complications, some children develop end-stage intestinal failure.

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

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クロライドチャネルを介した便秘治療

Treatment for Chronic Constipation with Chloride Channel-2 Activator

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Key Words: 慢性便秘，機能性便秘，過敏性腸症候群，大腸運動

Abstract

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

はじめに

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

便秘をきたす機能性消化管障害

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

便秘型過敏性腸症候群

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

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

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

■機能性便秘

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

■便秘の病態

機能性消化管障害とは，通常の臨床検査によっては，異常が検出されない程度の消化管機能の異常によって症状が生じる症候群である[2]。「通常の臨床検査によっては」という限定条件を付けたのは，最先端の科学的手法を使えば異常が検出されるからである。重度の便秘の場合には，通常の臨床検査によって異常が認められる場合が多く，その大多数は機能性消化管障害の範疇を越えた消化管運動異常症(gastrointestinal motility disorders)である[1]。慢性特発性偽性腸閉塞症(chronic idiopathic intestinal pseudo-obstruction)は立位腹部X線写真で鏡面像が見られることが多い。巨大結腸症(megacolon)は腹部X線写真で顕著な大腸ガス，大腸造影検査，大腸内視鏡検査あるいは腹部CTで拡張した大腸が見られる。

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

表1　IBSのRome III診断基準（引用:文献[3]）

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

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

表2　Bristol便形状尺度（引用:文献[3]）

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

表3　IBSの分類 (Rome III)（引用:文献[3]）

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

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

表4　機能性便秘のRome III診断基準（引用:文献[3]）

■下記の2項目以上の特徴を示す
- a. 排便困難による力み　≧　排便の25%
- b. 硬便 or 兎糞状便　≧　排便の25%
- c. 残便感　≧　排便の25%
- d. 直腸肛門の閉塞感　≧　排便の25%
- e. 排便時の用手努力　≧　排便の25%
- f. 排便回数　<　3回/週

■下剤を使わない限り軟便は稀である
■IBSの診断基準を満たさない

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

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

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

■便秘治療の概要

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

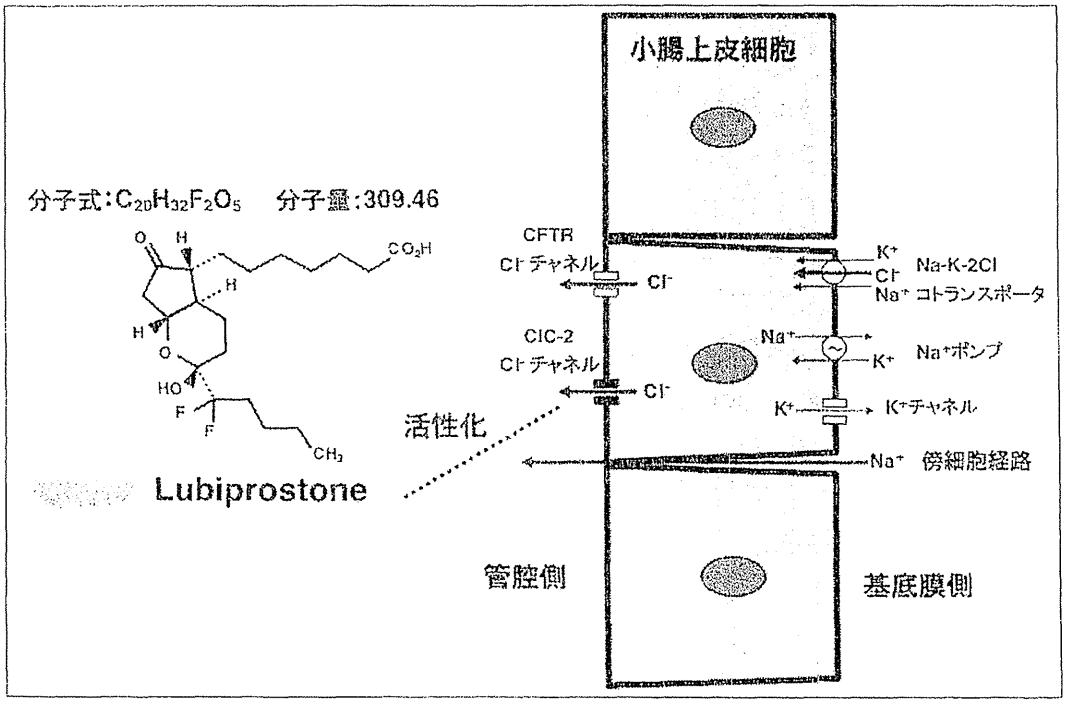

図1　クロライドチャネルとルビプロストン
ルビプロストンの構造式（左）とそのCl- channel-2 (ClC-2)への作用。小腸粘膜上皮にはCystic Fibrosis Transmembrane conductance Regulator (CFTR) Cl- channelもあるがルビプロストンはClC-2に特異的に作用する。

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

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

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

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

おわりに

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

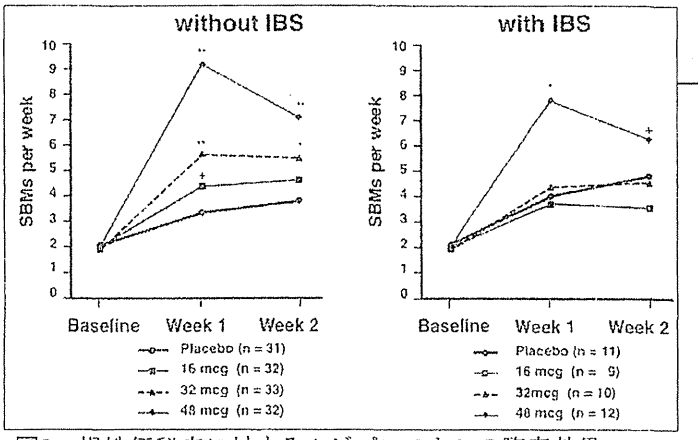

図2　慢性便秘症に対するルビプロストンの臨床効果
文献[6]より許可を得て引用。SBM: 自発排便回数。左が腹痛のない慢性特発性便秘症，右が便秘型過敏性腸症候群。

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Biliary atresia type I cyst and choledochal cust: can we differentiate or not?

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Abstract
Background/purpose It is difficult to discriminate between choledochal cust with obstructive jaundice and biliary atresia with a cyst at the porta hepatis in neonates or young infants. This review evaluates whether it is possible to differentiate between these two diseases. We here also provide an overview of our experience with type I cyst biliary atresia patients.
Methods Among all the biliary atresia infants who we treated, the infants who were diagnosed with type I cyst biliary atresia were identified and reviewed for their management and outcome. The clinical course and management in different reports were reviewed and compared to the cases presented to our institution.
Results Among the 220 biliary atresia cases, 11 (5 %; male/female: 4/7) were diagnosed to be type I cyst biliary atresia. Two received hepaticoenterostomy and nine received hepatic portoenteros. Three patients had severe late complications; overall, nine (81.8 %) were alive with their native liver and without jaundice.
Conclusions Patient with choledochal cust are likely to represent larger cysts and inversely, smaller, static, anechoic cysts are more likely to represent cystic biliary atresia. However, exceptional cases were yet presented, and a definitive diagnosis may not be reached. Thus a complete differentiation between choledochal cust from type I cyst biliary atresia is yet hard to reach.

