histological examinations when they were aged ⩾2 years and these patients were individually analyzed to obtain serial data. Among the other 16 patients, 4 underwent primary LDLT; 1 died suddenly at 11 months of age; 5 underwent LDLT before 2 years of age; 5 were <2 years of age at the time of this analysis; and 1 patient, who had undergone hepaticoenterostomy for type 2 BA, did not undergo a histological examination after reaching 2 years of age.

Statistical analysis

The categorical data are presented as frequencies (%), and the continuous data are presented as medians (ranges). Correlations between the ordinal and/or continuous data were assessed by Spearman's correlation coefficient (r). For logistic regression analyses, the *p* value of each independent variable was determined by the Wald chi-square value (Wald), which was calculated by squaring the ratio of the regression coefficient divided by its standard error. The diagnostic powers of the BALF score and the other fibrosis markers were assessed by area under the receiver operating characteristic curve (AUROC) analyses; an AUROC of 1.0 indicates a test of perfect diagnostic power, and that of 0.5 indicates a test without diagnostic power. The cut-off values were determined by maximizing the sum of the sensitivity and specificity on Youden's index [12]. *p* values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS 20.0 software (IBM SPSS, Chicago, IL, USA).

Results

Development of the BALF score by ordered logistic regression analysis

Baseline data corresponding to the 180 histology examinations for the development of the BALF score, stratified by histological fibrosis grade, are summarized in Table 1; the results of the ordered logistic regression analyses are shown in Table 2. In the univariate analyses, natural logarithms of the serum TB levels provided the most significant coefficients (Wald = 89.240, $p < 0.001$). In the multivariate analysis, natural logarithms of the

Table 2. Ordered logistic regression analyses for liver fibrosis grades, F0–F4.

Variable	Coefficient (95% CI)	Standard error	Wald	*p* value
Univariate analysis				
Log_e [TB (mg/dl)]	1.854 (1.470-2.239)	0.196	89.240	<0.001
Log_e [AST (IU/L)]	1.926 (1.493-2.358)	0.221	76.107	<0.001
Log_e [ALT (IU/L)]	1.218 (0.886-1.550)	0.169	51.737	<0.001
Log_e [GGT (IU/L)]	0.858 (0.617-1.100)	0.123	48.448	<0.001
Log_e [albumin (g/dl)]	-8.017 (-10.139--5.896)	1.082	54.871	<0.001
Log_e [ChE (IU/L)]	-3.218 (-3.948--2.487)	0.373	74.527	<0.001
Log_e [PT-INR]	2.627 (0.342-4.913)	1.166	5.078	0.02
Log_e [platelet count (× 10^9/L)]	-0.299 (-0.799-0.202)	0.255	1.370	0.24
Log_e [age (years)]	-0.438 (-0.742--0.134)	0.155	7.994	0.005
Multivariate analysis				
Log_e [TB (mg/dl)]	1.438 (0.974-1.903)	0.237	36.861	<0.001
Log_e [GGT (IU/L)]	0.434 (0.159-0.710)	0.140	9.557	0.002
Log_e [albumin (g/dl)]	-3.491 (-5.805--1.177)	1.181	8.745	0.003
Log_e [age (years)]	-0.670 (-1.031--0.308)	0.184	13.196	<0.001

TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ChE, cholinesterase; PT-INR, prothrombin time-international normalized ratio.

Table 3. Diagnostic accuracy of the biliary atresia liver fibrosis (BALF) score in predicting histological fibrosis grade.

	AUROC	95% CI	Cut-off	Sensitivity	Specificity	Accuracy
≥F1	0.91*	0.86-0.96	1.96	77.6%	100%	79.4%
≥F2	0.86*	0.81-0.92	2.42	86.6%	73.5%	81.7%
≥F3	0.91*	0.87-0.95	4.12	83.8%	81.3%	82.2%
=F4	0.94*	0.90-0.99	5.64	94.1%	93.2%	93.3%

*p <0.001.
AUROC, area under the receiver operating characteristic curve.

serum TB, GGT, and albumin levels, and age at examination were selected as significant independent variables. Based on the multivariate analysis, the BALF score equation was developed:

$$\text{BALF score} = 7.196 + 1.438 \times \text{Log}_e[\text{TB (mg/dl)}] + 0.434 \times \text{Log}_e[\text{GGT (IU/L)}] - 3.491 \times \text{Log}_e[\text{albumin (g/dl)}] - 0.670 \times \text{Log}_e[\text{age (years)}]$$

Diagnostic accuracy of the BALF score

Table 3 shows the AUROC, cut-off value, and diagnostic accuracy of the BALF score for each fibrosis grade. The BALF score had good diagnostic power for predicting each fibrosis grade (AUROCs = 0.86–0.94, p <0.001), and the cut-off values were calculated as 1.96 for a fibrosis grade ⩾F1, 2.42 for ⩾F2, 4.12 for ⩾F3, and 5.64 for F4; the score provided good diagnostic accuracy in diagnosing each fibrosis grade (79.4–93.3%).

