4. 胆道閉鎖症

A 概念，疫学

胆道閉鎖症（biliary atresia：BA）は，胎児期から出生前後に肝外胆管が完全に閉塞して，胆汁排泄ができなくなり，重篤な病態をきたす．わが国では，BAは出生約10,000人に1人の頻度で，男女比約1：1.7と女児に多い[1]．

B 病　因

病因はまだ解明されておらず，いくつかの仮説が述べられている．ウイルス感染説，胆管板形成異常（ductal plate malformation：DPM）を含む発生異常説，免疫異常説，血行異常説などが提唱されている．単一な原因で生じるのではなく，いくつかの要因が重なり合って発生するという考え方もある．いずれも確定的な結論は出ていない．

C 症状，病態

黄疸，灰白色便（薄い便色），濃褐色尿（ビリルビン尿），肝腫大が主な症状である．便色は典型例で灰白色であるが，種々の程度に黄色調を示すことが多い．診断時，灰白色便を認める症例は約70％である．生後しばらく黄色便がみられ，灰白色便に変わる症例があることより，肝外胆道閉鎖が生後完成する症例もあることを示している．現在わが国では，胆道閉鎖症早期発見のため，便色カードを用いたスクリーニングを開始している．この便色カードは母子手帳に綴じ込まれており，保護者が便色を確認することで，胆道閉鎖症の早期発見に繋げている[2]．早期では肝はあまり硬く触れないが，病態が進行すると，肝腫大，硬度が増してくる．また，胆汁うっ滞に伴う脂肪吸収障害のため，脂溶性のビタミンKが欠乏する．その結果，頭蓋内出血をきたし，これを契機に発見される例もみられる．

D 検　査

a．血液・生化学検査

高直接ビリルビン血症を認める．ALP，LAP，γGTPなどの胆道系酵素，総胆汁酸が上昇する．AST，ALTも上昇するが，著しく高値となることはまれである．血清脂質では総コレステロール，リン脂質が上昇する．閉塞性黄疸のときに血清中に出現するリポプロテインXはほぼ全例で陽性となる．

b．胆汁排泄判定の検査

・十二指腸液検査：十二指腸内にカテーテルを挿入，十二指腸液を採取，胆汁の有無を調べる．
・肝胆道シンチグラフィ：肝胆道系からの核種の排泄を捉える検査である．

これらの検査で胆汁排泄が確認できれば，BAは否定できる．臨床的には，一般的にBAの診断は困難でないが，他の疾患と鑑別が困難な場合，開腹胆道造影および肝生検が施行される．

E 病　型

本症の肝外胆管の閉塞形態を記載するため，病型分類が用いられる．この分類では，基本型分類，下部胆管分類，肝門部胆管分類の3つの組み合わせで表現される（**図1**）[3]．