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Keywords Biliary atresia · Choledochal cust · Cyst at the porta hepatis

Introduction

Biliary atresia (BA) is an obstructive condition in which all or parts of the extra hepatic bile ducts are absent [1]. Cystic BA is subtype of BA with a cyst at the porta hepatis. Type I BA is a case with atresia of the common bile duct and when a cystic dilatation of the porta hepatis connecting with intrahepatic bile ducts is accompanied of type I atresia, it is called a type I cyst BA (I cyst BA) [2]. Choledochal cyst (CC) is a rare medical condition with abnormal cystic dilatation of biliary tree in several parts and degrees. CC commonly present prior to the age of 2 years, although it can be diagnosed antenatally [1]. Both I cyst BA and CC are well-known causes of jaundice in neonates and young infants, with a cyst at the porta hepatis. However, cystic BA and CC are two entities with dramatically different management approaches and prognosis. Early surgical intervention should be required because age at surgery markedly affected outcome as judged by clearance of jaundice in the BA cases [3–5]. However, there are patients with cystic BA who are not relived from jaundice in spite receiving early hepatic portoenterostomy. In contrast, CC is a curable choledocal malformation that can have excellent prognosis after resection of the cyst and hepaticojejunostomy. Hence, it is very important to differentiate cystic BA from CC when a portal cyst is found in a fetus, neonate or young infant [6]. However, it is not easy to discriminate between CC and type I cyst BA in neonates or early infants in spite of the several diagnostic tests, and in many patients exploratory laparotomy with surgical cholangiography is required to establish a definitive diagnosis [7].

Yet the question still stands, is it possible to differentiate type I cyst BA from CC?

Here we present our experience in management of I-cyst BA cases with a review of literature that studied this disease.

Methods

Among the infants diagnosed with BA, infants further diagnosed as type I cyst BA during the period from January 1969 to December 2011 at Nagoya City University Hospital and Fujita Health University Hospital were included in the study. The diagnosis of BA was confirmed in all cases by perioperative clinical findings, and when available with cholangiography. Clinical records were reviewed for details on the operative biliary reconstruction, postoperative courses, and their outcomes. The cases which had interesting clinical courses were further expressed.

Statistical analysis

Kaplan–Meier survival curves were obtained and data analyses were performed with the commercially available statistical analysis software package SPSS 14 (Statistical Package for Social Sciences, Chicago, IL, USA).

Results

Two hundred and twenty infants (male/female, 92/128) with BA were managed in our institutions.

Among these infants 11 (5 %; male/female, 4/7) were identified to be with type I cyst BA (Table 1). Three cases received an initial surgical tubal drainage of gallbladder to relieve their jaundice and a corrective surgery was performed for BA after 49–203 days. Hepaticoenterostomy was performed in 2 cases and the remaining 9 cases received hepatic portoenterostomy. The median follow-up period for infants with I cyst BA was 22.8 years (range 0.4–42.1 years). Overall, nine (81.8 %) survived with their native liver and were free from jaundice (Fig. 1).

A female infant failed to clear her jaundice postoperatively and second girl who received liver transplantation for relapse of her jaundice at the age of 12 died at the age of 6 months and 12 years, respectively.

Two female patients developed gastroesophageal variceal hemorrhage at the age of 19 and 17 years old, and required endoscopic sclerotherapy. A male patient developed liver dysfunction reviled during his medical checkup at the age of 24 years. He had multiple intrahepatic stones and required the removal of the calculus via percutaneous transhepatic cholangioscopy at the age of 24 (Fig. 2).

Table 1 The number of biliary atresia (BA) cases and their type classifications, treated in Nagoya City University Hospital and Fujita Health University Hospital, between January 1969 and December 2011

Type I	13 cases (5.9 %) (M/F: 5/8)	Type I cyst	11 cases (5.0 %) (M/F: 4/7)
		Type I without cyst	2 cases (0.9 %) (M/F: 1/1)
Type II	6 cases (5.9 %) (M/F: 2/4)		
Type III	201 cases (91.4 %) (M/F: 85/116)		
Total	220 cases (M/F: 92/128)		

M/F male/female

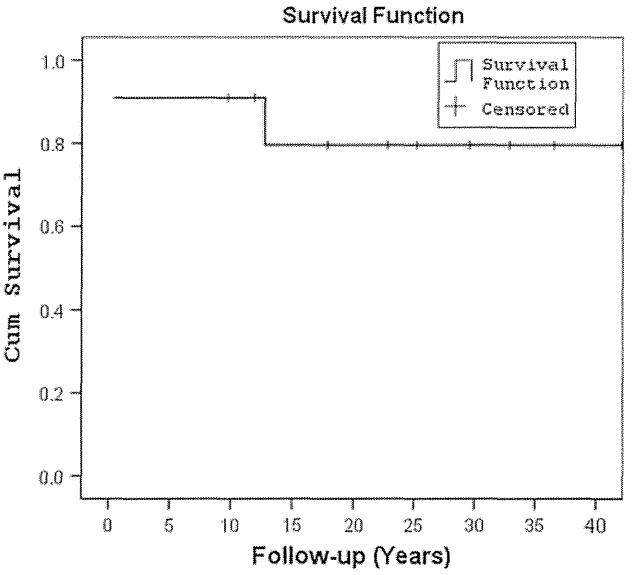

Fig. 1 Overall survival curve in 11 cases diagnosed as type I cyst BA. The median follow-up period for cases was 22.8 years (range 0.4–42.1 years), nine (81.8 %) survived

Case report

A 46-day-old female infant with persistent jaundice and acholic stools was referred to our hospital. Clinical jaundice and acholic stools were recognized around the end of the first month of life. Laboratory findings revealed a total bilirubin of 8.1 mg/dl, direct bilirubin of 7.1 mg/dl, AST of 184 IU/l, ALT of 208 IU/l, and γ-GTP of 1240 IU/l (normal: 2–45). Preoperative ultrasonography and CT scan revealed a cystic mass, 10 × 20 mm in diameter, at the porta hepatis and without intrahepatic bile duct dilatation. On exploratory laparotomy at 59 days of life, a cystic mass, 10 × 15 mm in diameter, was identified at the porta hepatis and contained bilious fluid without being identified