Comparisons of the BALF score, PELD score, and other non-invasive fibrosis markers

Fig. 2 shows the boxplots for the BALF score, PELD score, APRI, and levels of serum hyaluronic acid, type IV collagen 7S domain, and PIIINP *vs.* the histological fibrosis grade. Of these, the BALF score was most strongly correlated with the histological fibrosis grade (r = 0.77, p <0.001). The BALF score was equally distributed from F0 to F4. The diagnostic powers of the BALF score and the other markers for diagnosing fibrosis grades ⩾F2 and F4, assessed by AUROC analyses, are shown in Fig. 3. For diagnosing fibrosis grades ⩾F2, the BALF score had the highest diagnostic power (AUROC = 0.86, p <0.001), followed by the PELD score and the APRI (AUROC = 0.80, p <0.001), but the direct serum markers showed relatively low or no significant diagnostic power. The PELD score, hyaluronic acid levels, and type IV collagen 7S domain levels, as well as the BALF score, showed excellent diagnostic powers for diagnosing an F4 fibrosis grade (AUROC >0.90, p <0.001).

Changes in the BALF score before and after bile drainage surgery

The BALF scores for patients aged <1 year, before and after initial surgery (n = 31 and n = 29, respectively), compared to patients aged 1–2 years, after surgery (n = 28), are shown in Fig. 4. The BALF scores were apparently high before surgery, regardless of the fibrosis grades. Even after bile drainage surgery, patients aged <1 year showed high score values. The BALF scores in the patients aged 1–2 years were comparable with those for all patients aged ⩾1 year.

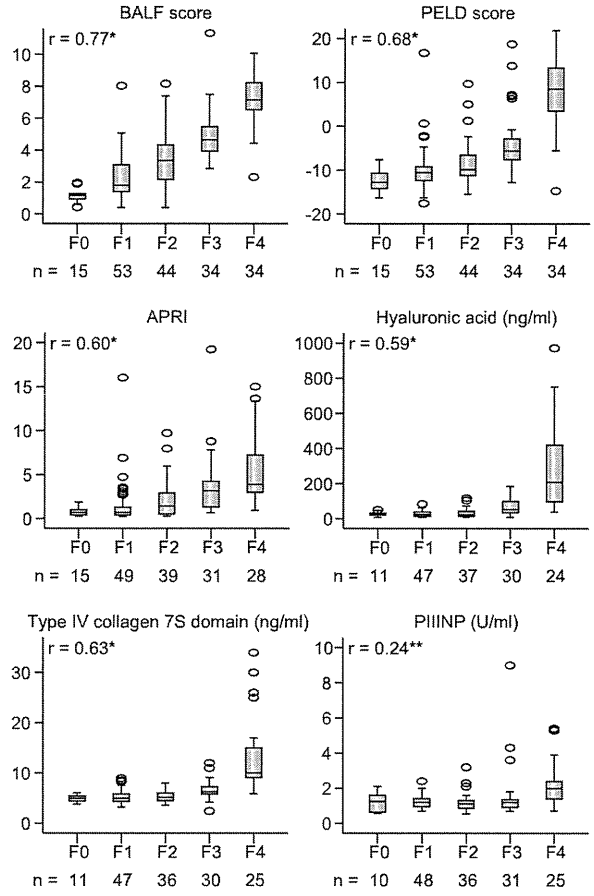

Fig. 2. Comparisons of the biliary atresia liver fibrosis (BALF) score, the pediatric end-stage liver disease (PELD) score, and several non-invasive fibrosis markers. Boxplots show the median values with the interquartile ranges, and error bars indicate the smallest and the largest values within 1.5 box-lengths of the upper and the lower quartiles. Outliers represent the individual points by circles. Correlations between the scores/markers and the histological fibrosis grades were evaluated by Spearman's correlation coefficient (r); *p <0.001, **p = 0.009. APRI, aspartate aminotransferase to platelet ratio index; PIIINP, procollagen type III amino-terminal peptide.

Serial liver histology and BALF score in each patient

The status of the initial operations and the most recent histological examinations for 15 patients are shown in Table 4. Cases 1–7 showed some liver fibrosis relief with BALF scores being equivalent to F0–1; these 7 patients achieved good physical growth and