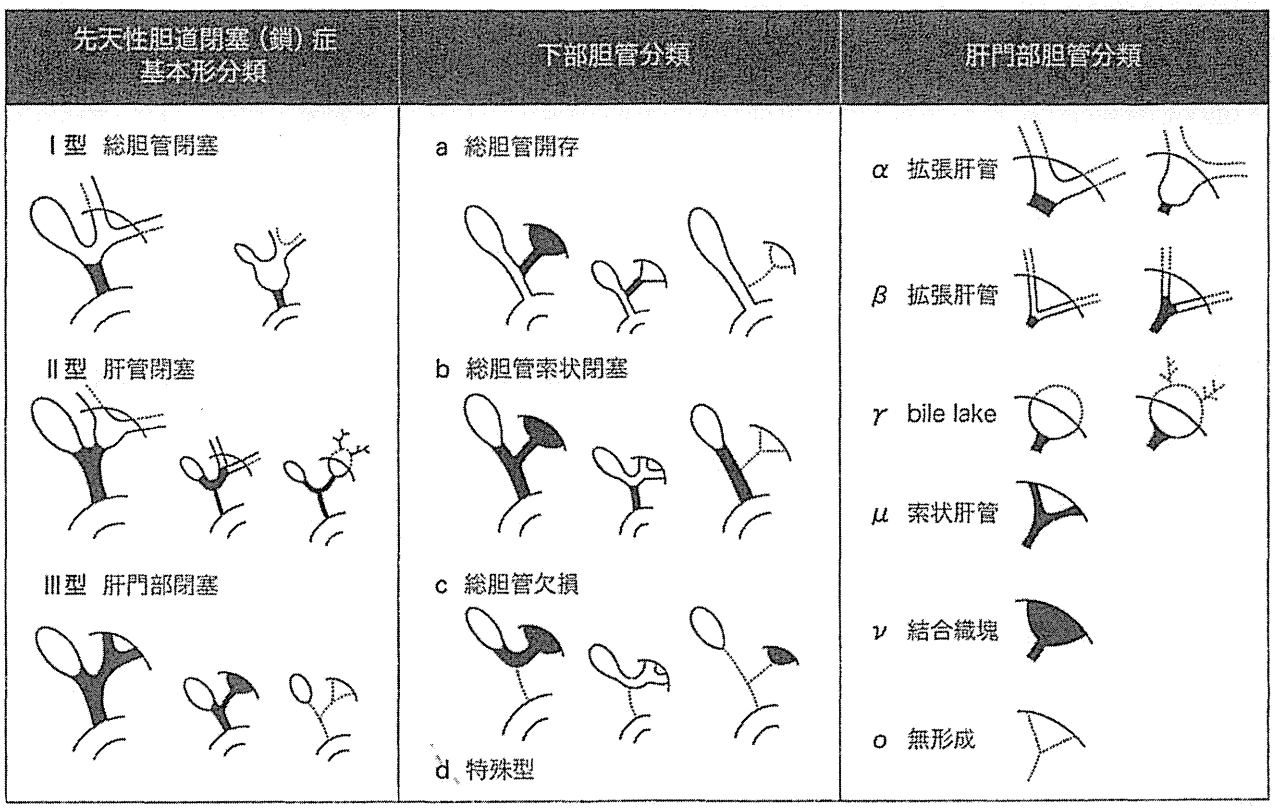

図1 胆道閉鎖症病型

［葛西森夫ほか：先天性胆道閉塞（鎖）症の新分類法試案．日小外会誌 12: 327-331, 1976 より引用］

基本型分類は，Ⅰ型（総胆管閉塞），Ⅱ型（肝管閉塞），Ⅲ型（肝門部閉塞）がある．Ⅰ型のうち，肝外胆管の拡張を伴う場合はⅠ cyst 型となる．

下部胆管分類は，総胆管の形態により，a（総胆管開存），b（総胆管索状閉塞），c（総胆管欠損），d（特殊型）がある．さらに，総肝管組織の有無により，それぞれ1（総肝管組織あり），2（総肝管組織なし）に分けられる．a～c の型に当てはまらないものは d の特殊型となる．

肝門部胆管分類は，α（拡張肝管），β（微小肝管），γ（bile lake），μ（索状肝管），υ（結合織塊），o（無形成）がある．

それぞれ，Ⅲ型が約 85%，b1 が約 60%，υ が約 65%であり，もっとも多い組み合わせは，Ⅲ-b1-υ となる．

F 病理組織所見

① 肝組織

肝組織には門脈域に不規則な線維性拡大が起こり，進行すると門脈域は相互に連結し，太い線維性架橋が形成される．小葉構築は改変し，胆汁性肝硬変の像を呈する．門脈域には様々な程度のリンパ球浸潤がみられる．好酸球の浸潤を伴うことが多い．門脈域辺縁には，BA の 20～40 % に DPM がみられる．門脈域周囲には細胆管増生が著明である．増生した細胆管は大小に拡張し，しばしば管腔内に胆汁栓がみられる．肝小葉には著明な胆汁うっ滞がみられる．とくに中心帯領域に高度である．肝細胞は多核巨細胞性変化を呈する．多核巨細胞は中心帯領域に目立つことが多い．類洞内には髄外造血が様々な程度でみられる（**図2～図4**）．

