of fibrosis progression in nonalcoholic steatohepatitis (NASH) [25], although the fibrosis in other types of hepatitis initially occurs in the periportal area. For assessing posttransplant fibrosis, we used the fibrosis scores in the NASH score for the PFIC1 recipients with steatosis and the Metavir score for the recipients without steatosis. The fibrosis scores in the recipients with steatosis were assigned as follows [25]: 1, perivenular fibrosis; 2, perivenular and periportal fibrosis; 3, bridging fibrosis; 4, cirrhosis. The fibrosis scores in the recipients without steatosis were assigned as follows [26]: 1, periportal fibrosis; 2, bridging fibrosis; 3, precirrhosis; 4, cirrhosis.

Statistical analysis

The survival rates were calculated by the Kaplan–Meier method, with a log-rank test. Statistical analyses were performed using SPSS Software Version 16.0 (SPSS, Chicago, IL, USA).

Results

Clinical course after LDLT

The mean hospital stay after LDLT was 70.7 ± 42.8 days (range 29–189 days). Viral infections and rejection, mainly during the early postoperative period, remain major complications [27]. Epstein-Barr virus and cytomegalovirus infections were detected after LDLT in 6 of 14 PFIC recipients (cases 5, 6, 8, 11–13) and were successfully treated. In all, 7 of the 14 PFIC recipients showed acute cellular rejection (ACR) after LDLT (cases 2, 4, 6, 11–14). Venous and biliary complications remain important [28, 29], and three recipients had stenosis of the hepatic vein or bile duct after LDLT (cases 1, 5, 7). These complications were successfully treated by interventional radiology or reconstruction as soon as possible after their detection.

Digestive symptoms after LDLT were confirmed in 10 of 11 PFIC1 recipients (90.9%) but were not encountered in any of the PFIC2 recipients. Cirrhotic findings including esophageal varix and splenomegaly (the longest diameter was >15 cm on imaging studies) even after LDLT were confirmed in 6 of the 11 PFIC1 recipients (54.5%). These PFIC1 recipients (cases 2, 3, 5, 7, 8, 10) underwent endoscopic or surgical therapy for esophageal varix and splenomegaly, including endoscopic injection sclerotherapy, endoscopic variceal ligation, and splenectomy. One PFIC1 recipient (case 2) suffered from de novo autoimmune hepatitis (AIH) and has been closely followed. Among the PFIC2 recipients, one recipient (case 14) received steroid pulse therapy and muromonab-CD3 therapy for refractory ACR during the early postoperative period, and the therapy was successful. The complications after LDLT are summarized in Table 2.

Histopathological findings after LDLT

Most PFIC patients underwent LNBs at intervals of 1–2 years after LDLT and histopathological follow-up according to these LNBs, although our institution does not employ a protocol biopsy. The mean number of LNBs after LDLT was 8.3 ± 5.1 times/recipient (range 3–23 times/recipient). The histopathological findings are summarized in Table 1.

Steatosis and steatohepatitis in the transplanted liver allografts

In all, 8 of 11 PFIC1 recipients exhibited steatosis after LDLT (72.7%); no steatosis was detected in the remaining 3 PFIC1 recipients. The changes in the degree of steatosis after LDLT in each case are shown in Fig. 1. Steatosis after LDLT in the steatosis-positive PFIC1 recipients seemed to begin during the early postoperative period, as the mean time to the initial confirmation of any steatosis was 71.5 ± 55.1 days after LDLT (range 21–191 days). Seven of the eight steatosis-positive PFIC1 recipients (87.5%) had ≥80% steatosis. The mean postoperative day for the steatosis to reach its peak among the steatosis-positive recipients was 229.6 ± 253.7 days (range 21–736 days). Seven of the eight steatosis-positive PFIC1 recipients had the complication of steatohepatitis (87.5%). In contrast, the PFIC2 recipients did not show any steatosis (Fig. 1).

Hepatic fibrosis in the transplanted allografts

Altogether, 9 of the 11 PFIC1 recipients exhibited fibrosis after LDLT, whereas it was not detected in the remaining 2 PFIC1 recipients. Two of the nine fibrosis-positive PFIC1 recipients (cases 2, 10) exhibited fibrosis without steatosis for other reasons (de novo AIH and chronic rejection, respectively). Only one PFIC1 recipient (case 4) had no steatosis or fibrosis, and another PFIC1 recipient (case 8) had steatosis but no fibrosis (F). Seven of the eight steatosis-positive PFIC1 recipients (87.5%) had F scores of ≥3, although one case stayed at F = 1 (case 11). The mean postoperative day for the F score to reach its peak among the eight steatosis-positive PFIC1 recipients was 1342.7 ± 1168.9 days (range 34–3254 days). The changes in the fibrosis scores after LDLT in each case are shown in Fig. 2. The initial confirmation of any fibrosis after

Table 2 Clinical courses and outcomes after LDLT

Case no.	Digestive symptoms	Complications (POD—treatment)	Outcome (POD)
1	Yes	Biliary stenosis (POD 3962—IVR)	Alive (6884)
2	Yes	ACR (moderate, PODs 100 and 2592—SPT)	Alive (6604)
		De novo AIH (POD 913—steroid)	
		Esophageal varices (POD 2546—EVL)	
3	Yes	Esophageal varices (POD 1624—EVL, EIS)	Dead (5032)
		Splenomegaly (POD 2595—splenectomy)	
		Rupture of splenic artery (POD 5032—hemostasis)	
4	Yes	Intraperitoneal bleeding (PODs 4 and 5—hemostasis)	Alive (5605)
		ACR (mild, PODs 13 and 2595—SPT)	
		Bad compliance of medicine and alcohol drinking	
5	Yes	EBV infection (POD 21—acyclovir)	Dead (4671)
		Bad compliance of medicine	
		Esophageal varices (POD 3529—EVL)	
		Splenomegaly (POD 3864—splenectomy)	
		Fatal dysrhythmia, myocarditis after re-LDLT on POD 4646 (POD 4671)	
		Biliary stenosis (POD 124—reconstruction)	
6	Yes	Cytomegalovirus infection (POD 136—ganciclovir)	Alive (4295)
		ACR (moderate, POD 140—SPT)	
		Intraperitoneal bleeding (POD 2—hemostasis)	
7	Yes	Stenosis of hepatic vein (POD 191—IVR)	Alive (4065)
		Splenomegaly (POD 1806—splenectomy)	
		Biliary stenosis (POD 1836—IVR)	
		Biliary stenosis (POD 48—reconstruction)	
8	No	Cytomegalovirus infection (POD 65—ganciclovir)	Alive (3384)
		Esophageal varices (POD 720—EIS)	
9	Yes	–	Alive (3265)
10	Yes	Chronic rejection (POD 182—Re-LDLT on POD 1393)	Dead (2005)
		Arterioportal shunt (POD 1825—Re-LDLT on POD 1986)	
		Rupture of esophageal varices (POD 2004—hemostasis)	
11	11	Cytomegalovirus infection (POD 33—ganciclovir)	Alive (2028)
		ACR (mild, POD 23—SPT)	
12	No	ACR (mild, POD 13—SPT)	Alive (2453)
		EBV infection (POD 27—acyclovir)	
		Cytomegalovirus infection (POD 34—ganciclovir)	
13	No	ACR (moderate, POD 14—SPT)	Alive (1601)
		EBV and EBV hepatitis (POD 34—acyclovir)	
		Cytomegalovirus infection (POD 103—ganciclovir)	
14	No	Refractory ACR (severe, PODs 7, 14, and 24—SPT and muromonab-CD3)	Alive (500)

The postoperative days (PODs) are shown as the days after the initial LDLT

ACR Acute cellular rejection, *EBV* Epstein-Barr virus, *EIS* endoscopic injection sclerotherapy, *EVL* endoscopic variceal ligation, *IVR* interventional radiology, *LNB* liver needle biopsy, *SPT* steroid pulse therapy

LDLT in the eight steatosis-positive PFIC1 recipients was 327.8 ± 353.4 days (range 34–932 days). As an example, the histopathological findings in case 6 are shown in Fig. 3. In contrast, the PFIC2 recipients did not exhibit any fibrosis (Fig. 2), although one recipient (case 14) temporarily showed an F score of 1 at PODs 39 and 47 owing to refractory ACR that was successfully treated.