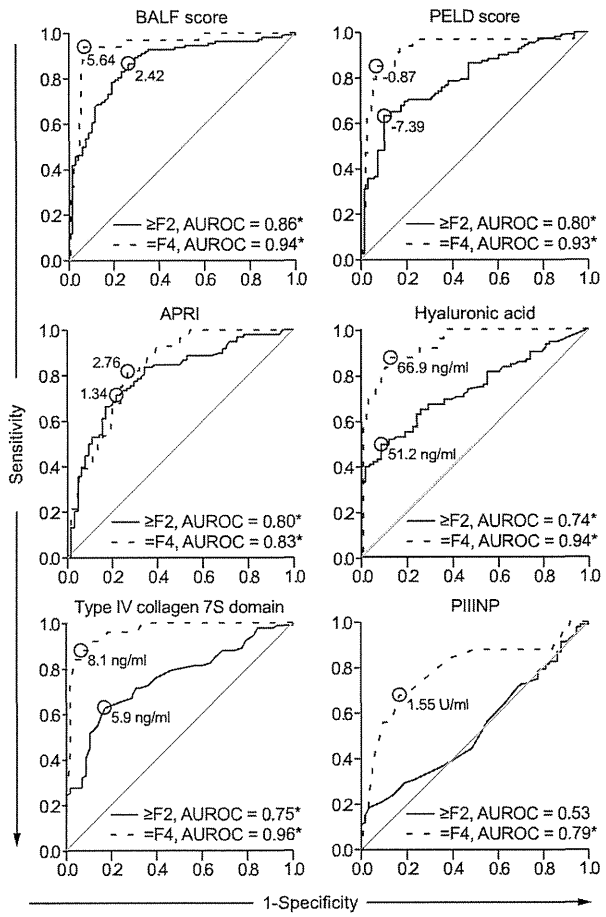

Fig. 3. The diagnostic powers of the biliary atresia liver fibrosis (BALF) score, pediatric end-stage liver disease (PELD) score, and non-invasive markers for liver fibrosis. The diagnostic power of each score/marker was assessed by calculating the area under the receiver operating characteristic curve (AUROC); solid lines, for diagnosing ≥F2; dashed lines, for diagnosing F4; gray lines, reference lines; circles, cut-off points (with cut-off values); *p <0.001. APRI, aspartate aminotransferase to platelet ratio index; PIIINP, procollagen type III amino-terminal peptide.

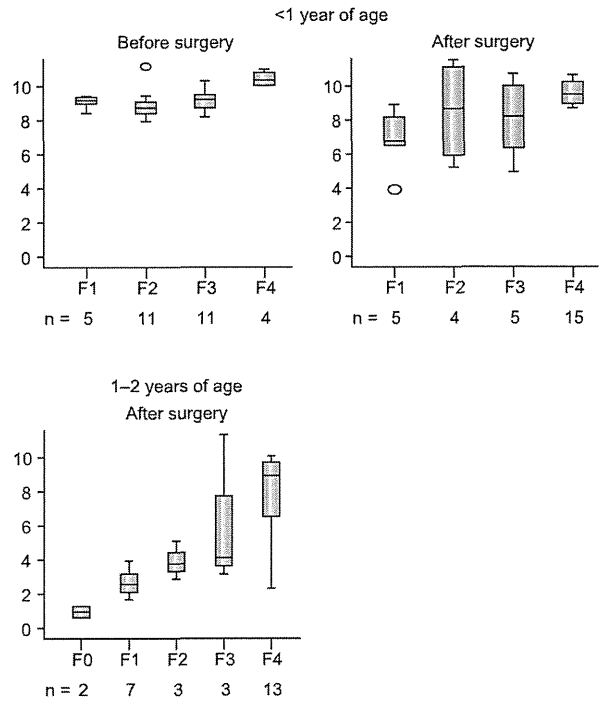

Fig. 4. Changes in the BALF score, before and after bile drainage surgery. Boxplots show the median values with the interquartile ranges, and error bars indicate the smallest and the largest values within 1.5 box-lengths of the upper and the lower quartiles. Outliers represent the individual points by circles.

social activity. Cases 8–12 showed the same grade of fibrosis in the initial and latest histological examinations; 3 of them had shown initial transient relief of liver fibrosis followed by worsening fibrosis, associated with repetitive cholangitis (Cases 10 and 11) or hepatopulmonary syndrome (Case 12). Cases 13–15 showed worsening liver fibrosis and relatively high BALF scores. Only Case 12 underwent LT during the study period; Cases 13–15 seemed likely to require LT in the near future due the presence of severe portal hypertension.

Discussion

Although hepatoportoenterostomy can achieve complete jaundice resolution in up to 60% of children with BA, liver fibrosis – a prominent feature of BA – may continue to progress [1,4,5]. Although LT in children with failed bile drainage surgery is certain, the timing of LT after successful bile drainage is debatable [13]. In Japan, grafts for LT rely almost entirely on living donors, especially from the parents of affected children [6]. Due to the increasing parental age and the required graft volume against the physical growth of the recipients, LDLT may not be possible, in some cases. Moreover, one large Japanese study indicated poor outcomes of adult-to-adult LDLT for postoperative BA patients, and the authors encouraged proactive consideration of LDLT at the earliest possible stage [14]. At our institution, hepatoportoenterostomy and LT for BA patients have been performed by the same team since the introduction of LDLT in 1995. To assess the native liver status more precisely, we introduced liver biopsies as the gold standard method for assessing liver fibrosis, with endoscopic screening of postsurgical BA patients. At first, liver fibrosis was supposed to progress in most BA patients, suggesting the future need for LT; only stable disease was believed to provide the patients and their parents with some relief. Thereafter, we noticed that certain patients demonstrated fibrosis improvement. Concerns about biopsy sampling errors were alleviated by serial liver histology, thus providing more substantial relief.

The BALF regression equation suggests that long-term native liver fibrosis in BA is influenced by the patient's bile drainage status, represented by the levels of serum TB and GGT. Some patients, especially older children or adults, develop decreasing liver synthetic capacity despite relatively small elevations in serum TB levels (data not shown). Thus, serum albumin levels represent a significant negative coefficient in the multivariate ordered logistic regression analysis. Additionally, the age at examination also showed a significant negative coefficient, suggesting that liver fibrosis could be improved over time, even in

Table 4. The status of 15 patients individually examined by serial liver histology.