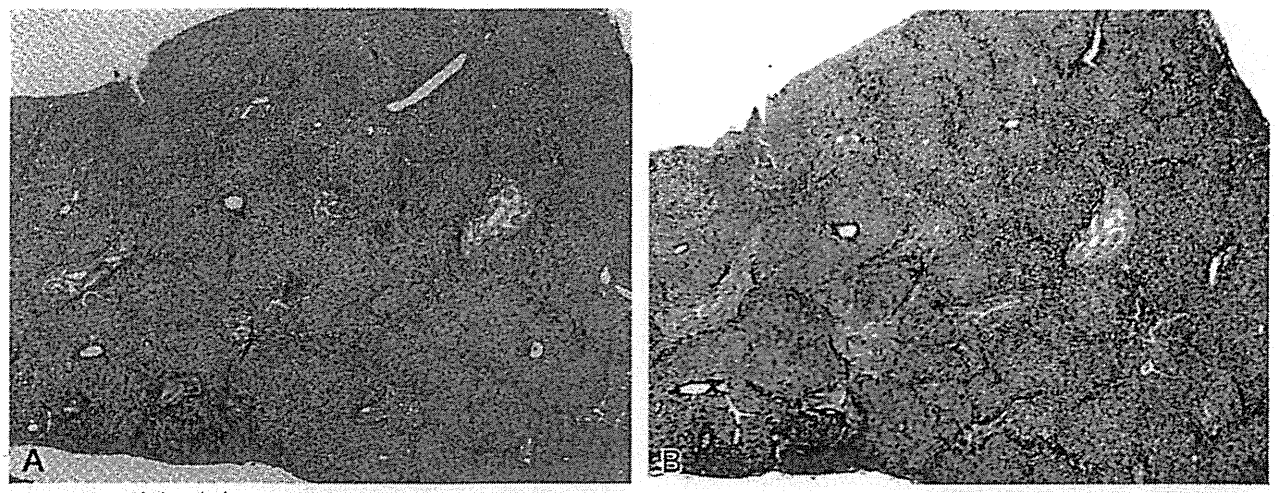

図2　HE染色（A），Azan染色（B）
弱拡像．門脈域は線維性に拡大，線維性架橋形成がみられ，小葉構築の改変傾向がみられる．

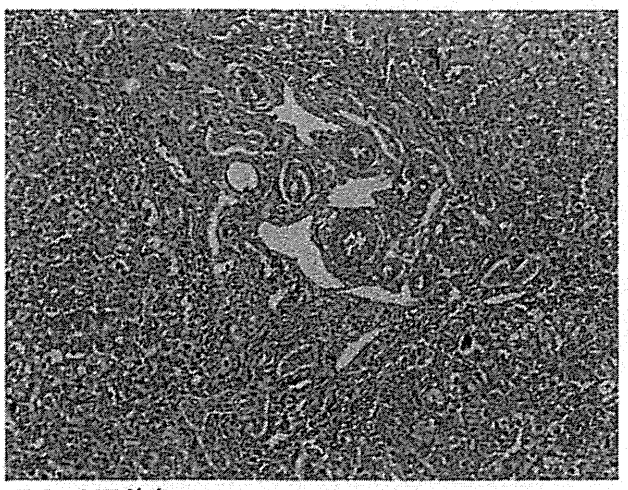

図3　HE染色
門脈域辺縁に胆汁うっ滞，細胆管の増生が目立つ．

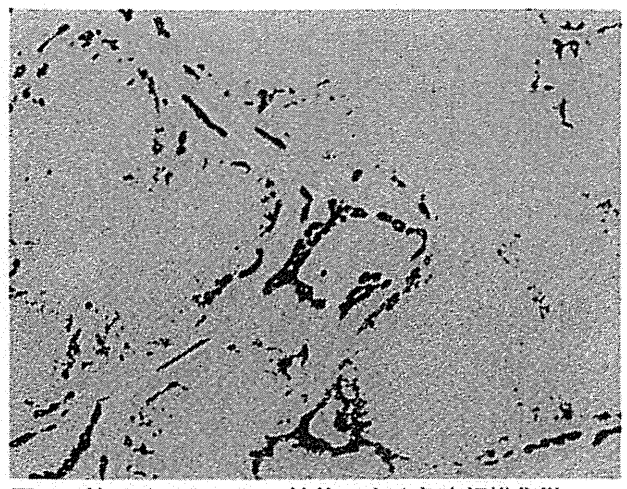

図4　抗サイトケラチン抗体による免疫組織化学
門脈域辺縁に細胆管の増生，DPMがみられる．

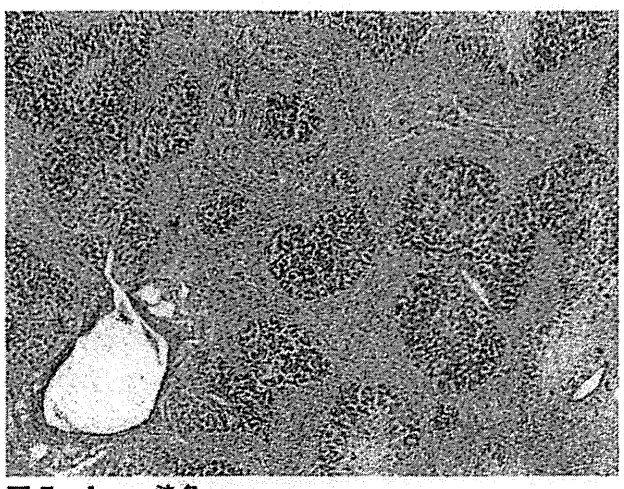

図5　Azan染色
剖検症例．太い線維性架橋形成がみられ，再生結節を形成している．

前述のように，病変が進行すると胆汁性肝硬変の像を呈し（**図5**），これに伴い小葉間胆管は傷害を伴う．胆管上皮配列の乱れ，胆管上皮の空胞形成，核濃縮・萎縮，胆管上皮内への炎症細胞浸潤がみられる．進行すると，胆管基底膜肥厚，胆管周囲線維化を伴い，胆管上皮の萎縮あるいは消失が起こる．最終的に小葉間胆管は消失する．また，門脈域の動脈は壁が肥厚し，門脈枝は狭小化する．