Treatment for PFIC recipients after LDLT

All the PFIC1 recipients received UDCA therapy. Therapy with a BA adsorptive resin for PFIC1 recipients has been introduced in our institution [18], and 7 of 11 PFIC1 patients (cases 1, 2, 5–7, 9, 11) received this treatment combined with supplementations of pancreatic enzymes,

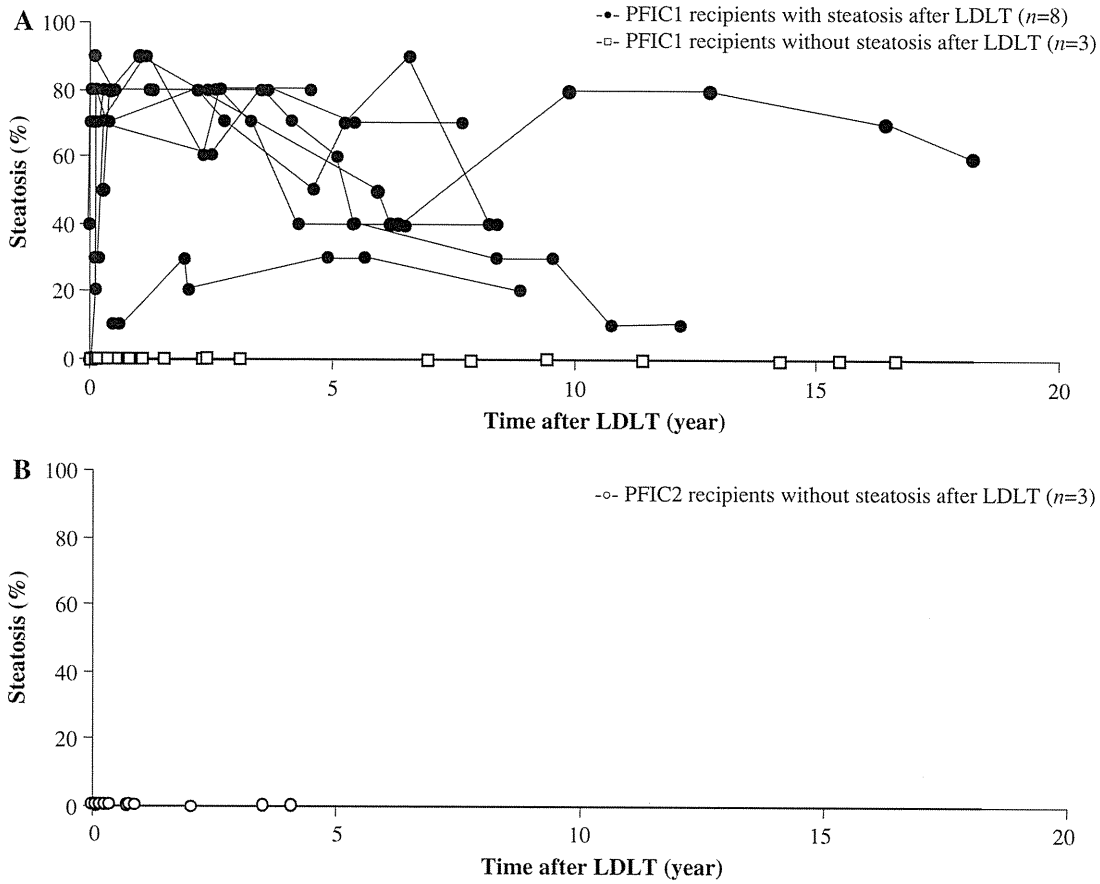

Fig. 1 Time course of steatosis in allografts after living donor liver transplantation (LDLT). **a** Temporal changes in the degree of steatosis after LDLT in progressive familial intrahepatic cholestasis type 1 (*PFIC1*) recipients. Eight PFIC1 recipients presented with steatosis after LDLT, and three PFIC1 recipients did not. Seven of the eight steatosis-positive recipients had the complication of steatohepatitis. *Filled circles* and *open squares* represent the degree of steatosis in PFIC1 recipients with and without steatosis after LDLT, respectively. **b** Temporal changes in the degree of steatosis after LDLT in PFIC type 2 (*PFIC2*) recipients. None of the three PFIC2 patients presented with steatosis after LDLT. *Open circles* represent the degree of steatosis in the PFIC2 recipients

protease inhibitors, bicarbonate, and fat-soluble vitamins. Positive or subtle effects against digestive symptoms were confirmed in all cases, although the symptoms persisted. Regarding the degree of steatosis and the fibrosis scores in the six steatosis-positive PFIC1 recipients who received these combined therapies (cases 1, 5–7, 9, 11), all of the recipients showed temporary responses to these treatments. However, in the histopathological findings of the latest LNBs, the degree of steatosis and the fibrosis scores for these six patients persisted at 46.7% ± 28.0% (range 10–80%) and 3.0 ± 1.1 (range 1–4), respectively. No specific treatment against steatosis were necessary in the three PFIC2 recipients.

Outcomes and survival rates after LDLT in the PFIC1, PFIC2, and other recipients

The mean observation periods were 11.9 ± 4.5 years for the PFIC1 recipients and 4.2 ± 2.7 years for the PFIC2 recipients. In all, 3 of the 11 PFIC1 recipients died, whereas all three PFIC2 recipients survived (Table 2). It should be noted that all three PFIC1 recipients with poor outcomes also had cirrhotic findings even after LDLT. One PFIC1 recipient (case 3) died after rupture of the splenic artery at POD 5032. Another PFIC1 recipient (case 5) underwent retransplantation on POD 4646 owing to graft loss but died from cardiac failure 25 days after the retransplantation. The third PFIC1 recipient (case 10) suffered from chronic rejection at 6 months after the LDLT and underwent retransplantation on POD 1393. Thereafter, an arterioportal shunt after the retransplantation caused graft loss, and yet another retransplantation was performed on POD 1986 after the initial LDLT. However, the esophageal varix ruptured on POD 2005 after the initial LDLT. The survival rates of the PFIC1 recipients at 5, 10, and 15 years after LDLT were 90.9%, 72.7%, and 54.5%, respectively. All three PFIC2 recipients survived. The survival rates of the other 703 recipients at 5, 10, 15, and