Case No.	Disease type	Initial operation			Recent histological examination		
		Age (days)	Procedure	Fibrosis grade	Age (years)	Fibrosis grade	BALF score
1	Type 1	17	Hepaticoenterostomy	F2	2.5	F0	1.26
2	Type 1	24	Hepaticoenterostomy	F3	12.5	F1	1.17
3	Type 1	31	Portoenterostomy	F2	6.4	F1	1.50
4	Type 1	55	Portoenterostomy	F2	11.0	F0	1.26
5	Type 3	78	Portoenterostomy	F3	3.3	F1	2.12
6	Type 3	74	Portoenterostomy	F3	18.3	F1	0.84
7	Type 3	74	Portoenterostomy	F2	18.8	F0	1.19
8	Type 3	47	Portoenterostomy	F2	7.1	F2	2.44
9	Type 3	47	Portoenterostomy	F1	14.8	F1	2.34
10	Type 3	105	Portoenterostomy	F2	7.8	F2	2.20
11	Type 3	51	Portoenterostomy	F3	8.1	F3	3.24
12	Type 3	105	Portoenterostomy	F3	9.3	F3	4.84
13	Type 3	56	Portoenterostomy	F1	9.3	F2	3.94
14	Type 3	56	Portoenterostomy	F1	7.1	F3	4.68
15	Type 3	57	Portoenterostomy	F2	3.5	F3	6.26

BALF, biliary atresia liver fibrosis.

BA patients. Recently, liver fibrosis has been indicated to be reversible in a number of liver diseases, but data for BA are limited [4]. A few serial liver histology reports from the 1960s to 1980s documented fibrosis relief in some cases [15–18]. Thereafter, only a few studies have involved postsurgical liver histology [19,20]; however, serial data have not been presented. In a subpopulation of the current study, 7 of the 15 patients who achieved long-term native liver survival revealed some liver fibrosis relief during the study period.

The BALF score is the first non-invasive fibrosis marker developed for postsurgical BA patients based on liver histology findings, including the findings of percutaneous needle biopsy examinations obtained from patients with good postoperative courses. However, the PELD score was developed based on poor outcomes, such as patient death or movement to an intensive care unit, in children awaiting LT [7,21]. Although the BALF and PELD scores share the same independent variables (natural logarithms of serum TB and albumin levels), the BALF score results were more spread out than the PELD score results in the low fibrosis grade groups (F0–F3); moreover, the PELD score results were more spread out among the patients with cirrhosis (F4) than were the BALF score results (Fig. 1). Thus, the BALF score appears to be suitable for all patients (F0–4), but the PELD score seems best suited for severely affected patients, such as those with cirrhosis (F4), reflecting the methods used for the development of each score. The APRI consists of only two variables, is much simpler to calculate, and has been investigated in relation to prognosis [22], portal venous pressure [23], and fibrosis grade [24] at the time of Kasai hepatoportoenterostomy. Moreover, the APRI was used as a surrogate fibrosis marker in a prospective study examining steroid therapy in BA patients [25].

Although the current study contains one of the largest series of native liver histologies reported for BA patients, several limitations remain. First, the current study used liver histology findings, obtained from liver biopsies or explanted liver examinations, as reference parameters. Since biopsies are limited by sampling errors [26] and observer variability [27], the histological results are subject to omissions and false-positive results. In addition, segmental bile drainage, often observed in postsurgical BA patients [28] or small biopsy samples, may have resulted in an increased level of sampling error [26]. Second, this study had a relatively small sample size and a heterogeneous study population. Not all of the patients were evaluated by serial liver histology, after surgery, and the number of examinations in the same patient also differed; we analyzed the data from the same patient as independent data. We could not provide a validation group for the newly developed BALF scoring system because of the small and heterogeneous study population.

In the present study, we developed a potential fibrosis marker for postsurgical BA patients that is non-invasive, practical, and easily accessible. Because of a lack of validation, the BALF score should be further investigated with regard to its relationship with several parameters, such as long-term outcomes, postsurgical complications, and liver fibrosis. However, we believe that the BALF score will be a useful surrogate fibrosis marker in a future interventional trial.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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新生児肝不全

虫明 聡太郎

はじめに

新生児の肝不全は稀な病態であるが，いかなる基礎疾患においても発症から肝不全へは急性かつ重篤な経過をとり，肝移植が行われてもその救命率は70%程度にとどまる。急性肝不全(acute liver failure:ALF)は，一旦この病態に陥ると，失われていく肝細胞機能を特異的に回復させる治療法はなく，成因となる疾患自体の治療が必要不可欠である。新生児ALFの原因疾患スペクトラムは成人とは異なっており，最も頻度の高い成因は肝臓の代謝疾患と周産期の後天性感染症であるが，成因の特定できない症例も多く存在する。一部の代謝疾患や単純ヘルペス感染症などでは的確に原因治療を行うことによって自己肝を守って救命することが可能である一方，肝移植が唯一の救命手段となることが多い。そのため，成因の如何にかかわらず，新生児ALFの治療は新生児科医とともに発症初期から小児肝臓疾患の専門家，および肝移植が可能な施設と連携して行うことが望ましい。