② 鑑別診断

a. 進行性家族性肝内胆汁うっ滞症2型

progressive familial intrahepatic cholestasis type 2

肝細胞巨細胞性変化・線維化は類似した所見である．BAでは，胆汁栓を伴う細胆管増生が非常に高度である．病期が進行すると，両者とも胆汁性肝硬変を呈し，鑑別は困難となる．

b. 肝内胆管減少症

paucity of intralobular bile ducts (PIBD)

肝細胞巨細胞性変化は共通の所見である．鑑別点は線維化，小葉間胆管の消失である．PIBDでは，小葉間胆管減少以外の組織変化は軽度である．BAでは，門脈域の線維性拡大，厚い線維性隔壁が形成される．進行したBAでは小葉間胆管の減少がみられる．また，肝巨細胞性変化はPIBDの方が軽度であることが多い．

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③ 肝外胆管閉塞部組織

肝門部の結合組織塊の組織所見は，線維化，炎症細胞浸潤を伴う瘢痕組織を主体とし，その中に径数十 μm から数百 μm の管腔様構造物が存在する．

索状になった肝管あるいは総胆管の組織所見も，線維化，炎症細胞浸潤を伴う瘢痕組織であり，管腔はまったく消失している．Ⅰ型やⅡ型において，開存している肝管は粘膜が脱落し，その壁は炎症細胞浸潤を伴い線維性に肥厚する．

G 予 後

① 肝線維化，肝門部結合組織塊

BAの肝病理組織像を主として肝線維化の程度によって分類し，予後との関連が検討されている．肝線維化は日齢とともに進行するが，手術日齢，線維化，病型は必ずしも相関しない．すなわち，症例ごとに肝病変の進行度に差があるということである．線維化を含めて，肝病変の進行した症例での治療成績は不良である．BAは，葛西手術なしでは多くが2歳までに胆汁うっ滞性肝硬変で死亡する．葛西手術は生後60日以内に施行されると予後が良好であるとされている．葛西手術で胆汁排泄は改善されるが，多くの症例では病状が緩徐に進行し，胆汁性肝硬変に至る．

肝門部の結合組織塊の病理組織学的所見と，葛西手術成績との関連が検討されている[4]．肝門部切離面に存在する最大胆管径によって，術後の胆汁流出量に関連があるといわれているが，関連がないという報告もある[5, 6]．また，最大胆管径には関連しないが，胆管様管腔構造物の総面積が関連するとの報告もある[7]．

② 術後合併症

葛西手術の成績が向上するとともに，成人期を迎える症例が増加してきている．それに伴い，長期合併症が問題となってきている．その代表的な問題点は，胆管炎，門脈圧亢進症（食道静脈瘤，脾機能亢進，肝肺症候群，門脈肺高血圧症）である[8]．

a. 胆管炎 *cholangitis*

胆管炎は葛西術後の重大な合併症の1つである．術後早期の胆管炎は胆汁排泄の著しい減少を招き，しばしば持続的な黄疸の原因となる．術後晩期の胆管炎合併症例で，とくに短期間に胆管炎を繰り返す場合には，背景に肝内胆管病変が存在することが多い．主な変化として，肝内胆管の拡張と肝内結石症が挙げられる．肝内胆管拡張や結石形成が肝両葉にびまん性にみられることもある．多発嚢胞を形成する症例は予後不良との報告もある．

b. 門脈圧亢進症 *portal hypertension*

本症術後の重要な晩期合併症のもう1つが門脈圧亢進症である．その中でもっとも頻度の高いのは食道静脈瘤と脾機能亢進症である．さらに，二次性肺血行異常として，肝硬変に続発して肺内動静脈シャントを形成する肝肺症候群と，肺高血圧

症を発症する門脈肺高血圧症がある．肝肺症候群は呼吸困難を訴え，チアノーゼ，太鼓ばち指を示すことが特徴である．コントラスト心エコーや肺血流シンチグラフィで診断される．門脈肺高血圧症は特徴的な症状や身体所見に乏しく，呼吸器症状が認められる頃にはすでに高度の肺高血圧症をきたしていることがある．

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5. その他（アラジール症候群）

A 概念，疫学

アラジール症候群（Alagille syndrome：AS）は，肝外胆道系が保たれているにも関わらず，肝内胆管の形成不全が認められる．また，本疾患群は胆管病変以外にも特徴的な顔貌，眼病変，脊椎異常，心血管系異常を伴う．ASは出生約7～10万人に1人の頻度で，性差はみられない．

B 病　因

ASの病因として，染色体20p12上にある*JAG1*の遺伝子の変異やNotchシグナル経路の異常との関連性が指摘されている[1-3]．これらの遺伝子は胆管発生に関与している．