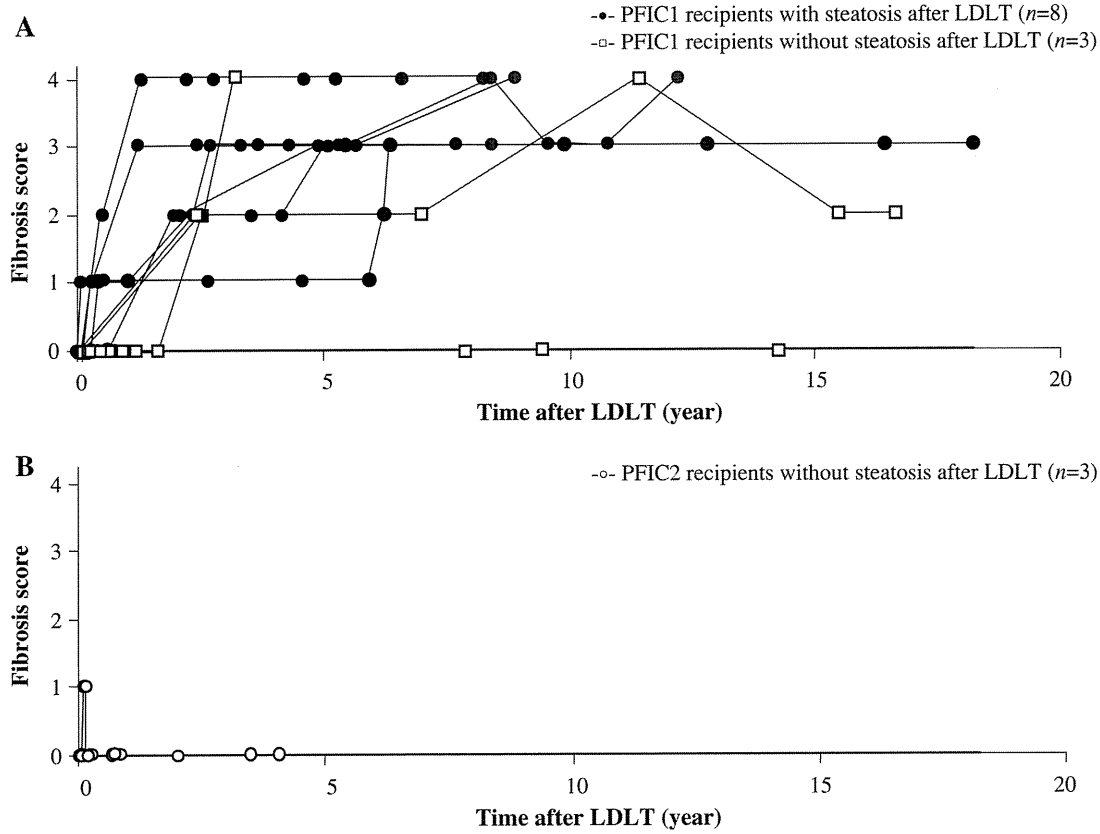

Fig. 2 Time course of fibrosis in allografts after LDLT. **a** Temporal changes in the scores for hepatic fibrosis after LDLT in PFIC1 recipients. Eight PFIC1 recipients with steatosis after LDLT subsequently developed positive fibrosis, and seven of these eight recipients had fibrosis (F) scores of ≥3. Among the three PFIC1 recipients without steatosis after LDLT, one recipient (case 4) showed no fibrosis, and two recipients (cases 2 and 10) had F scores of 4 due to reasons other than steatosis [de novo autoimmune hepatitis (AIH) and chronic rejection, respectively]. *Filled circles* and *open squares* represent the scores for hepatic fibrosis in the PFIC1 recipients with and without steatosis after LDLT, respectively. **b** Temporal changes in the scores for hepatic fibrosis after LDLT in PFIC2 recipients. All three PFIC2 patients had F scores of 0, although one recipient (case 14) temporarily had an F score of 1 at postoperative days (PODs) 39 and 47 owing to refractory acute cellular rejection (ACR), which was successfully treated. *Open circles* represent the scores for hepatic fibrosis after LDLT in the PFIC2 recipients

20 years after LDLT were 83.3%, 79.9%, 77.4%, and 76.5%, respectively.

Discussion

Although our PFIC1 recipients who received UDCA therapy showed only temporary effects and their steatosis and fibrosis persisted, therapy with UDCA (20–30 mg/kg/day) is considered for the initial therapeutic management of PFIC, especially in PFIC3 patients [1, 11, 21], although this therapy cannot be stopped in female patients during pregnancy [30]. We have no experience of LDLT for PFIC3 patients. However, some previous reports have documented PFIC3 recipients who underwent LDLT [31, 32], and LT was required at a mean age of 7.5 years in those patients [1]. We understand that even PFIC3 recipients require LT owing to resultant cirrhosis [33]. In our institution, the PFIC2 recipients maintained good graft conditions and showed excellent outcomes. We suggest that early LDLT may have a sufficient advantage for PFIC2 patients.

Steatosis is categorized in nonalcoholic fatty liver disease [25, 34]. Although steatosis itself is considered to be nonprogressive, steatosis with a developed fibroinflammatory counterpart can develop into cirrhosis [35, 36]. Continuous fat accumulation in hepatic cells is an initial step in the processes that result in necroinflammation and fibrosis in steatohepatitis [25, 37, 38]. Currently, oxidant stress, free fatty acids, lipid peroxidation products, and ATP depletion are focused on as factors that may induce cell injury and subsequent fibrosis in the fatty liver [39, 40]. Our results demonstrated that PFIC1 patients may have persistent steatosis progression even during the early

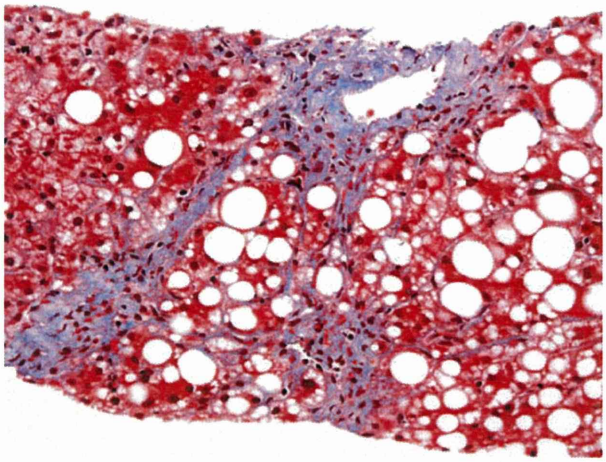

Fig. 3 Histopathological findings of steatosis and subsequent fibrosis after LDLT. A representative section from case 6 shows fibrosis with an F score of 3 at POD 468. In this case, 70% steatosis complicated by severe steatohepatitis was confirmed at POD 69 by hematoxylin-eosin staining (not shown), and the degree of steatosis worsened to 80% at POD 138. Subsequently, this case resulted in hepatic fibrosis with an F score of 3. (Masson trichrome and reticulin)

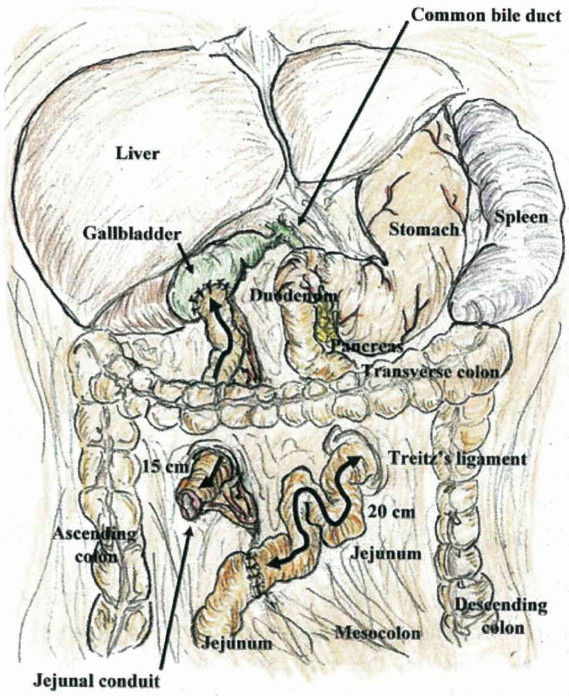

Fig. 4 Surgical technique for partial external biliary diversion (PEBD) in our institution. PEBD was performed as a cholecystojejunocutaneostomy. An isolated jejunal interposition 15 cm in length was made with the proper mesentery at a point 20 cm distant from Treitz's ligament. Next, the proximal side of this interposition was anastomosed to the body of the gallbladder in a side-to-end manner. The jejunal interposition was placed between the gallbladder and the skin; and end-stoma was made in the right lower quadrant of the abdominal wall

postoperative period after LDLT and that steatohepatitis after LDLT can be associated with subsequent fibrosis and allograft failure.

The extrahepatic features in PFIC1 patients do not improve or may be aggravated after LT [1, 9]. Chronic diarrhea may become intractable when biliary BS secretion is restored after LT [6, 9, 16], although diarrhea may be favorably managed by certain medications [9, 16]. Similar to these previous reports, our results confirmed digestive symptoms after LDLT in PFIC1 recipients but not in PFIC2 recipients. The clinical courses of our PFIC1 recipients were not satisfactory, and some of our PFIC1 recipients suffered from cirrhotic findings even a long time after the LDLT. The hyperdynamic state in cirrhotic recipients cannot be restored immediately, even after normalization of the portal pressure by LDLT [41–43]. We suggest that continuous graft damage including fibrosis in the PFIC1 recipients disturbed the restoration of their peculiar hemodynamics and that the persistence of these systemic hemodynamics may have resulted in fatal complications, such as rupture of dilated vessels, even a long time after the LDLT.