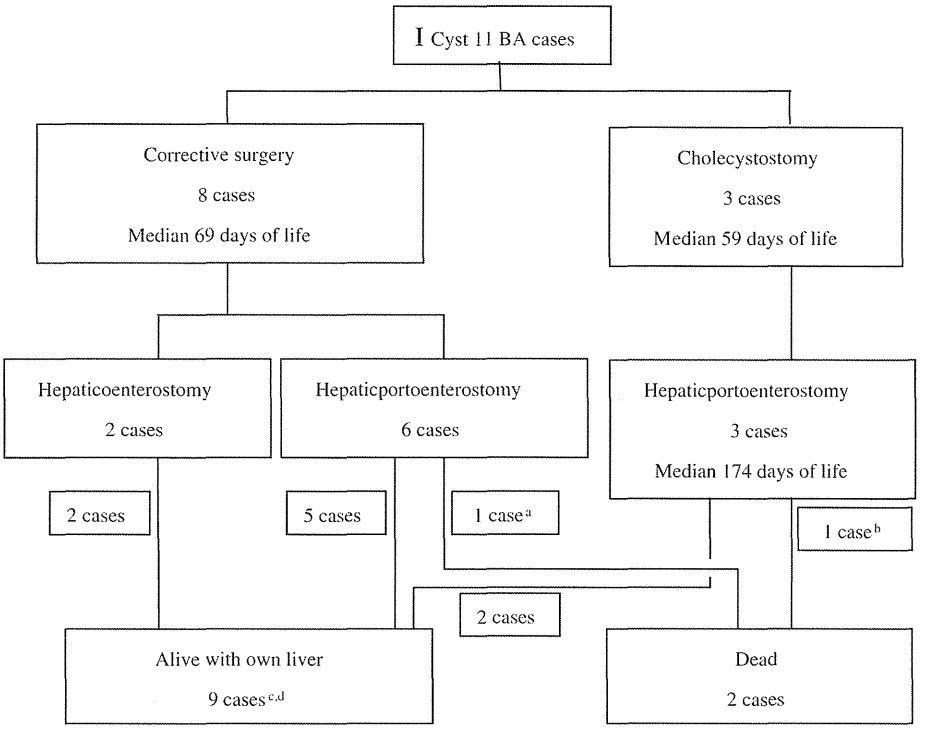

Fig. 2 A hierarchy figure presenting the selected operative procedures and outcomes of the 11 cases diagnosed as type I cyst BA. *a* A 6-month-old female infant failed to clear her jaundice and *b* a 12 year-old girl with post-liver transplantation for relapse of her jaundice; both cases died. *c* A case complicated from cholangitis and intrahepatic calculus (24-year-old male). *d* Two cases complicated from ruptured of esophageal varices (17- and 19-year-old females), and required endoscopic sclerotherapy

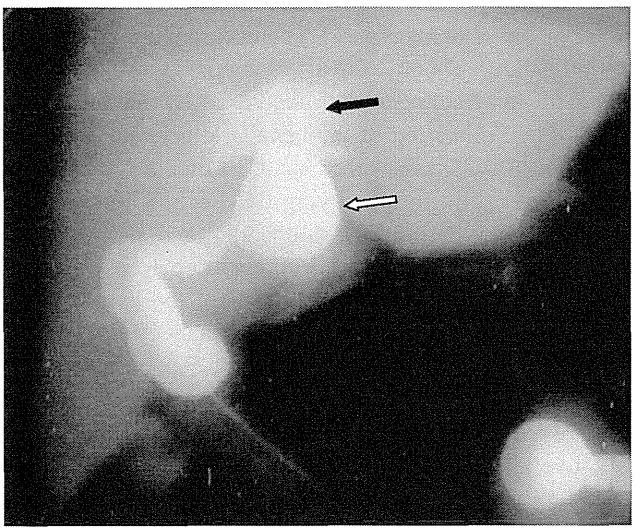

Fig. 3 Intraoperative cholangiogram. A cystic mass at the porta hepatis (*white arrow*) with connection to the cloudy intrahepatic bile ducts (*black arrows*) and no connection to the intestinal lumen

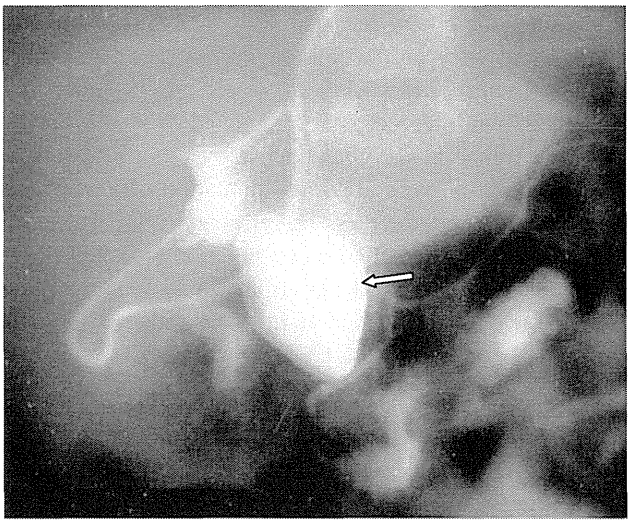

Fig. 4 Cholangiogram at the 39 postoperative days. Common bile duct with the abnormal pancreaticobiliary junction and dilatation in a fusiform shape (*arrow*) instead of the cystic mass at the primary operation

as the common bile duct at any part of hepatoduodenal ligament. Intraoperative cholangiography was carried out and it showed the cystic mass at the porta hepatis with connection to cloudy intrahepatic bile ducts and without identifying any connection with the intestinal lumen (Fig. 3). Tubal drainage of gallbladder was performed to relieve her jaundice and was diagnosed as I cyst BA. A radiographic image performed at the 39 postoperative days revealed the common bile duct with the abnormal pancreaticobiliary junction and dilatation with a fusiform shape instead of the cystic mass at the initial tubal drainage operation (Fig. 4). An average of 80 ml bile, containing low levels of amylase, was drained through the tube insured in her gallbladder and she became free from jaundice. At the 203 postoperative days hepatic portoenterostomy was performed, because the perioperative findings revealed an expanded common bile duct without apparent macroscopically structures of hepatic duct. The

histological findings showed that her cholestatic cirrhosis was somewhat severer than it was at the initial tubal drainage operation and no epithelial cell was found on the resected bile duct wall. She became free from jaundice and was doing well until the age of 17 years old, when she developed gastroesophageal variceal hemorrhage and required endoscopic sclerotherapy.

Discussion

Biliary atresia is an obstructive condition in which all or parts of the extra hepatic bile ducts are absent [1]. The etiology of BA is currently under investigation and two major forms of biliary atresia have been described: embryonic and prenatal [1]. The embryonic type accounts for 10–20 % and is associated with other congenital anomalies. The perinatal type accounts for the majority of cases [1]. According to the Japanese Biliary Atresia Registry, BA is classified into 3 types: type I, atresia of the common bile duct, type II, atresia of the hepatic duct, and type III, atresia of the porta hepatis and approximately 90 % of BA are type III [8]. Cystic dilatation of any part of the extrahepatic biliary tract may also occur, however, BA with a hilar cyst is an uncommon variant. The BA variant type I cyst constitutes <10 % [9] where a cystic dilatation of the common bile duct is accompanied of type I atresia.

On the other hand, choledochal cyst (CC) is a rare medical condition with abnormal dilatation of biliary tree in several parts and degrees. The etiology of CC is caused by an abnormal pancreaticobiliary junction proximal to the ampulla of Vater, resulting in an abnormal long common channel [1]. CC usually occurs in rather older children or adults [10], symptoms in CC patients appear in 22 % during the first year of life [11]. It is difficult to discriminate cystic BA from CC with obstructive jaundice and clay colored stools, although both are important causes of jaundice in neonates and young infants associated with a cyst at the porta hepatis.