C 症状，病態

a. 肝病変

多くは乳児期早期から胆汁うっ滞が出現し，黄疸，灰白色便を呈する．また，肝腫大，脾腫，皮膚掻痒，黄色腫がみられる．血液生化学検査では，直接ビリルビン，胆道系酵素（ALP，γGTPなど），総胆汁酸，総コレステロールなどが著明に上昇する．一般に黄疸は乳児期に高度で，それ以降で低下する傾向がある．

b. その他の病変

特徴的な顔貌（前額部突出，両眼離開，くぼんだ眼，尖った顎，鞍鼻など），眼病変（後部胎生環，網膜色素変性，網膜脈絡膜萎縮など），脊椎異常（蝶形椎体，椎弓欠損など），心血管系異常（末梢性肺動脈狭窄，大動脈狭窄，心室中隔欠損症など）が認められる．

D 病理組織所見（図1）

肝病理所見の特徴は，肝内胆管の減少，あるいは完全な消失である．肝組織内に存在する小葉間胆管数と門脈域総数の比（小葉間胆管数/門脈域数比＝B/P比）0.6以下（基準値は0.9～1.8）がASの診断基準となっている．ただし，生後6ヵ月未満では，胆管減少が明らかでないことがあり，診断に苦慮することもある．肝線維化の進行は緩徐で，肝硬変への進行例は少ないとされている．門脈域には炎症細胞浸潤はないか，あっても軽微であり，門脈域辺縁に細胆管増生がみられることがある．肝小葉には，軽度の肝細胞の巨細胞性変化，胆汁うっ滞がみられる．

また，最近の筆者らの検討では，AS症例に存在する小葉間胆管に変化が認められた．すなわち，

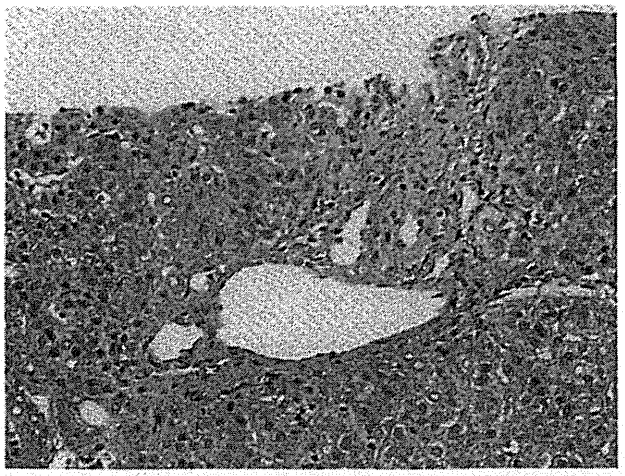

図1　HE染色
門脈域には明瞭な小葉間胆管が認められない．門脈域に炎症細胞浸潤は軽度である．動脈壁は肥厚が目立つ．
［症例は順天堂大学小児科 鈴木光幸先生のご厚意による］

小葉間胆管には不規則な管腔構造，胆管上皮細胞の配列の乱れなどがしばしばみられる．しかも小葉間胆管の変化のみならず，門脈狭小化，動脈壁肥厚も認められる．このような所見から，ASの肝病変の成因として，門脈の3つ組である胆管，門脈，動脈の形成異常が示唆される．

B 鑑別疾患

a. 胆道閉鎖症 *biliar atresia (BA)*

前項「胆道閉鎖症」を参照．まれに，ASで高度な線維化および細胆管増生を示し，BAの組織像に類似することがある．また，ASに肝外胆管の閉塞を合併することがあり[4]，BAと誤診されることがある．ASに肝門部空腸吻合術（葛西手術）を施行すると予後不良であるといわれている．

b. 進行性家族性肝内胆汁うっ滞症2型

progressive familial intrahepatic cholestasis type 2

前項「胆道閉鎖症」を参照．

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Stool Color Card Screening for Early Detection of Biliary Atresia and Long-Term Native Liver Survival: A 19-Year Cohort Study in Japan

Yan-Hong Gu, MD, MSc, PhD[1,2], Koji Yokoyama, MD[3], Koichi Mizuta, MD, PhD[4], Takashi Tsuchioka, MD, PhD[5], Toyoichiro Kudo, MD, PhD[6], Hideyuki Sasaki, MD, PhD[7], Masaki Nio, MD, PhD[7], Julian Tang, PhD[8], Takayoshi Ohkubo, MD, PhD[1], and Akira Matsui, MD, DMSci[6]

Objective To evaluate the sensitivity and specificity of a stool color card used for a mass screening of biliary atresia conducted over 19 years. In addition, the age at Kasai procedure and the long-term probabilities of native liver survival were investigated.