The outcomes of LDLT in our PFIC1 recipients are still not sufficient, nor were they in a previous report [44]. Donor selection for LDLT is limited ethically, socially, and medically, although repeated retransplantation can augment the long-term survival of pediatric PFIC1 patients. Our findings for the early postoperative occurrence of steatosis and fibrosis oblige us to reconsider the timing of LDLT and to challenge some other therapies for PFIC1 patients. Partial external biliary diversion (PEBD) has been documented as a possibility for PFIC patients [45, 46]. Some patients with PFIC may benefit from PEBD [47], although its effects remain controversial [45, 46]. The criteria for identifying PFIC patients who could benefit from UDCA or PEBD are unclear [48], although nasobiliary drainage and gene mutations are reported to select potential responders to PEBD [48]. LT represents the only alternative if these therapies fail [49].

After our experience with the 11 PFIC1 recipients described here, in 2009 we introduced PEBD as an anticipatory surgery before LDLT in a female PFIC1 patient aged 1.8 years (Fig. 4). We are closely following this case, and her clinical symptoms, which include itching, bad temper, agrypnia, and digestive symptoms. They fortunately diminished during the first year after PEBD. The histopathological findings in follow-up LNBs revealed that the liver damage has not progressed based on the intraoperative LNB findings. Although we have not had sufficient experiences of PEBD for PFIC1, we now consider this anticipatory surgery before LDLT if the overall considerations, including the donor limitation and patient status,

indicate its possibility. We do not believe that PFIC1 contraindicates LDLT because not all of our PFIC1 recipients necessarily suffered graft losses after LDLT. However, we hope that optimal control by PEBD and possible procrastination with a stable status until LDLT may contribute to the long-term quality of life in PFIC1 patients under the donor limitation situation. On the other hand, we performed total external biliary diversion (TEBD) in one PFIC1 recipient at retransplantation (case 10), although we had no experience with TEBD at the initial LDLT. We cannot confirm the effects of LDLT accompanied by TEBD because this recipient suffered graft loss owing to an arterioportal shunt after the retransplantation.

Only one mutated allele or no mutation is identified in a few PFIC patients (<10%) [1]. Mutations that may map to regulatory sequences of the genes is a possible explanation for this observation. A gene related to the transcription of PFIC genes or protein trafficking could also be involved [50]. It cannot be negated that other unidentified genes involved in bile formation may be responsible for the PFIC phenotypes. The mutated protein may have a dominant-negative effect on the expression and/or function of the protein in a heterozygous state [51]. Modifier genes and environmental influences could play roles in the expression of PFIC [52]. The possibility of PFIC recurrence after LT owing to alloimmunization of the recipient against the FIC1, BSEP, and MDR3 proteins of the donor remains a theoretical matter of debate. It is hypothesized that PFIC patients with a severe mutation leading to the absence of the gene product would be immunologically naive for the FIC1, BSEP, and MDR3 gene products [1]. In LDLT based on donor relationships with parents, it can be expected that the heterozygous status of the liver allograft will lead to a predisposition for developing lithiasis or cholestasis favored by immunosuppressive drugs that may interfere with canalicular protein function [53]. We think that this possibility is rare because we performed LDLT in which the donor origins were parents in 10 of 11 cases without PFIC recurrences, and this possible hypothesis was not reported in previous series [49].

Some investigators have documented that more advanced strategies, including cell transplantation, gene therapy, or specific targeted pharmacotherapy, may represent alternative therapies for all PFIC types in the future [48]. Our own results and a review of the mechanisms in previous articles have demonstrated that LT, including LDLT, may have advantages in PFIC2 patients as a definitive therapy and that the clinical courses and outcomes after LDLT are still not sufficient in PFIC1 patients owing to postoperative steatosis/fibrosis. As PFIC1 patients do require LT during the disease course, we suggest that the therapeutic strategies for PFIC1 patients, including the timing of LDLT under the donor limitation, should be reconsidered. The LDLT should not be performed in PFIC1 patients until effective interventions can be made to correct the metabolic defects, although PFIC2 is good indication for LDLT. The establishment of more advanced treatments for PFIC1 patients is required to improve the long-term prognosis.

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Conflict of interest None of the authors has a conflict of interest.

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ORIGINAL ARTICLE

Prescription trends for treatment of paediatric gastroenteritis at a Japanese hospital between 1997 and 2007

F. Kita* MS, Y. Shibata† BS, T. Yorifuji‡ MD PhD, T. Nakahata‡ MD PhD, J. Kawakami† PhD and K. Kawakami* MD PhD

**Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, †Department of Hospital Pharmacy, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka and ‡Department of Pediatrics, Kyoto University Hospital, Kyoto, Japan*

SUMMARY

Objective: **We aimed to investigate recent trends in prescriptions for the treatment of paediatric gastroenteritis in Japan over a 10-year period (1997–2007).**

Methods: **In this retrospective cohort study, we collected data for 2295 prescriptions for 1241 putative cases of paediatric gastroenteritis, which were treated between 1997 and 2007 at Hamamatsu University Hospital, Hamamatsu, Japan.**

Results: **The most frequently prescribed drugs were probiotics (n = 621), followed by anti-emetics (n = 474). In most years between 1997 and 2007, more cases were treated with probiotics than with any other drug type (30·6–63·3% of cases), with the percentage increasing between 2005 and 2007. In contrast, the frequencies of anti-emetic and antipyretic prescriptions remained fairly stable, and prescriptions for antibiotics decreased slightly over the study period. Anti-emetics were commonly used in this hospital.**

Conclusion: **Although experimental evidence upon which to base recommendations is lacking, Japanese evidence-based guidelines are critical for improving the quality of treatment of paediatric gastroenteritis.**

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Correspondence: K. Kawakami, Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshida Konoecho, Sakyoku, 606-8501 Kyoto, Japan. Tel.: +81 75 753 4459; fax: +81 75 753 4469; e-mail: kawakami-k@umin.ac.jp

***Keywords*: children, database, gastroenteritis, guideline, prescription**

INTRODUCTION

The symptoms of infectious gastroenteritis generally include diarrhoea, vomiting and fever. Among children, the major cause of gastroenteritis is viral infection, with viruses such as rotaviruses, enteroviruses, adenoviruses and noroviruses having been implicated in gastroenteritis outbreaks. Worldwide, viral diarrhoeal disease is a leading cause of paediatric morbidity and mortality, with 1·5 billion episodes and 1·5–2·5 million deaths estimated to occur annually among children aged <5 years (1, 2).

The World Health Organization; the European Society of Paediatric Gastroenterology, Hepatology and Nutrition; and the US Centers for Disease Control and Prevention have all issued guidelines for the treatment of children with gastroenteritis (1995, 2001 and 2003, respectively) (3–5). All of these guidelines recommend that even in the absence of signs of dehydration, oral rehydration treatment should be administered, but drugs (e.g. antidiarrhoeal agents, anti-emetics and antibiotics) should not. However, previous studies in the US, Italy and France have revealed that, in many cases, paediatric patients are in fact often being administered such drugs, especially anti-emetics (6–9). Treatment of vomiting in children using anti-emetics remains a controversial issue.

In Japan, infectious gastroenteritis is common among children, with approximately 900 000 to one million episodes being reported annually (10). The Japanese Ministry of Health, Labour and Welfare

(MHLW) has issued a short document on the management of noroviruses, which recommends that antidiarrhoeal agents not be administered, to avoid prolonging the infection (11). To date, no official guidelines on the drug treatment of gastroenteritis have been issued in Japan. Furthermore, there are no data available on the usage of anti-emetics for the treatment of paediatric gastroenteritis in Japan (particularly with respect to formulation). To better understand recent prescription trends with respect to treatment of gastroenteritis among children in Japan, in this study, we gathered data on prescriptions for paediatric gastroenteritis patients treated at Hamamatsu University Hospital between 1997 and 2007.

METHODS

Data for this retrospective cohort study were obtained using the drug order entry system at the Department of Hospital Pharmacy, Hamamatsu University Hospital, Hamamatsu, Japan. The database is based on the physician order entry system providing electronic information on each patient's characteristics including date on visit, birth date, gender, diagnostic code, prescription drugs and related clinical departments. There were 607 beds, and the number of outpatients was 1119/day from April 2007 to 31 March 2008 at Hamamatsu University Hospital.