Clinicians need to be aware of such cystic BA (including type I cyst) and how to distinguish it from CC to avoid inadequate initial surgical intervention [12].

Recently, improvements in perinatal diagnosis by advances in fetal ultrasonography (US) are leading to more frequent prenatal diagnosis of cystic BA or CC [13]. In these cases, the cyst could be identified at the right upper quadrant of the abdomen, which could be miss diagnosed, if confused with the gall bladder or the umbilical vein. Other common cystic lesions which appear similar to CC and cystic BA and could also cause misdiagnosis, include hydronephrosis, duodenal duplication, intestinal atresia, mesenteric cyst, and ovarian cyst. Recent development of ultrafast magnetic resonance imaging (MRI) techniques has allowed MRI to become an important further confirmatory investigation to US in fetal imaging. MRI is useful for the differentiation of biliary cystic malformation and other cystic lesions at the right upper quadrant in the fetal abdomen [14], but it is still not easy to discriminate between cystic BA and CC.

Saito et al. [15] showed that perinatal transition of the cyst size in biliary cystic malformation cases could be helpful in assessing the level of bile flow. Perinatal small cystic mass at the porta hepatis during gestation can include some cystic BA with poorer bile flow, on the other hand in CC cases, their cysts grew larger perinatally. Also, other previous reports showed that size of the cyst in fetus and neonates were different between cystic BA and CC, literatures stated several diameter for differentiation, as the smaller cystic diameter (<1.5 cm [16], <2.5 cm [17, 18], and <2.1 cm) [6] favor a cystic BA over CC (>4 cm) [18], or the mean width and length of the cysts in CC (62.2 ± 39.9 and 41.1 ± 30.7 mm, respectively) were significantly larger than those in cystic BA (16.2 ± 13.2 and 8.9 ± 6.5 mm) [6]. The small cysts in the hepatic hilum are highly suspicious for cystic BA [6, 12, 17, 19], however, there were clear exceptions to these rules [5, 6] and it is, in addition, hard to draw a clear line between a large cyst and a small cyst [5]. The ultrasonography finding of gallbladder abnormalities, triangular cord sign (an abnormal hyperechogenic triangular area in the porta hepatis), and dilatation of the hepatic artery, are useful in identifying BA. On the other hand, other ultrasonography findings are useful in identifying CC, such as intrahepatic bile duct dilatation, normal gallbladder, and sludge in the cyst [5], and hence, further specific and objective US features for differentiation and diagnosis of the two diseases are needed in neonates and early infants.

Huang et al. [20] reported that MR cholangiopancreatography (MRCP) yields a high degree of accuracy in the diagnosis of biliary atresia and CC. However, MRCP could only give information similar to US, unless the patency of the biliary tract is proved, in differentiating cystic BA and CC.

Then would invasive imaging studies such as endoscopic retrograde cholangiopancreatography (ERCP) and/or percutaneous transhepatic cholangiography (PTC) be useful for differentiating cystic BA and CC?

Several authors showed that ERCP is feasible and safe in the workup of neonatal cholestasis when other imaging modalities are inconclusive [21–23]. PTC is also an effective modality for diagnosis of cholestatic disorders in neonates, including BA patients [4, 24]. CC is differentiated from cystic BA by the patency of the biliary tract from intrahepatic bile duct to duodenum. These imaging studies are essentially useful for differentiating non-surgical and surgically correctable causes of cholestasis, such as

neonatal hepatitis and BA, respectively, which in turn prevents explorative laparotomy in the non-surgically correctable cases. On the other hand, ERCP and/or PTC are not essential in all cases of cystic malformation of the porta hepatis with obstructive jaundice and acholic stools, because early surgical intervention will be required after all and a definitive diagnosis would be given by intraoperative cholangiography.

Jiexiong et al. [19] showed that similar histological features such as inflammation of the liver and proliferation of the canalicular bile ducts could been found by the percutaneous liver biopsy in patients with both cystic BA and in some cases CC. Okada et al. [7, 13] have suggested that to assess fibrosis or biliary tract expression of neural cell adhesion molecule 1(CD56) may permit discrimination of cystic BA and CC. These reports are very interesting although included small number of patients.

Furthermore, the CD56-immunostaining is not widely performed. Thus the authors deny that the preoperative liver biopsy is essential for the diagnosis of these cases.

In conclusion, it is not easy to discriminate between cystic BA and CC with obstructive jaundice and gray colored stools in neonates or early infants in spite of the availability of several diagnostic tests including laboratory analyses [7, 19], and in these patients exploratory laparotomy with surgical cholangiography is essential to establish a final diagnosis.

Nio et al. [8], identified 3 characteristic bile duct images: namely, cloudy (numerous fine proliferative ductules demonstrated a cloudy pattern), treelike (interlobular bile ducts were clearly demonstrated like a tree structure) and mixed type (the cholangiogram consisted of both components of cloudy and treelike pattern).

In the case we fully presented, she was diagnosed as I cyst BA with the typical cloudy intrahepatic bile duct but her cholangiogram at 39 days after the initial operation showed patency between the intrahepatic bile duct and the duodenum. The radiological finding in this case could classify it to be CC, but the postoperative course and the findings of bile duct on the porta hepatis during her second operation confirm the diagnosis to be BA. Masumoto et al. [25] reported a case of cystic BA changing from I cyst BA to IIId (i.e., cystic BA without connection between the cyst at the porta hepatis and intrahepatic bile duct). By the current classification, we cannot fully differentiate cystic BA and CC by the patency of the extrahepatic bile duct without intraoperative cholangiography findings.

Early surgical intervention should be required in cases that cannot exclude BA from their diagnosis, because age at surgery has a marked influence on the outcome as judged by clearance of jaundice in these cases [3, 4, 6]. However, the optimal time to treat CC patients in early infants has not been established. Obstructive jaundice and increasing cyst size are indications for early surgery for definitive CC case [4, 18].

The management of CC at any age is by excision and hepaticojejunostomy which is similarly the optimal definitive procedure for CC in infants [4]. On the other hand the optimal operative procedure for the cystic BAs remains controversial. Takahashi et al. [26] showed excellent long-term outcome by hepaticojejunostomy in cystic BA. Other reports showed that hepatic portoenterostomy was effective after an unsuccessful hepaticojejunostomy for cystic BA [9, 12, 27]. Similar to other surgical groups, we also perform hepatic portentoerostomy for the treatment of cystic BA cases with insufficient diameter of hepatic duct for anastomosis [9, 12].

The postoperative course of CC in early infancy is usually satisfactory and long-term complications from complete cyst excision are rare [1]. The prognosis on type I BA (including I cyst) is usually much better than that of the other types [8]. However, Nio et al. [9] reported that the incidence of late cholangitis was considerably higher in type I patients. They also mentioned that patients with treelike pattern in their cholangiogram in corrective surgery showed excellent long-term prognosis [9]—they were more like patients with CC rather than BA.