疾患概念

肝不全とは，肝細胞の変性・壊死，あるいは代謝的機能障害により，肝臓の合成，代謝，および浄化能が低下した状態である。急性肝不全ではトランスアミナーゼ値の上昇，高ビリルビン血症，血液凝固能低下が短期間に進行し，重症化に伴って腹水，栄養障害，さらに意識障害(肝性脳症)などの症状をきたす。このうち初発症状出現から8週以内に高度の肝機能障害に基づいてプロトロンビン時間が40%以下，ないしはINR値1.5以上を示すものがALFと定義される[1]。さらに，ALFは肝性脳症が認められない，ないしは昏睡度がⅠ度までの「非昏睡型」と，昏睡Ⅱ度以上の肝性脳症を呈する「昏睡型」(いわゆる劇症肝不全)に分類される。しかし，小児，特に新生児では肝性脳症の判断が容易でなく，肝臓の予備能が小さいため，発症後は昏睡の有無にかかわらず急速な重篤化を十分予測して全身状態の観察を行うことが重要である。

むしあけ そうたろう　近畿大学医学部奈良病院小児科
〒630-0293　奈良県生駒市乙田町 1248-1
E-mail address : mushiake@nara.med.kindai.ac.jp

新生児肝不全の病態的特性

新生児期には肝不全による症候はその原因によって異なる。先天性感染症や新生児ヘモクロマトーシス，一部のミトコンドリア関連疾患などでは子宮内からの病態が生後すぐに症状となって現れる。細菌感染やウイルス感染，あるいはミルク摂取の開始後に発症する代謝異常症(ガラクトース血症，遺伝性果糖不耐症，高チロシン血症)では，出生直後には異常がみられない。血族婚や流産，周産期死亡歴や同胞の肝疾患の有無などについての詳細な病歴聴取が重要である。

以下に，新生児における肝不全の病態的特性を記述する[2,3]。

1．一般状態と神経症状

初期には活気がない，哺乳量が少ない，嘔吐しやすい，体重増加不良といった非特異的な症状しかみられないことも多い。黄疸の程度はさまざまで，特に代謝異常症では軽度かほとんど問題にならない場合もある。脳症の発現はむしろ遅れて現れる症候で，刺激に対する反応が乏しい，易刺激

性や昼夜逆転といった傾向が脳症を疑わせるが，新生児期に肝性昏睡の進行度を客観的に把握することは困難である。痙攣を呈する場合は，脳症よりまず髄膜炎，あるいは低血糖を疑うべきである。

2. 低血糖

新生児・乳児ではブドウ糖・グリコーゲン蓄積量が少なく，糖新生能も低いため肝不全状態では低血糖に陥りやすい。低血糖は治療経過中に栄養やグルコース投与が減少した際に突然生じるので注意が必要である。

3. 血液凝固障害

新生児において血液凝固能の異常をみた場合には，まずビタミンK欠乏を疑うべきであり，ビタミンKの補充による改善が認められなければ肝不全と考えて原因診断を急がなければならない。一方，肝不全では血液凝固因子の低下とともに抗凝固系因子(アンチトロンビン，プロテインC，プロテインS)の低下も潜在的に進む。そのため，新生児では侵襲的な処置や外傷による出血がなければ出血傾向の存在に気づかれにくいことに注意が必要である。

4. 免疫力低下と高サイトカイン血症

肝での補体産生の低下と好中球機能の低下により，液性，細胞性免疫ともに低下するため細菌感染が重篤化しやすい。一方，肝不全状態では産生されたサイトカインの肝での処理能が低下しているため，重症感染から高サイトカイン血症が誘導される。また，重症感染は肝移植の適応禁忌となり，敗血症に至ると多臓器障害への進展から救命率は著しく低下する。

5. 腎機能低下(肝腎症候群)

いわゆる肝腎症候群は，門脈圧亢進に伴う臓器血管の拡張が高度となり，それに対してレニン-アンギオテンシン，バソプレシンやカテコラミン系が反応することによる腎血流量低下がその主たる原因であるが，腎機能低下は重症感染に伴う全身性の血圧低下や薬剤の腎毒性も原因となる。

6. 脳浮腫と脳症

高アンモニア血症，低Na血症，炎症性サイトカインの上昇を伴った脳血流の増加が脳浮腫と脳症の中心的な成因となる。脳アストロサイトはグルタミン酸からグルタミンを合成することによってアンモニアを処理する。高アンモニア血症の環境下ではアストロサイト内のグルタミン濃度とともに浸透圧が上昇して細胞浮腫をきたすと考えられている。新生児や乳児では血管内皮の透過性が亢進しやすいためにサイトカインの影響を受けやすく，肝不全状態における脳症の進行は年長児や成人に比して急速である。

7. 黄疸

黄疸の程度はさまざまで，特に代謝異常症では軽度かほとんど問題にならない場合もある。一方，新生児ヘモクロマトーシスなどでは数十 mg/dL に達することもある。重篤な肝不全では代謝障害の一部としてビリルビン抱合能が低下するため，総ビリルビンに占める直接ビリルビンの比率(D. bil/T. bil比)が低下することが肝不全の進行の指標となる。しかし，新生児では生理的に間接ビリルビン優位の黄疸があるため，生後早期には判断が難しい。