The study population is consisted of inpatients and outpatients who had been diagnosed with infectious gastroenteritis between 1 January 1997 and 31 December 2007 according to the International Classification of Diseases, Tenth Revision (ICD-10) (12). For inclusion, patients needed to have been aged between 6 months and 6 years at the time a prescription was written.

Age and sex data were collected for each patient. For each prescription, we ascertained the drug name, dosage and clinical department where the patient was when the drug was prescribed. The medicines prescribed were then appropriately categorized using the drug tariff code issued by MHLW.

The study design was approved by the ethical review boards of Kyoto University School of Medicine (No. E-383) and Hamamatsu University School of Medicine (No. 19-144).

RESULTS

Patients and prescriptions

We analysed data for a total of 1241 putative cases of gastroenteritis diagnosed, receiving at least one medication between 1997 and 2007. The median age of patients was 2·1 years, and 56·7% were male (Table 1).

A total of 2295 prescriptions were filled for patients diagnosed with paediatric gastroenteritis during the study period. The 10 most frequently prescribed medication types were probiotics (n = 621 prescriptions), anti-emetics (n = 474), antibiotics (n = 206), antipyretics (n = 180), expectorants (n = 127), antihistamines (n = 109), antitussives (n = 106), antidiarrhoeals (n = 90), antipruritics (n = 55) and bronchodilators (n = 52) (Table 2). Of these, 91·5% were prescribed by staff in the paediatrics department, and 4·3%, 1·4% and 1·0% by staff in the emergency, paediatric surgery and otorhinolaryngology departments.

Changes in prescription trends

For our analysis of changes in prescription trends over the study period, we selected probiotics, anti-emetics, antibiotics, antipyretics and antidiarrhoeal agents for further study, because they were the most common agents directed at the diarrhoea itself or its symptoms. In almost every year between 1997 and 2007, more cases were treated with probiotics than with any other drug type (30·6–63·3% of cases), with the proportion tending

Table 1. Data on the study population and prescriptions

Patients	
Total number of putative cases	1241
Male sex (%)	56·7
Median age (years)	2·1
Prescriptions	
Total number of prescriptions	2295
Median number of medicines co-prescribed	3 (range: 1–10)
Source of prescription (%)	
Paediatrics	91·5
Emergency	4·3
Paediatric surgery	1·4
Otorhinolaryngology	1·0
Other department	1·8

Table 2. Number of prescriptions written for the 10 most commonly prescribed drug types

Medicines	Number of prescriptions
Probiotics	621
Anti-emetics	474
Antibiotics	206
Antipyretics	180
Expectorant agents	127
Antihistamine	109
Antitussive	106
Antidiarrhoeal agents	90
Antipruritic	55
Bronchodilator	52
Others	275

to increase between 2005 and 2007 (Fig. 1). In contrast, the percentage of paediatric gastroenteritis cases treated with anti-emetics and antipyretics remained fairly stable, and the percentage of cases treated with antibiotics underwent a modest decrease over the study period. Interestingly, the percentage of cases treated with antidiarrhoeal agents was small, and decreased over the study period. These results show that, for paediatric gastroenteritis, prescription trends changed over the period 1997–2007.

Prescription of anti-emetics and patient age

The percentage of cases that were treated with anti-emetics increased with patient age (Table 3). During the study period, 32·3% of cases for patients aged 0–2 years and 47·7% of cases for patients aged 3–5 years were treated with anti-emetics. There are no marked difference in the percentage of

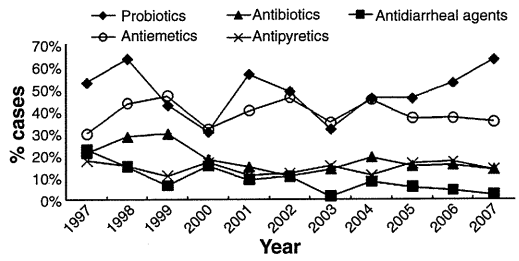

Fig. 1. Prescriptions for each of five common drug types given as a percentage of the total number of cases.

Table 3. Anti-emetic prescriptions for patients diagnosed with paediatric gastroenteritis during 1997–2007

	Prescriptions of anti-emetics		
		Number	%
Total patients	N = 1241	474	38·2
Age			
0	N = 238	67	28·2
1	N = 347	121	34·9
2	N = 183	62	33·9
3	N = 168	74	44·0
4	N = 163	78	47·9
5	N = 142	73	51·4
Sex			
Male	N = 704	256	36·4
Female	N = 537	218	40·2

prescription of anti-emetics between male and female. The anti-emetic prescribed was domperidone in almost all cases (n = 470, 99·6% of all anti-emetics prescriptions). For 83% of the cases for which a domperidone suppository was prescribed, the patient was administered this treatment only once (74%) or twice (9·0%) (Table 4). Although there was no difference between suppositories and dry syrup with respect to the total number of prescriptions, there was greater variation in the frequencies of the prescriptions for patients who were prescribed dry syrup.

DISCUSSION

Main results

The results of our study of prescription trends for paediatric gastroenteritis treatment at Hamamatsu University Hospital between 1997 and 2007 show that several types of drugs were used to treat symptoms, such as vomiting, diarrhoea and fever. More cases were treated with probiotics than with any other drug type, with the percentage of cases treated in this way having increased recently. Although several major guidelines for the treatment of paediatric gastroenteritis clearly recommend oral rehydration and advise against medications, we found that anti-emetics were commonly used in Japan. Furthermore, we found that the percentage of cases treated with anti-emetics remained fairly stable during the study

Table 4. Frequency of domperidone prescription for the treatment of paediatric gastroenteritis

	Once		Twice		Three times		Four times		Five times		More than six times		Total no. prescriptions
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Domperidone suppository	126	74	16	9	9	5	7	4	6	3	8	5	172
	1 day		2 days		3 days		4 days		5 days		>6 days		Total no. prescriptions
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Domperidone dry syrup	27	16	47	27	31	18	32	19	19	11	15	9	171

period. These results indicate that overseas guidelines have little effect on prescriptions for the treatment of paediatric gastroenteritis in Japan.

Trends in prescriptions for paediatric gastroenteritis

We found that the percentage of cases treated with probiotics has recently increased (particularly during the last 3 years of the study). During the 10-year study period, almost all of probiotics prescribed was *Enterococcus faecalis* (86·3%), followed by *Bifidobacterium* (11%). It is known that *E. faecalis* is a common component of the human intestinal flora (13).

Probiotics have been successfully used to prevent and reduce the severity or duration of paediatric rotaviral diarrhoea (14, 15), which indicates that probiotics may be an effective adjunct in the management of paediatric gastroenteritis. It is thought that probiotics act in part by competing with pathogens for receptor sites or intraluminal nutrients, and in part by enhancing the host's immune defenses (16, 17). Clinical trial data demonstrating the efficacy of probiotics for the treatment of paediatric gastroenteritis may have contributed to the recent increase in probiotic use observed in the present study. Over the past several years, some reviews of clinical trials of efficacy of probiotics indicate that the treatment of acute gastroenteritis with some probiotic strains was effective (18). However, as these trials tended to be of limited sample size and, given the large number of strains of probiotics available, the data is insufficient to confirm efficacy. Furthermore, well-controlled clinical trials are needed to verify the efficacy of probiotics for Japanese children with gastroenteritis.

In contrast to probiotic use, use of antibiotics declined during the study period. Even when a bacterial cause is suspected for gastroenteritis, the potential benefits of antibiotic therapy must be carefully weighed against the potentially harmful consequences, such as development of antimicrobial-resistant infections (19, 20). It is possible that Japanese paediatricians are widely aware of this risk, and are acting accordingly.

Over the study period, the percentage of cases treated with antidiarrhoeal agents remained very small, and decreased over time. The antidiarrhoeal agents prescribed included loperamide (75·6% of antidiarrhoeal prescriptions) and scopolia powder extracts containing hyoscyamine and scopolamine (24·4% of antidiarrhoeal prescriptions). Both agents reduce intestinal lumen motility, but loperamide is an opioid receptor agonist and hyoscyamine and scopolamine are muscarinic receptor agonists. There are some reports of loperamide causing adverse events including opiate-induced ileus, drowsiness and nausea caused by the effects of atropine (21, 22). Release of a document by the Japanese MHLW advising against the administration of these antidiarrhoeal agents (11) might have contributed to the limited use of these agents in the present study. Drugs not specific to gastroenteritis, including expectorant agents, antihistamine and antitussive, did not show any remarkable changes during the study period (data not shown). As it is well known that symptoms such as cough can be

involved frequently in patients with gastroenteritis, drugs not specific to gastroenteritis might have been prescribed when necessary (23, 24).