In conclusion, cystic lesion of the porta hepatis in a fetus, newborn, or early infant might be the common finding of cystic BA and CC. It is difficult to differentiate between cystic BA and CC on the basis of clinical manifestation, even with using several imaging modalities in some cases. Early definitive surgery should be required in these patients when cystic BA is doubtful. It is a fact that in very rare cases a definitive diagnosis to differentiate between cystic BA and CC was not reached, and intraoperative cholangiography is effective in reaching the final diagnosis. Thus a preoperative definitive diagnosis between CC and I cyst BA is not essential.

Conflict of interest None.

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REVIEW ARTICLE

Redo surgery for biliary atresia

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Abstract The Kasai redo surgery is important for treating biliary atresia. In the era of liver transplantation (LTx), pediatric surgeons must accurately select patients for redo surgery and ensure that potential LTx can be performed later. Although optimal timing for redo varies among cases, appropriate timing is essential. We reviewed the significance, optimal timing, operative procedures, and indications of Kasai redo surgery. Between 1989 and 2011, 2,630 patients were registered in the Japanese Biliary Atresia Registry (JBAR), and the data collected from JBAR regarding Kasai redo surgery were analyzed. Patients were divided into two groups, Group 1 (1989–1999, $n = 1{,}423$) and Group 2 (2000–2011, $n = 1{,}207$). The redo incidence significantly reduced in Group 2. Although no significant difference was found in the native liver jaundice-free survival rates between the two groups, the overall survival rate at initial registry was significantly higher in Group 2. This may be because of the limited number of patients selected for redo and increased availability of early LTx. Patients who achieved sufficient bile drainage following the initial Kasai surgery but developed sudden bile flow cessation were the best candidates for Kasai redo surgery; it should be performed only once for this subset.

Keywords Biliary atresia · Kasai portoenterostomy · Redo surgery · Liver transplantation

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Introduction

The Kasai surgery for biliary atresia was developed more than 50 years ago. Since then, the surgical outcomes have markedly improved, and an increasing number of patients have survived with their native livers for very long periods. In the era of liver transplantation (LTx), the Kasai surgery is still regarded as a first-line surgical procedure for patients with biliary atresia. However, a substantial number of patients have ultimately required LTx; therefore, adequate consideration for LTx is essential at the time of the Kasai surgery and during postoperative patient care. The Kasai redo surgery has played an important role for patients who developed recurrent jaundice following the initial Kasai surgery. Because the role of the redo surgery may have changed in the era of LTx, the significance, optimal timing, operative procedures, and indications of the Kasai redo surgery were reviewed.

The significance of the Kasai redo surgery

Before the era of LTx, the Kasai surgery was the only procedure that could prolong survival for patients with biliary atresia. In these circumstances, the Kasai redo surgery was commonly performed, and patients with poor bile drainage often underwent as many as three or more surgeries.

In Japan, LTx became available in the early 1990s, a time when several arguments regarding the Kasai surgery were introduced. For instance, the Suruga II procedure, a reconstructive procedure with an external biliary conduit to prevent cholangitis that was widely performed in Japan, was abandoned because transplant surgeons criticized this procedure for impairing the LTx outcomes [1]. The role of

Kasai redo surgery was also discussed. Since the advent of LTx, an alternative procedure offering increased survival has become widely available, and the necessity and indications for the Kasai redo surgery, which may have an adverse impact on the LTx outcome, have become major topics of debate. The role of the Kasai redo surgery has apparently been changing.

Some researchers have reported that the Kasai redo surgery should not be performed because more than 70 % patients with biliary atresia have ultimately required LTx [2]. In addition, other researchers have advocated that instead of the Kasai surgery, LTx should be performed as a primary surgery [3, 4]. However, the LTx surgical outcomes have reportedly been worse in infants than in older patients, regardless of whether LTx was the primary or the rescue procedure following a failed Kasai surgery. It would be a great advantage if the Kasai redo surgery could re-establish good bile drainage or delay the need for LTx [5, 6].

Although LTx surgical outcomes have markedly improved, the possibility of surgical mortality and morbidity still exists, and long-term LTx outcomes have not yet been fully elucidated. The problems associated with LTx, such as high medical costs and shortage of donors, need to be resolved. Currently, the policy of proceeding with an appropriate combination of LTx and the Kasai surgery, including redo surgery, is preferred for selected patients [7].

Optimal timing for the Kasai redo surgery

The optimal timing for the Kasai redo surgery, which also has been a topic of debate, has not yet been determined. Lilly et al. [8] advocated prompt redo when required. One recommendation was that the redo should be performed as a quasi-emergency surgery [9] and another was that the period between the cessation of bile drainage and the redo should be less than 1 month [10]. In contrast, native liver survivors, who underwent the Kasai redo surgery several months after developing recurrent jaundice, have been reported [11]. Another author has reported that even considerably late redo surgeries have been successful, particularly in older patients in whom good bile drainage following the initial Kasai surgery was once established but suddenly stopped [12]. Recurrent jaundice because of cholangitis is likely to result in irreversible persistent jaundice leading to liver failure in infants. Granulation tissue completely blocks the biliary fistula of the porta hepatis immediately during the early postoperative course following the initial Kasai surgery; thus, prompt redo must be seriously considered in these patients. However, in older children, internal fistulae between intrahepatic bile ducts and the jejunum at the porta hepatis are well developed, and recurrent jaundice often completely recovers after medical treatment using antibiotics, ursodeoxycholic acid, and steroids. Although the optimal timing for the Kasai redo surgery may vary among cases, care should be taken to ensure appropriate timing because objective methods for assessment of the appropriate timing for each patient do not exist.

In our institution, we decided that the indication for the Kasai redo surgery is 1 month after the initial Kasai surgery, if the patient developed cessation of bile drainage immediately after the surgery. In older patients with recurrent jaundice, we try all other medical treatments before surgery. In addition, the indications for redo surgery should be considered after a complete assessment of liver pathology, hepatic functional reserve capacity using 99mTc-GSA scintigram, availability of LTx, and the patient's social background.

Procedural details of the Kasai redo surgery

Some authors have reported the efficacy of granulation tissue curettage at the porta hepatis during Kasai redo surgery or when using endoscopic techniques without re-anastomosis [13, 14]. However, many pediatric surgeons have followed a procedure similar to that used during the initial Kasai surgery, which included dividing the previous hepatic anastomosis, resecting the granulation tissue, and creating a new anastomosis between the porta hepatis and jejunum in the redo surgery [7, 10].

Technically, the Kasai surgery involves initiating peritoneal adhesiolysis away from the vicinity of the porta hepatis where dense adhesions usually exist, taping the hepatoduodenal ligament during the early stage, preparing for Pringle's maneuver in case of unexpected bleeding, and dissecting in the vicinity of the hepatic hylum, taking particular care not to injure the Roux-en-Y limb to achieve secure reanastomosis. Resection of the granulation tissue and reanastomosis are similar to the maneuvers used in the initial Kasai surgery.