8. 肝腫大

発症時に腫大していた肝臓の萎縮は，小児でも最も重要な劇症化の徴候のひとつであるが，**表1**にあげた新生児の肝疾患では肝萎縮をきたすものは少ない。脾腫や腹水といった門脈圧亢進に伴う徴候は早期に肝硬変に向かう新生児ヘモクロマトーシスや高チロシン血症で認められる。

9. その他

三桁後半から四桁以上に至る高度のトランスアミナーゼ値の上昇は，ウイルス感染や薬剤(中毒)性，あるいは循環障害による広範囲な肝細胞傷害，壊死を示唆する。逆に，多くの代謝疾患ではトランスアミナーゼ上昇は中等度以下にとどまることが多い。

表1　新生児肝不全の原因疾患と検査

疾患名	検査
一般検査 (スクリーニング，および病状評価)	血算，Na，K，Cl，Ca，P，Mg，BUN，クレアチニン，総ビリルビン，直接ビリルビン，AST，ALT，LDH，ALP，γGTP，乳酸，アンモニア，血液ガス，血型，クームステスト，各種培養検査，α-フェトプロテイン，血液凝固能(プロトロンビン時間，プロトロンビン活性(INR)，フィブリノーゲン，D-ダイマー)，アンチトロンビンⅢ
高チロシン血症Ⅰ型	尿中サクシニルアセトン，血漿アミノ酸分析，α-fetoprotein，骨X線
ガラクトース血症	新生児マススクリーニング検査(ボイトラー法，ペイゲン法，酵素法)
遺伝性果糖不耐症	*ALDOB*遺伝子解析
α_1アンチトリプシン欠損症	血清α_1アンチトリプシン
新生児ヘモクロマトーシス	血清鉄，UIBC，フェリチン，唾液腺生検(鉄染色)，腹部MRI
ミトコンドリア関連疾患	乳酸/ピルビン酸比，静脈血ケトン体分画，尿中有機酸分析，ミトコンドリアDNA解析，ミトコンドリア呼吸鎖関連酵素活性(肝生検，筋生検)，髄液中乳酸，CK，CK-MB，CK-BB
尿素サイクル異常症	血漿アンモニア，尿中オロット酸(尿中有機酸分析)
シトリン欠損症	血漿アミノ酸分析，SLC25A13遺伝子解析，肝生検
胆汁酸代謝異常症	尿中胆汁酸分析
先天性グリコシル化異常症	トランスフェリン等電点電気泳動
感染症	HAV，HBV，HHV-1，2，6，CMV，EBV，HSV，VZV，echovirus，adenovirus，enterovirus，parbovirus 19，paramyxovirusの血清抗体価(母児とも)，血清保存，便培養，梅毒(VDRL)
血球貪食症候群，マクロファージ活性化症候群	血清トリグリセライド，コレステロール，フェリチン，骨髄穿刺
新生児ループス	母体自己抗体(抗SS-A，抗SS-B，抗U1RNP抗体)
薬剤性・中毒性	被疑薬剤血中濃度，DLST
循環不全	心臓超音波検査，BNP

成因と鑑別のための検査

ALFの成因は代謝異常，感染，中毒，自己免疫，循環不全，および腫瘍関連の六つに分けることができる。このうち新生児では代謝異常と感染の占める割合が高い。我が国の全国調査(1995～2010年)では1歳未満の急性肝不全症例63例中，成因が特定された症例は確診・疑診を含めて34例(54%)で，そのうちウイルス感染が16例，代謝疾患が12例であった[4,5]。

表1に新生児ALFの原因となり得る疾患とそれらの診断に有用な臨床検査を示す[6,7]。シトリン欠損症の発症は新生児期を過ぎてからのことが多く，一般に予後良好であるが，乳児期早期に肝の線維化が進行して肝移植の適応となる場合がある。高チロシン血症Ⅰ型は我が国では報告例が少なく，明らかな血漿チロシン値の上昇と胆汁うっ滞や肝の線維化を呈するものの尿中サクシニルアセトンの上昇や肝組織でのフマリルアセト酢酸ヒドラーゼの低下が証明されない非Ⅰ型高チロシン血症が経験されるが，詳細な原因や疫学は不明である。

対応と治療

肝機能異常や胆汁うっ滞性黄疸に気づいたら必ず血液凝固能をチェックする。プロトロンビン時間の延長が認められれば，まずビタミンKの投与を行い，投与後12時間で有意な改善がない，またはさらなる低下が認められる場合には，急性肝不全を強く疑って小児肝疾患の集学的治療が可能な医療機関へ移送すべきである。同時に，下記の項目に配慮した初期対応をとる[7]。