Study design From 1994 to 2011, the stool color card was distributed to all pregnant women in Tochigi Prefecture, Japan. Before or during the postnatal 1-month health checkup, the mothers returned the completed stool color card to the attending pediatrician or obstetrician. All suspected cases of biliary atresia were referred for further examination. Diagnosis was confirmed by laparotomy or operative cholangiography for high-risk cases before the Kasai procedure. Patients with biliary atresia were followed from the date of their Kasai procedure until liver transplantation, death, or October 31, 2013, whichever comes sooner.

Results A total of 313 230 live born infants were screened; 34 patients with biliary atresia were diagnosed. The sensitivity and specificity of stool color card screening at the 1-month check-up was 76.5% (95% CI 62.2-90.7) and 99.9% (95% CI 99.9-100.0), respectively. Mean age at the time of Kasai procedure was 59.7 days. According to Kaplan-Meier analysis, the native liver survival probability at 5, 10, and 15 years was 87.6%, 76.9%, and 48.5%, respectively.

Conclusions The sensitivity and specificity of the stool color card have been demonstrated by our 19-year cohort study. We found that the timing of Kasai procedure and long-term native liver survival probabilities were improved, suggesting the beneficial effect of stool color card screening. *(J Pediatr 2015;166:897-902).*

Biliary atresia is the most frequent hepatic cause of death in early childhood, with an incidence of 0.7 in 10 000, 0.6 in 10 000, and 0.5 in 10 000 live births in the US, UK, and France, respectively.[1-3] In Japan, the incidence is greater, affecting approximately 1.0 in 10 000 live births.[4] Biliary atresia is characterized by a complete inability to excrete bile as a result of sclerosing inflammation of the extra, and possibly intra, hepatic bile ducts.[5] Patients with biliary atresia have 3 main clinical features: pale-pigmented stools, prolonged jaundice, and dark urine. Pale-pigmented stools appears within the first month after birth for most patients, and 2-5 months for others.[4,6] Although there is strong evidence that biliary atresia develops before birth and progresses after birth, its etiology remains unclear. The Kasai procedure[7] commonly is used as a first-line treatment for all types of biliary atresia.[8,9]

Prognosis for patients with biliary atresia is primarily related to the patient's age at the time of Kasai procedure and the anatomy of the bile duct remnant.[8-10] It is generally acknowledged that a Kasai procedure performed early, especially one that is performed before the patient reaches 60 days of age, can improve the long-term native liver survival and reduces likelihood of liver transplantations.[10,11] In Japan, 66.1% of living-donor liver transplantations performed for recipients younger than 18 years of age were attributable to biliary atresia.[12]

Serinet et al[10] highlighted the importance of screening for biliary atresia. The concept of a stool color card for mass screening was introduced for the first time to the local population in Tochigi Prefecture by Matsui and Dodoriki in early 1994, which resulted in early Kasai procedure (<60 days of age) in 2 of 3 patients with biliary atresia.[13] Since then, the stool color card had been distributed in the prefecture until March 2011. Subsequently, the concept of stool color card for mass screening was adopted and used in Taiwan in 2002 and resulted in earlier referral of patients with biliary atresia nationwide.[14]

In this present study, we aimed to determine the sensitivity and specificity of stool color card screening during the 19-year period, as well as its effect on the

JBAR Japanese Biliary Atresia Registry

From the [1]Department of Hygiene and Public Health, Teikyo University School of Medicine; [2]Graduate School of Public Health, Teikyo University, Tokyo; Departments of [3]Pediatrics and [4]Transplant Surgery, Jichi Medical University; [5]Department of Surgery, Dokkyo Medical University, Tochigi; [6]Department of Hepatology, National Medical Center for Children and Mothers, National Center for Child Health and Development, Tokyo; [7]Department of Pediatric Surgery, Tohoku University School of Medicine, Miyagi; and [8]Department of Education for Clinical Research, National Center for Child Health and Development, Tokyo, Japan

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timing of Kasai procedure and long-term native liver survival in the Tochigi cohort.

Methods

Participants were all infants born to mothers living in Tochigi Prefecture, situated about 100 km north of Tokyo (**Figure 1**; available at www.jpeds.com), from August 1994 to March 2011. Infants born in Tochigi Prefecture to mothers who lived outside of the prefecture before giving birth were not included. Under the Maternal and Child Health Law in Japan acted since 1965, all children in the country go through the same postnatal health management.

The stool color card (3rd edition; **Figure 2**) was placed within the Maternal and Child Health Handbook that was given to all pregnant women by their respective local government according to the Maternal and Child Health Law in Japan. Before or during the infant's 1-month health checkup, the mothers were asked to fill in the corresponding number of the image on the stool color card (**Figure 2**) that most resembled the color of her infant's stool. The card was then submitted to the attending pediatrician or obstetrician. A positive result was defined as a stool color determined by the guardian that matched either image 1, 2, or 3 before or during the infant's 1-month health checkup.