Indications for the Kasai redo surgery

The Kasai redo surgery may offer long-term native liver survival or increase the time until LTx is required in patients who developed cessation of bile flow following the initial Kasai surgery. In contrast, it can cause increased difficulty in LTx. Patient selection for the Kasai redo surgery is a topic of debate between pediatric surgeons and transplant surgeons.

Forty-nine patients who underwent the Kasai redo surgery in our institution between 1954 and 1990 were divided

into the following two groups, according to their postoperative courses following the initial Kasai surgery: patients who had achieved good bile drainage, Group A ($n = 29$) and patients with poor or no bile drainage, Group 2 ($n = 20$). Jaundice was resolved in 21 of 29 patients (74 %) of Group A and in no patients in Group 2. We concluded that we should perform the Kasai redo surgery only in patients with good bile drainage following the initial Kasai surgery [15]. Similar results have been reported from other institutions in other countries [8, 16].

Transplant surgeons have claimed that multiple Kasai surgeries were associated with increased operative blood loss [17], longer surgical time [7], and higher LTx morbidity [18]. Because of these reports, pediatric surgeons are hesitant to perform Kasai redo surgeries. Other researchers have reported that the Kasai surgery, including the redo surgery, did not definitively affect LTx outcomes [8, 19], and the benefit of Kasai redo surgery should be appreciated.

Currently, a consensus has been reached that patients who achieved sufficient bile drainage following the initial Kasai surgery and then developed sudden cessation of bile flow were the best candidates for Kasai redo surgery, and it should be performed only once for this selective subset of patients [7, 19].

Pediatric surgeons should strive to appropriately perform the initial Kasai surgery, properly select patients for the redo surgery, and ensure that LTx remains possible in the event that may be required later.

Analysis of data from the Japanese Biliary Atresia Registry (JBAR)

According to the data from the Japanese Liver Transplantation Society, a total of 6,195 liver transplants were performed in 65 institutions in Japan till 2010. The most frequent indication was cholestatic disease, including biliary atresia, followed by neoplastic disease. The trend in the number of patients who underwent LTx markedly increased during the 1990s in Japan (Fig. 1) [20].

The JBAR was initiated in 1989 by the Japanese Biliary Atresia Society. The aim of the JBAR is to study the epidemiology and etiology of biliary atresia and to improve surgical outcomes of the Kasai surgery. Each patient is followed up for 30 years. The initial registry data for each year were collected until August of the next year when the patient underwent the initial Kasai surgery. In total, 2,630 patients were registered in the JBAR until 2011 (Fig. 2) [21].

We used the JBAR data to analyze the incidence and outcomes of Kasai redo surgery. Patients were chronologically divided into two groups, Group 1 (1989–1999, $n = 1{,}423$) and Group 2 (2000–2011, $n = 1207$). The majority of patients in both groups underwent the Kasai surgery (Table 1). Data regarding the jaundice disappearance rate (JDR) after the initial Kasai surgery, incidence of Kasai redo surgery, JDR after redo surgery, native liver jaundice-free survival rate, and overall survival rate at the time of registration every year were compared between the two groups.

The JDR after the initial Kasai surgery was 63 % in Group 1 and 61 % in Group 2 (ns). The incidence of the redo surgery was 28 % in Group 1 and 15 % in Group 2 ($p < 0.0001$). The JDRs after redo surgery were 34 and 36 % (ns) and the native liver jaundice-free survival rates were 57 and 55 % in Groups 1 and 2, respectively (ns). The overall survival rate was 90 % in Group 1 and 95 % in Group 2 ($p < 0.0001$) (Tables 1, 2).

The incidence of Kasai redo surgery was significantly reduced in Group 2. Furthermore, no significant difference was observed in the native liver jaundice-free survival rate between the two groups, but the overall survival rate was significantly higher in Group 2. These results may be attributed to the improved availability of early LTx and limited number of patients selected for the redo surgery.

The JDRs were essentially the same between the two groups. Although no obvious improvement in the Kasai surgery outcomes was achieved for this time period, improved availability of LTx in recent years did not affect the Kasai surgery outcomes. The reduction in the incidence of Kasai redo surgery by ~50 % may be explained by

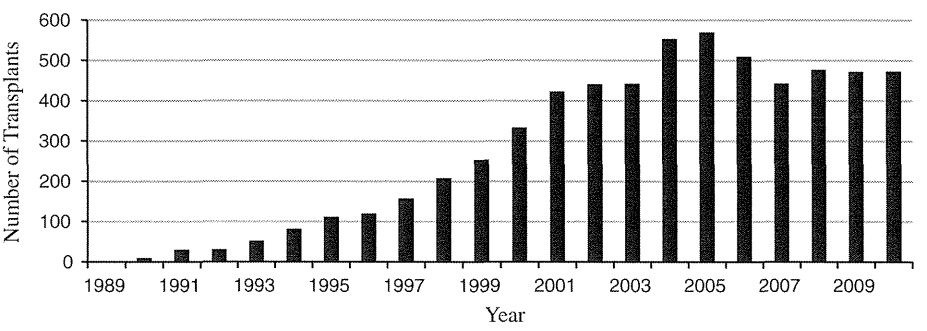

Fig. 1 Trend in the number of recipients of liver transplantation in Japan [20]. A total of 6,195 liver transplants were performed in 65 institutions in Japan until 2010. The number of recipients of liver transplantation markedly increased during the 1990s in Japan

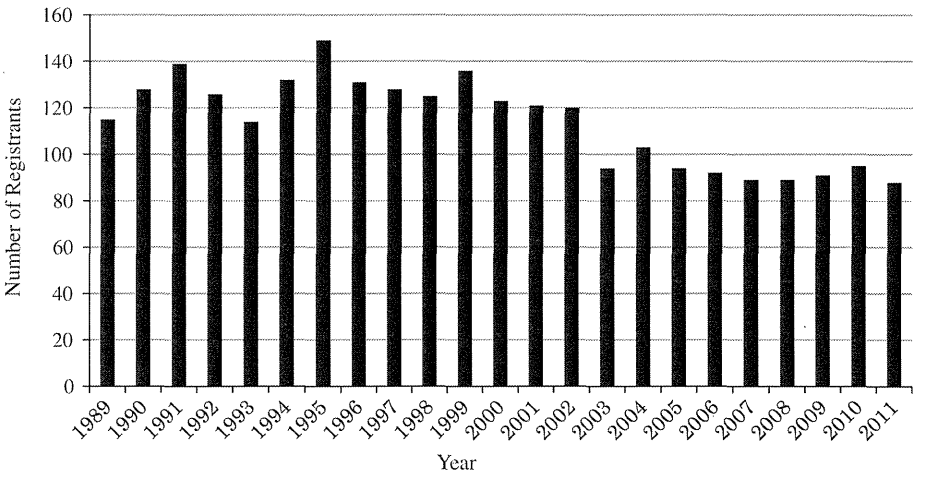

Fig. 2 Trend in the number of Japanese Biliary Atresia Registry (JBAR) registrants [21]. The number of Japanese Biliary Atresia Registry (JBAR) registrants in each year was between 110 and 150 before 2003 and approximately 90 in 2003 or later. A total of 2,630 patients were registered until 2011