表2　原疾患に対する特異的治療

疾患名	検査
高チロシン血症Ⅰ型	NTBC〔2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione〕，フェニルアラニン・チロシン除去ミルク
ガラクトース血症	ガラクトース除去(乳糖除去ミルク)
遺伝性果糖不耐症	果糖，ショ糖除去
新生児ヘモクロマトーシス	デスフェラール®，セレン，プロスタグランジンE_1，ビタミンE，ガンマグロブリン大量療法
アセトアミノフェン肝障害	N-アセチルシステイン*
尿素サイクル異常症	安息香酸ナトリウム，アルギニン，血漿交換，または腹膜透析，蛋白除去ミルク
単純ヘルペス感染症	アシクロビル
B型肝炎	ラミブジン，エンテカビル，アデフォビル
血球貪食症候群，マクロファージ活性化症候群	化学療法(エトポシド，デキサメサゾン，シクロスポリン)，末梢血幹細胞移植

N-アセチルシステイン*はその他の成因によるALFにも有効との報告がある。

・ガラクトース血症が否定できるまで乳糖除去ミルクに変更する。
・血糖と電解質を頻回にチェックし，補正に努める。
・広域ペニシリン，またはセフェム系抗菌薬を投与する。
・単純ヘルペスの診断を急ぎ，結果を得る前からアシクロビルを治療量で開始する。
・母体のHB抗体価をチェックする(特にHBe抗体陽性母体からの出生児は要注意)。
・消化管出血予防を目的として制酸剤の静注投与を開始する。
・鎮静剤は人工呼吸を行わない限り投与しない。

診断に基づく特異的治療法を**表2**に示す。我が国の全国調査では，B型肝炎や単純ヘルペスの母児感染例に対してラミブジンやアシクロビルの投与を行って肝性昏睡Ⅳ度から救命・治癒し得た症例が報告されている。また，血球貪食症候群による肝不全では免疫抑制療法や化学療法が奏功する場合が少なくない。小児ALFの原因として欧米で多くを占めるアセトアミノフェン肝障害は我が国ではほとんど報告がないが，これに対する特異的治療薬として用いられるN-アセチルシステイン(ミトコンドリアと肝細胞質内のグルタチオン量を高めることによる抗酸化物質として作用する)は，そのほかの原因によるALFにおいても有効かつ安全で，非移植救命率と移植後の生存率を改善させたとの報告がある[8]。

人工肝補助療法と肝移植

有効な原因治療法がない，あるいは行っても改善が期待できない場合の最も有効な治療は人工肝補助療法と肝移植である。我が国では欧米より人工肝補助療法(血液浄化療法)が進歩しており，近年，小径(6 Fr)ダブルルーメンカテーテルや新生児・小児用の血漿交換，持続濾過透析カラムが開発され使用可能となっている。血液浄化療法では安定した脱血ルートを確保することが重要であるが，新生児では一旦血液凝固能が著しく低下した状態に陥ると，ルート確保自体が困難となって出血や循環動態変動のリスクが高まるため，小児外科医に依頼してできるだけ早めのルート確保に努めるべきである[9]。

一般に，人工肝補助療法としては急速に低下する血液凝固能を補う目的で血漿交換(plasma exchange：PE)を行い，終了後に継続して持続的濾過透析(continuous hemodiafiltration：CHDF)が行われることが多い。血液凝固能は保たれていながら高アンモニア血症の回避が求められるOTC欠損症ではHFDまたは腹膜透析(peritoneal dialysis：PD)が選択される。

人工肝補助療法の継続によって昏睡型ALF(劇症肝不全)からの回復もあり得る。しかし,新生児や乳幼児では中枢神経障害を遺さず救命するためにはやはり肝移植が最も有効な治療手段である。小児全体を対照とした調査では,英国,北米と日本における小児ALFに対する肝移植施行率は,それぞれ41%,57%,74%と日本が最も高いが,これには保護者の側から「自らドナーとなって患児を救命したい」という申し出があることが多いこと,また健康保険制度が整っていることが一因となっていると考えられる。近年では外科的技術の進歩に伴って新生児に対する肝移植成績が向上し,2008~2010年の3年間を対象とした我が国での調査では,生後2カ月未満発症のALF8症例中5例に対して生体肝移植が施行され,うち4例が救命されており,すでに複数の施設において生後2週未満,体重2,700g未満の児に対する生体部分肝移植が実施されている。

ただし,生体肝移植はドナーを得て初めて成立し得る治療である。そのため,短期間に移植が必要となる可能性を判断し,家族に対して的確な説明と情報提供が行われなければならない。特に新生児・乳児では発症から中枢神経障害の進行が速いため,原因診断と治療を進めると同時に肝移植へのワークアップを考慮した医療連携が必要である。

おわりに

新生児発症の重篤な肝障害については,近年多くの原因疾患の鑑別が可能となり,一部の感染症や代謝疾患では原因治療によって救命・治癒が可能となってきた。一方,未だ成因不明の症例も少なくなく,原因治療のない疾患に対しては多くの場合肝移植が唯一の救命的治療とならざるを得ない。しかし,厳密には新生児の肝移植適応と禁忌を客観的に判定する基準はなく,原因診断に基づいて予測される一般的な予後と,個々の症例における肝予備能,中枢神経障害の程度,感染や他臓器の合併症から総合的に判断するしかない。今後はさらに,ALFの新たな成因が解明されることと,より客観的な肝移植適応と成績に関する情報を患者家族に提供できるよう,症例数と知見が重ねられていくことが期待される。