Prescription of anti-emetics

Currently in Japan, there are two anti-emetics that have been approved to reduce gastroenteritis-related vomiting: domperidone and metoclopramide (a dopamine antagonist). Other anti-emetics, including ondansetron and granisetron (a 5-HT_3 serotonin antagonist), have been approved for the treatment nausea and vomiting, induced by chemotherapy but not by gastroenteritis. Accordingly, the most commonly prescribed anti-emetic in this Japanese study was domperidone. In an Italian study, a similar trend was found, with the most common anti-emetic prescribed for paediatric gastroenteritis being domperidone, followed by metoclopramide (8). In the present study, we found that anti-emetics were more likely to be prescribed for older children. This trend might reflect prescribers' concerns about the adverse events associated with these dopamine antagonists, especially in young children, although these are not frequent (25, 26). We found that the majority of anti-emetic suppository prescriptions were for one or two doses. Similarly, in a previous US study, the majority of anti-emetics prescriptions (63·6%) were for after discharge and for 1 day or less (7).

Treatment of vomiting in children using anti-emetics is still a controversial issue. Ondansetron is reportedly effective in decreasing vomiting (27–29). In contrast, however, a systematic review of the effectiveness and safety of anti-emetics in children yielded only weak and unreliable evidence of the benefits of ondansetron and metoclopramide over placebo in reducing the number of episodes of vomiting due to gastroenteritis (30). Thus, anti-emetics might not be justified for the treatment of paediatric gastroenteritis, given the weak evidence of their effectiveness.

Limitations of the study

In this study, we obtained data from the database of a medical order entry system. Therefore, the patients' symptoms (e.g. dehydration, vomiting and diarrhoea) were not well characterized. Furthermore, the database does not include drugs for injection, but we assume that few of these would have been used for the treatment of gastroenteritis in children. The study cohort was defined based on assignment of the ICD-10 code at initial presentation; however, our methodology did not allow us to confirm the accuracy of the diagnosis. Finally, this study was conducted using prescription data obtained from a single hospital. However, despite Hamamatsu University Hospital serving as a secondary referral centre receiving patients with chronic disease, it also treats patients with other types of disease, just like a suburban clinic, therefore we think that our results are very likely to be representative of the general clinical situation in Japan.

CONCLUSIONS

There have been very few studies on prescription trends in Japan. In the present study, we established that prescription trends for the treatment of paediatric gastroenteritis changed little over a recent 10-year period. These results indicate that in the absence of any Japanese guidelines on the treatment of paediatric gastroenteritis, prescription patterns may reflect the individual preferences of physicians. Clearly, development of official, evidence-based Japanese guidelines would be a vital tool for improving the quality of medical practice. In Japan, we still lack strong evidence upon which to base recommendations relating to medical treatment (including probiotics and anti-emetics) of paediatric gastroenteritis. To redress this situation, we have initiated clinical research that aims to assess the effectiveness and safety of anti-emetics for gastroenteritis among children in Japan.

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Testicular thecoma in an 11-year-old boy with nevoid basal-cell carcinoma syndrome (Gorlin syndrome)

Masakatsu Ueda[a], Akihiro Kanematsu[a], Hiroyuki Nishiyama[a], Koji Yoshimura[a], Kenichiro Watanabe[b], Tohru Yorifuji[b], Yoshiki Mikami[c], Toshiyuki Kamoto[a], Osamu Ogawa[a,*]

[a]*Department of Urology, Kyoto University Graduate School of Medicine, Kyoto, Kyoto 606-8507, Japan*
[b]*Department of Pediatrics, Kyoto University Graduate School of Medicine, Kyoto, Kyoto 606-8507, Japan*
[c]*Department of Pathology, Kyoto University Graduate School of Medicine, Kyoto, Kyoto 606-8507, Japan*

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Thecoma;
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Abstract We report a case of testicular thecoma in an 11-year-old Japanese boy with nevoid basal-cell carcinoma syndrome (Gorlin syndrome). He presented with left testicular swelling and underwent a radical orchiectomy on suspicion of a malignant paratesticular tumor. The tumor arose from the testis exophytically and was diagnosed as a thecoma histopathologically. Ovarian thecoma-fibroma group tumors are closely associated with Gorlin syndrome or with abnormalities in *PTCH*, a candidate gene for the syndrome. The occurrence of an extremely rare testicular thecoma in this case (the second in the literature) suggests that such an etiological association may also exist in the pathogenesis of testicular tumors.

A thecoma is a benign stromal tumor typically seen in the ovary and characterized by spindle-shaped cells forming luteinization [1]. The pathogeneses of ovarian thecoma and fibroma are closely associated with a tumorigenic syndrome called *nevoid basal-cell carcinoma syndrome* (Gorlin syndrome) or abnormalities in its candidate gene, *PTCH* [2]. Herein, we report the first case of a testicular thecoma in a boy with Gorlin syndrome.

1. Case report

An 11-year-old boy was referred to us for painful scrotal swelling. His uncle had died of a cerebellar tumor. The boy had previously been diagnosed with a cerebellar medulloblastoma at 7 months of age and received a series of surgeries, adjuvant multidrug chemotherapies, and radiation therapy. Since the age of 7 years, he had been administered leuprolide as a treatment of premature elevation of testosterone. Concurrently, the boy was diagnosed with Gorlin syndrome based on the presence of skin lesions and odontogenic keratocysts, but without detectable *PTCH* gene mutations.

At presentation, his external genitalia were at the prepubertal stage. He had palpably normal bilateral testes but swelling in the left paratesticular area. He was diagnosed with epididymitis based on magnetic resonance imaging (Fig. 1A) and spontaneous resolution of the pain. Seven months later, however, the paratesticular lesion increased in size and formed a firm nontender mass. Magnetic resonance imaging revealed a heterogeneous 21-mm mass adjacent to

* Corresponding author. Tel.: +81 75 751 3337; fax: +81 75 751 8507.
E-mail address: ogawao@kuhp.kyoto-u.ac.jp (O. Ogawa).

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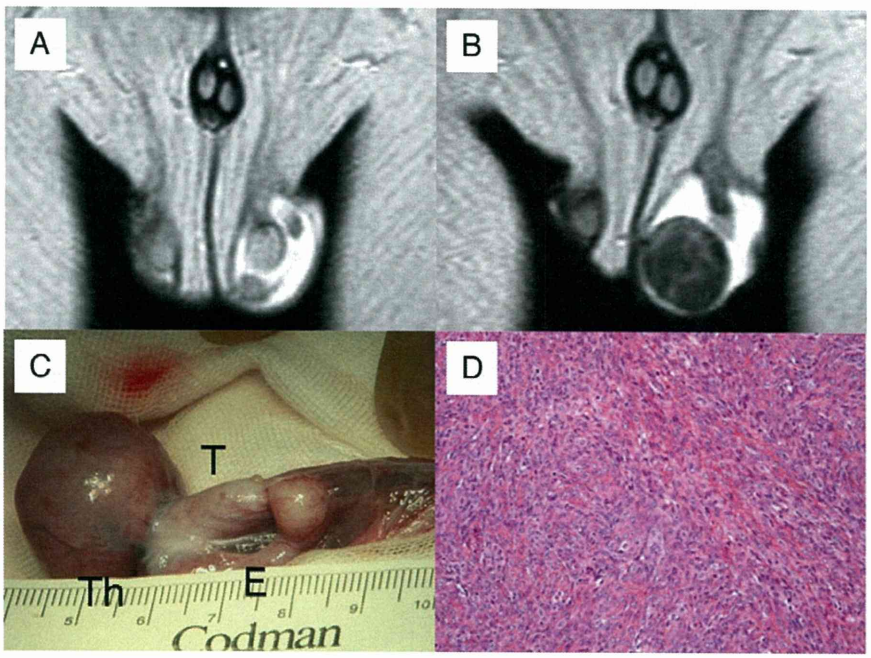