Table 1 The initial surgery for registrants of Japanese Biliary Atresia Registry (JBAR) [21]

Period	1989–2011	1989–1999	2000–2011
Initial surgery			
Kasai surgery	2,598	1,415	1,183
LTx	15	2	13
Expl Lap	12	2	10
Not Performed	5	4	1

LTx liver transplantation, *Expl Lap* exploratory laparotomy

Table 2 Status of the registrants at initial registration to the Japanese Biliary Atresia Registry (JBAR) [21]

Period	1989–2011	1989–1999	2000–2011	*p*
N	2,630	1,423	1,207	
JDR % after the initial Kasai surgery	61	63	61	ns
Redo %	21	28	15	<0.0001
JDR % after redo	35	34	36	ns
NLJF survival %	56	55	57	ns
Overall survival %	93	90	95	<0.0001

JDR jaundice disappearance rate, *NLJF* native liver jaundice free

patient selection. However, if patients were appropriately selected, the JDR should have been considerably elevated. Good candidates for Kasai redo surgery may have missed their chance and directly undergone LTx. The issue of appropriate patient selection for redo surgery needs to be resolved.

In conclusion, a consensus has been obtained to some extent regarding the indications, optimal timing, and techniques of Kasai redo surgery, but further discussion is needed along with improvements in both the Kasai surgery and LTx outcomes. Currently, patients who develop sudden cessation of bile flow after achieving sufficient bile drainage following the initial Kasai surgery are the best candidates for Kasai redo surgery, and redo surgery is employed only once for this selective subset.

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ORIGINAL ARTICLE

Multicenter randomized trial of postoperative corticosteroid therapy for biliary atresia

Japanese Biliary Atresia Society · Masaki Nio · Toshihiro Muraji

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Abstract
Purpose We aimed to evaluate early response to two different corticosteroids doses after Kasai portoenterostomy for biliary atresia (BA).
Methods A prospective, randomized trial was performed in infants from the nationwide BA registry with type 3 BA. Sixty-nine infants were randomized to receive either 4 mg/kg/day (group A, $n = 35$) or 2 mg/kg/day prednisolone (group B, $n = 34$). The corticosteroids were started on postoperative day 7, and the dose was tapered toward day 30. Results of liver function tests on days 31 and 60 were compared between the groups.
Results Mean bilirubin, AST, ALT, and GGT levels did not significantly differ between the groups. However, the levels of total and direct bilirubin of infants <70 days old at surgery significantly differed between the groups. Four patients from group A and five from group B, dropped out of the study. Complications during the first month after PE were comparable between the groups.
Conclusions An initial 4 mg/kg/day dose did not significantly improve liver function, except that bilirubin levels were lower in the subgroup of infants <70 days old at surgery. There were no significant complications with either dose of corticosteroids.

Keywords Biliary atresia · Corticosteroid · Prospective randomized trial · CMV infection

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Introduction

Corticosteroids have been used empirically since many years in Japan for enhancing bile flow after Kasai portoenterostomy (PE) for biliary atresia (BA). The use of steroids was found in Kasai's early publication, in which the dose of prednisolone was 20 mg/day, which equated to approximately 4 mg/kg/day [1]. Karrer and Lilly [2] subsequently reported a more aggressive use of steroids. Multiple retrospective uncontrolled studies [3–8] showed that the administration of steroids after Kasai PE for BA was beneficial. Furthermore, in 2004, the Japanese Biliary Atresia Society (JBAS) performed a nation-wide retrospective survey involving postoperative steroid use [9] and reported that only marginally significant differences in native liver survival rates between patients receiving ≥4.0 mg/kg/day steroids and a non-steroid group. Complications were uncommon when steroid administration was started 1 week after surgery.

We conducted a prospective, multi-center, randomized trial at institutions registered to JBAS to test the hypothesis that postoperative administration of 4 mg/kg/day corticosteroids compared to a 2 mg/kg/day dose starting 1 week after Kasai PE would increase bile flow, and that this dose would facilitate alleviation of jaundice in the early postoperative period in a large proportion of infants. This paper summarizes our results and details the adverse effects

encountered during the study, which was conducted from July 2006 through August 2011.

Patients and methods

We included patients with type 3 (obstruction at the porta hepatis) BA. Patients with intrahepatic bile ducts visualized on operative cholangiography, so-called "correctable BA", were excluded because in the correctable cases, good bile drainage is often achieved without exogenous steroid administration. Postoperative prophylactic antibiotics were standardized: intravenous cephems and aminoglycosides for the first 2 weeks, followed by oral trimethoprim/sulfamethoxazole for the next 16 days. Ursodeoxycholic acid (20 mg/kg/day) was given from day 7. No other choleretics such as phenobarbital were administered.

CMV infection was a concern among some of Japanese pediatric surgeons. We have circulated guidelines for the diagnosis and recommended management of CMV infection during the steroid challenge. Briefly, the management guideline for CMV infection is as follows: (1) preoperative determination of CMV-IgM; (2) if negative, the study proceeds. Baseline determination of CMV in urine or quantification of CMV-DNA in blood before POD 7 is recommended for future reference; (3) if positive, initiation of ganciclovir is strongly recommended at the time of seroconversion with deterioration of liver function during the steroid challenge.

The parents of eligible patients were approached to participate in this study, either preoperatively or within a few days postoperatively. After informed consent was received from patients' parents, the patients were randomized by the JBAS office into two groups (Fig. 1): group A, receiving prednisolone at 4 mg/kg/day (divided in 2 doses) orally starting on the seventh postoperative day (POD) or intravenously if oral intake was not started, with dose tapered by 1 mg/kg/day every 5 days until POD 26 or group B, receiving prednisolone at 2 mg/kg/day, one dose orally starting on POD 7 or intravenously if oral intake was not started. This dose was tapered by 1 mg/kg/day every 7 days until POD 26. In both groups, the dose was 0.5 mg/kg/day from POD 27 to 30. The total dose was 52 mg/kg for group A and 29 mg/kg for group B. A subgroup analysis was also performed in those infants who were less than 70 days old at surgery ($n = 38$) between the same two different regimens as group A and B.

The primary outcomes were laboratory values for liver function tests at 1 and 2 months after surgery, including levels of serum total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl-transpeptidase (GGTP). Ethical approval for the study was obtained at individual institutional review board in each institution and written informed consent was obtained from parents or each patient's guardian before administration of steroids.