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V.研究班名簿

小児期発症の希少難治性肝胆膵疾患における包括的な診断・治療ガイドライン作成に関する研究班

区　分	氏　名	所　属　等	職　名
研究代表者	仁尾　正記	東北大学大学院医学系研究科・小児外科学分野	教　授
研究分担者	松井　陽	聖路加国際大学・看護学部	特任教授
	橋本　俊	名古屋市立大学大学院医学研究科・分子神経生物学	研究員
	安藤　久實	愛知県心身障害者コロニー・発達障害研究所・小児外科（小児肝・胆・膵）	総　長
	北川　博昭	聖マリアンナ医科大学・外科学・小児外科	教　授
	虻川　大樹	宮城県立こども病院総合診療科・小児科学・小児肝臓消化器病学	科　長
	林田　真	九州大学病院・小児外科	共同研究員
	佐々木　英之	東北大学病院・小児外科	講　師
	島田　光生	徳島大学大学院消化器・移植外科	教　授
	神澤　輝実	東京都立駒込病院	副院長
	藤井　秀樹	山梨大学	理　事
	遠藤　格	横浜市立大学消化器・腫瘍外科学	教　授
	濵田　吉則	関西医科大学・小児外科	教　授
	窪田　正幸	新潟大学医歯学総合研究科・小児外科学分野	教　授
	鈴木　達也	藤田保健衛生大学・小児外科	教　授
	漆原　直人	静岡県立こども病院・外科系診療部	部　長
	須磨崎　亮	筑波大学医学医療系・小児科	教　授
	田口　智章	九州大学大学院医学研究院・小児外科学分野	教　授
	前田　貢作	神戸大学大学院医学研究科・小児外科学	客員教授
	近藤　宏樹	近畿大学医学部奈良病院・小児科	講　師
	木下　義晶	九州大学大学病院・総合周産期母子医療センター	准教授
	岡田　忠雄	北海道教育大学教育学部札幌校・養護教育専攻医科学看護学分野	教　授
	清水　教一	東邦大学医学部小児科学講座　医療センター大森病院・小児科	准教授
	位田　忍	地方独立行政法人大阪府立病院機構大阪府立母子保健総合医療センター・消化器・内分泌科	診療局長（内科）
	清水　俊明	順天堂大学医学部・小児科	教　授
	松藤　凡	聖路加国際大学・聖路加国際病院・小児外科	副院長
	玉井　浩	大阪医科大学・小児科	教　授
	八木　実	久留米大学医学部外科学講座・小児外科部門	主任教授
	工藤　豊一郎	国立成育医療研究センター・肝臓内科	医　長
	黒田　達夫	慶應義塾大学医学部・外科学（小児）	教　授
	杉浦　時雄	名古屋市立大学大学院医学研究科　新生児・小児医学分野	助　教
	村上　潤	鳥取大学周産期・小児医学	講　師
	韮澤　融司	杏林大学医学部・小児外科学	教　授
	呉　繁夫	東北大学大学院医学系研究科・小児病態学分野	教　授
	坂本　修	東北大学大学院医学系研究科・小児病態学分野	准教授
	田尻　仁	大阪府立急性期・総合医療センター・小児科	主任部長
	乾　あやの	済生会横浜市東部病院・小児肝臓消化器科	部　長
	虫明　聡太郎	近畿大学医学部奈良病院・小児科	教　授
	米倉　竹夫	近畿大学医学部奈良病院・小児外科	教　授
	依藤　亨	大阪市立総合医療センター・小児内分泌代謝病学	部　長
	鹿毛　政義	久留米大学病院・病理診断科・病理部	教　授
	原田　憲一	金沢大学　医薬保健研究域医学系	教　授
	猪股　裕紀洋	熊本大学大学院・小児外科学・移植外科学分野	教　授
	岩中　督	東京大学大学院医学系研究科・小児外科	特任研究員
研究協力者	石橋　広樹	徳島大学病院小児外科・小児内視鏡外科	教　授
	伊藤　玲子	国立成育医療研究センター・肝臓内科	医　師
	風間　理郎	東北大学病院・小児外科	助　教
	金森　豊	国立成育医療研究センター外科	医　長
	新開　真人	神奈川県立こども医療センター外科	部　長
	鈴木　光幸	順天堂大学医学部・小児科	助　教
	田川　学	筑波大学附属病院・小児科	病院講師
	田中　拡	東北大学病院・小児外科	助　教
	谷川　健	久留米大学病院・病理診断科・病理部	助　教
	戸川　貴夫	名古屋市立大学大学院医学研究科新生児・小児医学分野	大学院生
	中澤　温子	東海大学医学部基盤診療学系病理診断学	准教授
	林　久允	東京大学大学院・薬学系研究科分子薬物動態学教室	助　教
	別所　一彦	大阪大学・小児科	講　師
	細村　直弘	山梨大学医学部外科学講座第１教室	助　教
	松田　政徳	山梨大学医学部外科学講座第１教室	准教授
	矢田　圭吾	徳島大学病院小児外科・小児内視鏡外科	助　教
	吉田　雅博	化学療法研究所附属病院・人工透析・一般外科	教　授
	和田　宏来	筑波大学大学院人間総合科学研究科	大学院生
	渡邊　智彦	東北大学大学院医学系研究科・小児外科学分野	大学院生