The Department of Pediatrics at the Jichi Medical University in Tochigi Prefecture (as the stool color card office), Japan was notified of all positive cases as soon as possible by telephone or fax. All stool color cards were collected and sent to the stool color card office at Jichi Medical University on a weekly basis. At the office, the cards were rechecked to confirm whether all corresponding numbers were properly recorded and that positive cases had been properly attended to. At the initial phase (first 3 years), all staff was trained on how to manage positive cases detected by the stool color card.

Verbal informed consent was obtained from all participants. The study protocol was reviewed and approved by the Ethics Board of the National Center for Child Health and Development.

Patients with Biliary Atresia and Long-Term Follow-Up

For patients with positive stool color card results, the possibility of other types of infantile cholestasis was eliminated by a pediatric specialist or pediatric hepatologist through clinical, biochemical, radiologic, histologic, and genetic investigations when necessary. A final diagnosis for high-risk cases was determined by laparotomy and/or by operative cholangiography prior to Kasai procedure by a pediatric hepatologist or surgeon. None of the false positive cases underwent any invasive procedures. All patients with biliary atresia received Kasai procedure at the soonest possibility performed in accordance with the Japanese Society of Pediatric Surgeons classification.[15]

Patients with biliary atresia in Tochigi Prefecture received Kasai procedure and were followed up regularly by their respective hospital (across 8 medical centers). Long-term follow-up was possible because all Japanese residents are covered by at least 1 health insurance plan that allows access to any necessary procedures post-Kasai procedure.[16] In addition, pediatric patients with any of the 514 intractable chronic diseases (including biliary atresia), defined by Ministry of Health, Labour and Welfare of Japan, are supported by a medical aid program.[16] Postsurgical procedures in Tochigi Prefecture are consistent with those in other areas of Japan. To ensure that no patient with biliary atresia in Tochigi Prefecture was overlooked, the patient list in our study was compared with that of the medical aid program covering the 514 intractable chronic diseases.

For the investigation of native liver survival probabilities, patients with biliary atresia in this study were observed from the date of Kasai procedure until liver transplantations, death, or October 31, 2013, whichever occurred sooner.

Statistical Analyses

Four reference data sets were used: nationwide data during stool color card screening between 1994 and 2011 from the Japanese Biliary Atresia Registry (JBAR), nationwide data before stool color card screening between 1989 and 1994 from JBAR,[17] Tochigi Prefecture data before stool color card screening between 1987 and 1992,[4] and Tochigi Prefecture data before stool color card screening between 1989 and 1991[18] (**Table I**). To quantify uncertainty, 95% CIs were used. The records of approximately 80%-90% of nationwide patients with biliary atresia diagnosed in hospitals that are part of the Japanese Society of Pediatric Surgeons were documented in JBAR. All patients with biliary atresia in our study were registered in JBAR. According to the Act on the Protection of Personal Information, only statistical data and not individual data can be used. Student t test or one-sample t test was performed to compare age at Kasai procedure. Kaplan-Meier analysis and the log-rank test were used to estimate the native liver survival probabilities with age (in months) as the time scale. IBM SPSS Statistics 21 (IBM Corporation, Armonk, New York) was used for statistical analysis. $P < .05$ was considered statistically significant.

For analytical purposes, all 34 patients with biliary atresia were first considered as a whole (termed "all cases"), and then as 2 separate groups: patients identified using stool color chart and referred promptly (**Table I**).

Results

There were 313 230 live births in Tochigi Prefecture from August 1994 to March 2011 (**Figure 1**). We collected the stool color cards of 264 071 infants, yielding a return rate of 84.3% at the 1-month health check-up; 2014 showed a positive result, and 26 of them were diagnosed with biliary atresia. Finally, a total of 34 patients were diagnosed with biliary atresia in Tochigi prefecture during the study period. A patient with Alagille syndrome detected by the stool color card (stool color corresponding to image 2) at