Fig. 1 Magnetic resonance imaging of the left intrascrotal mass (T2-weighted) at first (A) and second referral (B). C, Gross appearance of the tumor. D, Microscopically, the tumor consisted of spindle cells, with occasional luteinized cells that are immunoreactive for inhibin α (figure not shown). Th indicates thecoma; T, testis; E, epididymis.

the left testis (Fig. 1B). Germ cell tumor markers were negative. Testosterone was 29.9 ng/dL (reference range, 18-150 ng/dL), estradiol was 11.3 pg/mL (reference range, 5-16 pg/mL), luteinizing hormone was 0.9 mIU/mL (reference range, <1-5 mIU/mL), and follicular stimulating hormone was 1.4 mIU/mL (reference range, 2-7 mIU/mL). There were no signs of metastasis on radiography. An inguinal exploration revealed a well-circumscribed tumor located at the caudal end of the testis (Fig. 1C). Because the intraoperative pathologic examination could not exclude a malignant mesenchymal tumor, a left radical orchiectomy was performed. Histopathologically, the tumor arose from the tunica albuginea of the testis. Spindle cells were predominant, with occasional luteinization (Fig. 1D). The luteinized tumor cells were positive for inhibin α and calretinin and negative for MyoD and desmin. Consequently, the diagnosis of thecoma was established. The patient has remained free from recurrence for 2 years.

2. Discussion

Thecoma is an extremely rare tumor in the testis, with just one previously reported case [3]. Typically, thecomas are benign stromal tumors arising from ovarian theca cells and constitute 1% of all ovarian tumors [1]. Ovarian stromal tumors are classified into either thecoma or fibroma, and occasionally clumped together as a thecoma-fibroma group.

Gorlin syndrome is a disorder characterized by malformations of the skin, nerves, eyes, and bone [4], with frequent loss of heterozygosity at 9q22.3 or abnormalities in the *PTCH* gene, a homolog of the patched gene in *Drosophila* [5]. Gorlin syndrome patients without detectable *PTCH* mutations, as in the present case, are believed to have germinal mosaicism [6]. The syndrome is associated with basal cell carcinoma, ovarian tumor, and medulloblastoma (as found in the present case). Many women with this syndrome develop ovarian thecoma or fibroma at a mean age of 30 years [2,7]. In parallel with these findings, loss of heterozygosity at 9q22.3 is observed in 40% of sporadic ovarian thecoma-fibroma cases [8], suggesting a strong pathogenic association between *PTCH* abnormalities and thecoma-fibroma development.

A possible explanation for the occurrence of testicular thecoma is one analogous to the association between Gorlin syndrome and ovarian thecoma-fibroma, although the absence of a genetic linkage in the present case precludes a definitive conclusion. The cytotoxic chemotherapy against the prior cerebellar tumor may have enhanced a genetic predisposition to thecoma. Thus, thecoma-fibroma should be taken into the differential diagnosis for male patients with Gorlin syndrome presenting with an intrascrotal mass. Because bilateral lesions are seen in the ovary, testis-sparing surgery and contralateral surveillance should be recommended [7].

3. Conclusion

The present case may suggest the existence of an unreported tumorigenic mechanism in the male gonads.

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Preoperative diagnosis of congenital segmental giant megaureter presenting as a fetal abdominal mass

Hirofumi Goto, Akihiro Kanematsu*, Koji Yoshimura, Yu Miyazaki, Takashi Koyama, Tohru Yorifuji, Hiroyuki Nishiyama, Osamu Ogawa

Kyoto, Japan

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Abstract We describe a case of congenital segmental giant megaureter in a boy that presented as a fetal abdominal mass. He also had bilateral undescended testes, bilateral vesicoureteral reflux, and segmental aniridia. He presented with hypoglycemia in the neonatal period that resolved. Postnatal magnetic resonance imaging, voiding cystourethrography and radionuclide imaging established the diagnosis, and a ureteroureterostomy was performed at 12 months.

Congenital segmental giant megaureter (CSGM), which comprises an extremely rare subgroup of megaureter, has not been accurately diagnosed preoperatively [1-4]. Herein, we present the first report of successful preoperative diagnosis of this disease by a comprehensive imaging series.

1. Case report

The patient was born at 39 weeks gestation and had a birth weight of 4648 g. His mother was 32 years of age, and this first gestation was achieved by in vitro fertilization embryo transfer. Fetal echography at an early gestational stage revealed an abdominal cystic mass. Magnetic resonance imaging (MRI), which was performed prenatally and postnatally, revealed a cystic lesion between the right kidney and the urinary bladder. The intensity of the fluid in the cystic mass was identical to that of urine (Fig. 1).

At birth, the patient had several congenital abnormalities, including bilateral undescended testes, micropenis, and segmental aniridia. He also presented with hypoglycemia. No apparent chromosomal anomalies were detected.

A dimercaptosuccinic acid (DMSA) renal scan showed hypoplasia of the left kidney and hyperplasia of the right kidney, and indicated that the cystic mass was unlikely to be extrarenal pelvis (Fig. 2, left). Voiding cystourethrography (VCUG) showed bilateral vesicoureteral reflux (VUR). The contrast material that refluxed to the right ureter drained into a dilated space and subsequently into the right renal pelvis, establishing the diagnosis of CSGM (Fig. 2, right).

Diuretic renography was performed with the range of interest set to discriminate the overlap between the cystic lesion and the right renal pelvis. The radionuclide in the renal pelvis and cystic dilatation showed responses to furosemide, demonstrating the absence of a functional obstruction. The patient retained stable renal function (serum creatinine, 0.3 mg/dL) without any febrile urinary tract infection

* Corresponding author. Department of Urology, Kyoto University, Kyoto, Japan. Tel.: +81 75 751 3337; fax: +81 75 751 3740.
E-mail address: aqui@kuhp.kyoto-u.ac.jp (A. Kanematsu).

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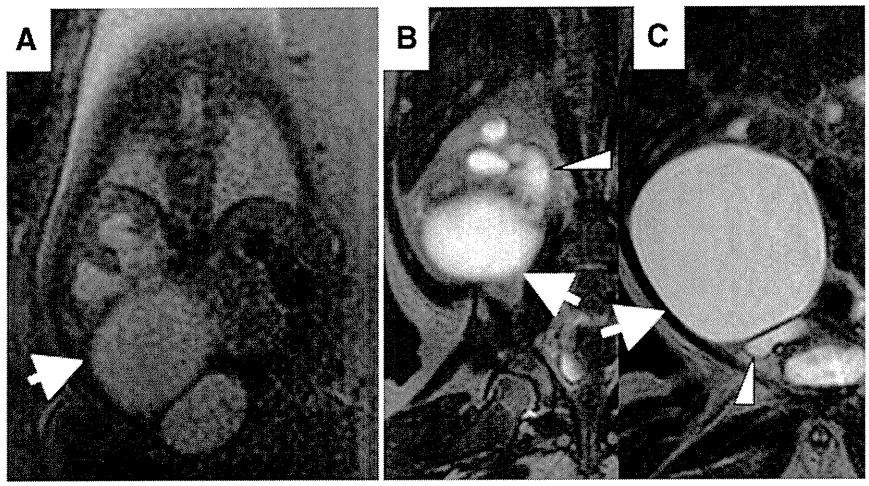

Fig. 1 A, Fetal MRI at 35 (right) weeks of gestation. Coronal single-shot fast spin-echo T2-weighted images showed a cystic mass (arrow) located between the right kidney and the urinary bladder. B. Postnatal MRI at day 2. Coronal T2-weighted images showed the proximal and distal ureter (triangles) located near the cystic mass (arrow).

episodes under prophylactic antibiotics. However, intractable pyuria persisted and the cystic lesion was considered to be the focus.