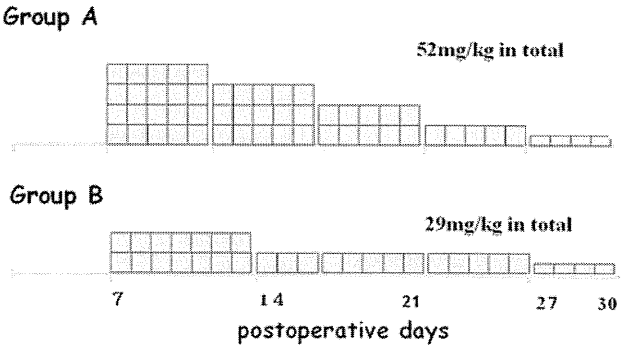

Fig. 1 Corticosteroid regimens in two groups. Corticosteroids were started from the seventh POD in both groups. Group A (*above*): 4 mg/kg/day for 5 days as an initial dose which was tapered every 5 days over the subsequent 3 weeks. A total dose is 52 mg/kg. Group B (*below*): 2 mg/kg/day for 7 days as an initial dose and a half dose was maintained over the subsequent 13 days. *One box* indicates 1 mg/kg/day. A total dose is 29 mg/kg

Before the study, a sample size was set based on the results of data analysis using sample cases from institutions wherein steroid regimen was identical to that of either group A or group B. Among the patients in the sample cases with preoperative serum bilirubin levels >7.0 mg/dL, the highest postoperative bilirubin level was 3.95 and the lowest level was 2.96, with a standard deviation of 2.15, at 1 month after surgery. Statistical analysis was performed using the Student t test with an α level of 0.05 and $1 - \beta = 0.8$. This suggested that 71 infants should be recruited into each arm of the trial. Categorical data were compared with Fisher exact test and nonparametric comparisons of liver function tests were performed with a Mann–Whitney test to assess the significance of differences. A difference was regarded as significant at $p < 0.05$.

Results

In total, 69 postoperative patients were randomized to receive an initial prednisolone dose of either 4 (group A) or 2 mg/kg/day (group B). Group A comprised 35 patients (male patients 14, female patients 21), with age at Kasai PE ranging from 21 to 153 days (median 63 days). Group B comprised 34 patients (male patients, 12; female patients, 22), with the age at Kasai PE ranging from 20 to 111 days (median 60 days). No differences were observed in the preoperative demographics between groups A and B (Table 1).

No differences were observed in the postoperative liver function tests between groups A and B. However, the mean levels of total bilirubin and direct bilirubin were

Table 1 Preoperative liver Function tests and age at Kasai portoenterostomy

	Group A ($n = 35$)	Group B ($n = 34$)	p
Age at Kasai operation (days)	63 (21–153)	60 (20–111)	NS
BASM	1	1	NS
Age at kasai operation <70 days	46 (21–63)	48 (20–67)	NS
t-/d- bilirubin (mg/dl)	9.0/5.2	8.3/5.4	NS
AST (IU/L)	118	163	NS
ALT (IU/L)	74	128	NS
GGT (IU/L)	480	452	NS

NS not significant, *BASM* biliary atresia splenic malformation

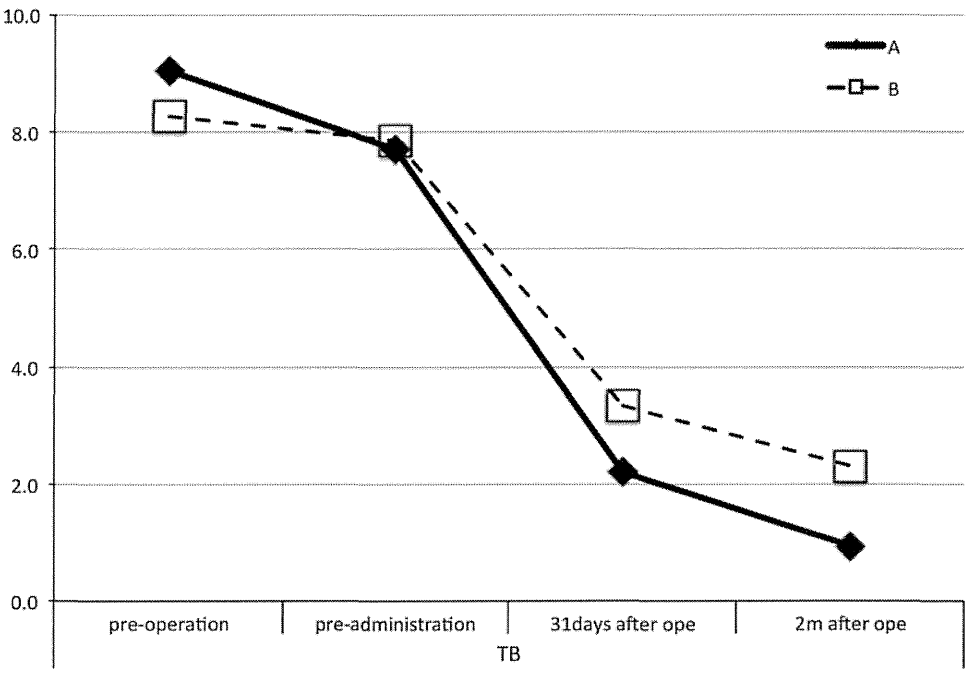

Fig. 2 Postoperative mean total bilirubin levels in subgroup A ($n = 15$, square, 4 mg/kg/day) versus subgroup B ($n = 23$, diamond, 2 mg/kg/day). The level were 2.2 versus 3.4 mg/dL at 1 month, $p = 0.04$ and 0.9 versus 2.3 at 2 months, $p = 0.013$)

significantly lower in subgroup A ($n = 15$) than in subgroup B ($n = 23$) at both 1 and 2 months, postoperatively. The total bilirubin levels were 2.2 versus 3.4 mg/dL at 1 month ($p = 0.0271$) and 0.9 versus 2.3 mg/dL at 2 months ($p = 0.0319$, Fig. 2). The direct bilirubin levels were 1.3 versus 2.2 mg/dL at 1 month ($p = 0.0275$) and 0.5 versus 1.5 mg/dL at 2 months ($p = 0.0190$, Fig. 3). No differences were observed in the other liver function test results. The mean values of the enzymes measured in postoperative liver function test did not differ significantly between the groups.

Nine patients dropped out of the study: four from group A, two because of ileus, one cholangitis, and one unknown reasons and five from group B, three because of increased dose, one cholangitis, and one gastrointestinal bleeding. Eight patients in group A and six in group B had postoperative cholangitis (Table 2).

Other complications included infections. Cytomegalovirus (CMV) infection was observed in two patients in group A on days 12 and 17, respectively, and in one patient in group B. All three cases of CMV infection were associated with liver dysfunction, but the patients were successfully treated with ganciclovir. Influenza A was observed in one patient from group A on day 41, while rotavirus infection was observed in another patient of the same group on day 13. This patient showed liver dysfunction that lasted for 7 days. One patient from group B patients developed *Candida* sepsis on day 57, which was treated with antibiotics and withdrawal of central line. One patient in group A had hypertension on day 9, with systolic pressure 120–140 mmHg that spontaneously returned to normal. Additionally, one patient from group A presented with moon face 3 weeks after surgery.

Discussion

We conducted a preliminary questionnaire regarding the design of this prospective study and we learned that a vast majority of Japanese pediatric surgeons currently use corticosteroids after Kasai operation [9] and they tend to think that setting up a non-steroid group is no more ethical and