Based on these findings, we elected to perform cystoscopy, retrograde pyelography, ureteroureterostomy and bilateral orchidopexy simultaneously at age 12 months. During cystoscopy, the bilateral ureteral orifices opened ectopically into the bladder neck. Retrograde pyelography confirmed the diagnosis of CSGM, delineating the interphase of the noncystic part of the ureter with cystic dilatation (Fig. 3, left). Through a 5-cm flank incision, the dilatated portion was resected between the proximal duplicated renal collecting system and the distal ureter, and a stented end-to-end ureteroureterostomy was performed (Fig. 3, right). Postoperative diuretic renography showed no obstruction in the right upper urinary tract. However, he experienced two breakthrough febrile urinary tract infection episodes after the procedure, necessitating a VUR repair at 18 months of age. The ureters were dissected extravesically and anastomosed to the bladder cross-trigonally with tapering of the distal right ureter. Intraoperatively, the vas deferens was noted to enter into the ureters bilaterally.

2. Discussion

Urinary tract dilatation occurs in approximately 1.5% of all neonates, and is classified into hydronephrosis, hydroureteronephrosis and megacystis-megaureter, according to the obstruction point [5]. CSGM is an extremely rare condition, with less than 10 cases reported in the literature, and has not been accurately diagnosed preoperatively before this report [1-4]. Diagnosis of CSGM is challenging because it cannot be classified into any of the above categories and its etiology may not be explained by an obstruction.

This case presents several novel points for imaging of CSGM. First, this is the first reported case in which MRI

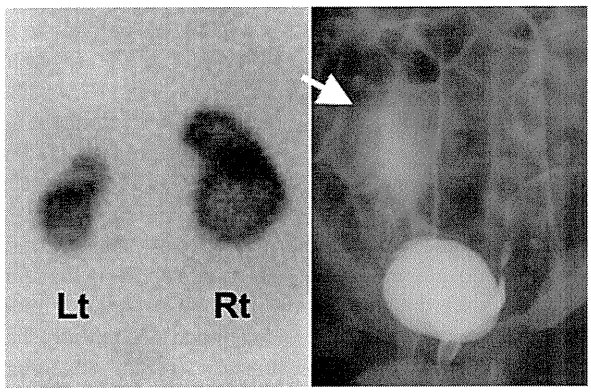

Fig. 2 Left, DMSA renal scan. The cystic mass was unlikely to be a dilated renal pelvis. Right, The VCUG revealed bilateral VUR. The refluxed contrast medium drained into the cyst (arrow).

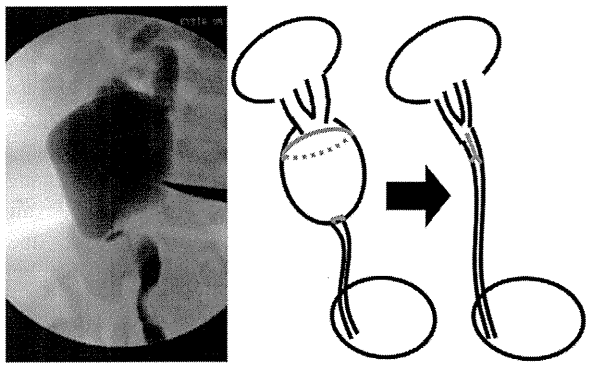

Fig. 3 Left, A retrograde pyelogram delineated the entire upper urinary tract. Right, Schema of the operation. The cystic dilatation was resected and the ureter was repaired by end-to-end anastomosis.

was fully used for prenatal and postnatal diagnosis of CSGM. The ureter proximal and distal to the cystic dilatation was visualized in postnatal images, thus proving the diagnostic utility of MRI (Fig. 1). Second, our prenatal diagnosis was hydronephrosis with a huge extrarenal pelvis, and DMSA was useful for negating this possibility. Third, VCUG was performed as part of the standard workup, and it was fortuitous that the presence of VUR assisted in the diagnosis (Fig. 2). Fourth, diuretic renography was useful to rule out a functional obstruction. Fifth, retrograde pyelography allowed us to develop a precise plan before making an incision (Fig. 3). Collectively, the establishment of a preoperative diagnosis enabled us to plan minimally required surgery under appropriate informed consent from the parents, instead of an emergency neonatal abdominal exploration, as has been frequently reported in previous cases.

The patient had multiple problems, including neonatal hypoglycemia, bilateral undescended testes, segmental aniridia and developmental retardation, all of which can be associated with chromosome 11 disorders (eg, WAGR and Beckwith-Wiedeman syndrome) [6]. Although there was no apparent genetic disorder at the genome level, genetic mosaicism could not be ruled out, and the patient is currently under surveillance for nephroblastoma.

This case illustrates that, although extremely rare, CSGM can be accurately diagnosed by a series of modern imaging techniques, if it is included in the differential diagnosis of prenatal and neonatal urinary tract dilatation.

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Cognitive and affective impairments of a novel SCA/MND crossroad mutation Asidan

K. Abe[a], Y. Ikeda[a], T. Kurata[a], Y. Ohta[a], Y. Manabe[a], M. Okamoto[a,b], K. Takamatsu[a,b], T. Ohta[a,b], Y. Takao[c], Y. Shiro[a], M. Shoji[a], T. Kamiya[a], H. Kobayashi[d] and A. Koizumi[d]

[a]*Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama University, Okayama;* [b]*Department of Neurology, Ohta Memorial Hospital, Fukuyama;* [c]*Deparment of Neurology, Kurashiki Heisei Hospital, Kurashiki; and* [d]*Department of Health and Environmental Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

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Background: A variety of hereditary spinocerebellar ataxia (SCA) develops a broad spectrum of both ataxia and non-ataxia symptoms. Cognitive and affective changes are one such non-ataxia symptoms, but have been described only in hereditary SCAs with exonic CAG gene expansion.

Methods: We newly found intronic hexanucleotide GGCCTG gene expansion in NOP56 gene as the causative mutation (=SCA36) in nine unrelated Japanese familial SCA originating from Asida river area in the western part of Japan, thus nicknamed Asidan for this mutation. These patients show unique clinical balance of cerebellar ataxia and motor neuron disease (MND), locating on the crossroad of these two diseases. In the nine families, 14 patients were clinically examined and genetically confirmed to Asidan. In the present study, we examined cognitive and affective analyses on 12 patients (seven men and five women) who agreed to join the examination with average age at onset of 53.1 ± 3.2 years, average duration of 12.1 ± 5.2 years, and current average age at 65.1 ± 6.2 years.

Results: The 12 Asidan patients demonstrated a significant decrease in their frontal executive functions measured by frontal assessment battery (FAB) and Montreal cognitive assessment (MoCA) compared with age- and gender-matched controls, whilst mini-mental state examination (MMSE) and Hasegawa dementia score-revised (HDS-R) were within normal range. The decline of frontal executive function was related to their disease duration and scale for the assessment and rating of ataxias (SARA). They also demonstrated mild depression and apathy. Single-photon emission tomography (SPECT) analysis showed that these Asidan patients showed decline of regional cerebral blood flow (rCBF) in a particular areas of cerebral cortices such as Brodmann areas 24 and 44–46.

Conclusion: These data suggest that the patients with Asidan mutation show unique cognitive and affective characteristics different from other hereditary SCAs with exonal CAG expansion or MND.

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Introduction

Spinocerebellar ataxia (SCA) is a neurodegenerative disorder consisted of heterogeneous subgroups of hereditary cases with late onset, progressive dysarthria, and gait/limb ataxias. We have reported that some hereditary SCAs such as SCA1, SCA2, SCA3, and SCA6 slightly affect motor neuron system with skeletal muscle atrophy [1–5], which was recently confirmed by Schmitz-Hübsch *et al.* [6]. Cognitive and affective characteristics have also been described in SCA1 [7], SCA2 [8,9], SCA3 [10–12], and SCA6 [13–15]. Motor neuron disease (MND) and amyotrophic lateral sclerosis (ALS) are another neurodegenerative disorder again consisted of heterogeneous subgroups of hereditary and sporadic cases with adult onset, progressive motor palsy, and skeletal/tongue muscle atrophy. More than 10 subtypes of hereditary ALS have been reported

Correspondence: Prof. Koji Abe, MD, PhD, Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama University, 2-5-1 Shikatacho, Kitaku, Okayama 700-8558, Japan (tel: +81 86 235 7365; fax: +81 86 236 7368; e-mail ID: abekabek@cc.okayama-u.ac.jp)