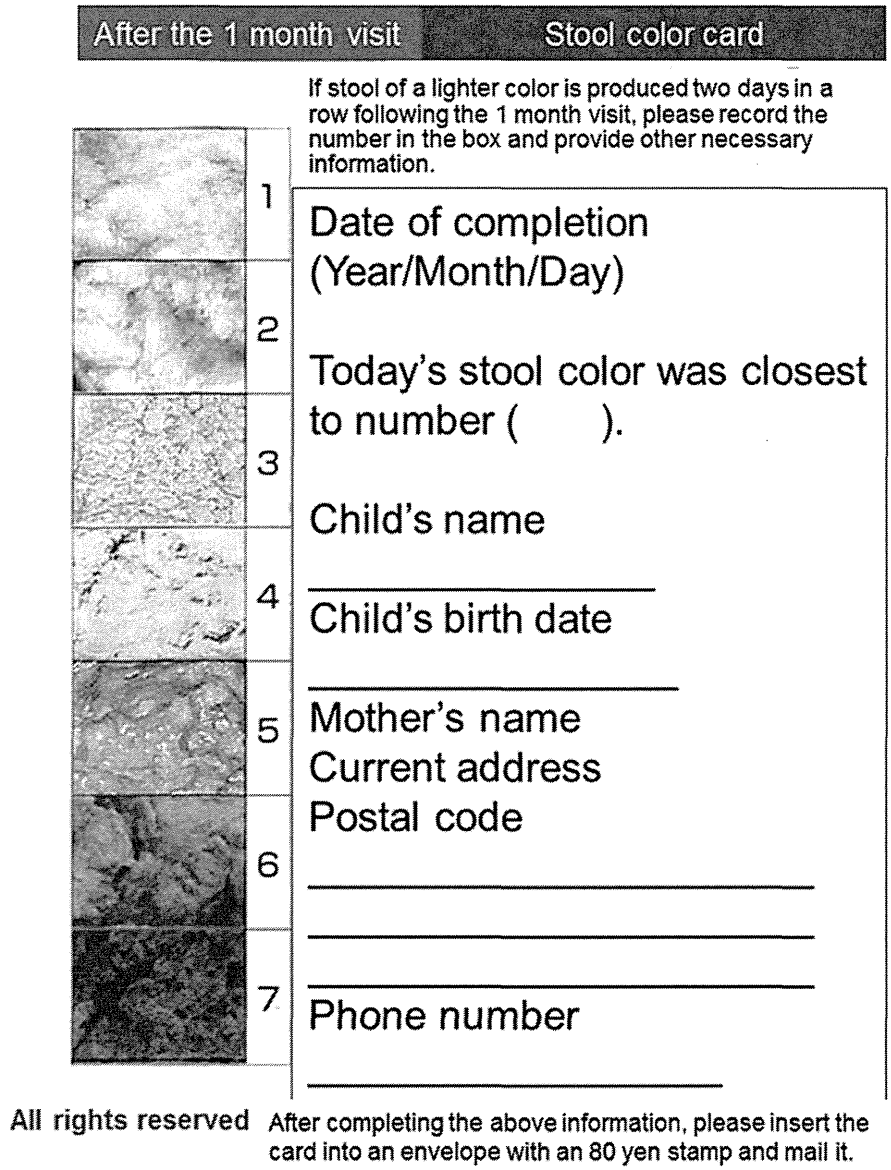

Figure 2. The 3rd edition stool color card used in Tochigi Prefecture from August 1994 to March 2011 consisted of 7 photographic images of stool color taken in both healthy infants and infants with biliary atresia. Images 1-3 denote abnormal stool color, whereas images 4-7 reflect normal stool color.

1-month health checkup was excluded. At the 1-month health checkup, the sensitivity, specificity, positive predictive value, and negative predictive value were 76.5% (26/34, 95% CI 62.2-90.7), 99.9% (313 018/313 196, 95% CI 99.9-100.0), 12.7% (26/204, 95% CI 8.2-17.3), and 99.9% (313 018/313 026, 95% CI 99.9-99.9), respectively. Incidence of biliary atresia was 1.1 in 10 000 infants (34/313 230, 95% CI: 0.7-1.5).

Among the 34 patients with biliary atresia, 8 were missed at the 1-month check-up (**Figure 1**). Of these patients, 2 (Patients 1 and 2) were in a neonatal intensive-care unit for more than a month after birth. Because their overall condition was poor, their guardians and the medical staff overlooked the presence of abnormal stool color. These 2 patients received Kasai procedure at 45 and 88 days of age, respectively. They did not undergo liver transplantations until October 2013. For 3 patients (Patients 3, 4, and 5), their guardians used the stool color card and reported pale-pigmented colored stool at the 1-month health checkup. However, no further examination was performed by their respective pediatricians because the infants did not present with visible jaundice. These 3 patients eventually underwent Kasai procedure at 62, 77, and 109 days after birth, respectively. Subsequently, Patients 3 and 5 underwent liver transplantations at 5 and 12 months of age, respectively. The guardian of 1 of the patients (Patient 6) failed to use the stool color card. The patient received Kasai procedure at 97 days of age and underwent liver transplantation at 72 months. One patient (Patient 7) did

Table I. Age at the time of the Kasai procedure in Tochigi cohort vs reference data, before and during stool color card screening

		Before stool color card screening		During stool color card screening	Tochigi stool color card cohort (August 1994-March 2011)		
	Year	Tochigi	JBAR	JBAR	All patients (N = 34)	Patients identified using stool color card and referred promptly (n = 30)	Patients with type III biliary atresia (n = 25)
Age at time of Kasai procedure, d							
Mean or mean ± SD	1987-1992[4]	70.3					
	1994-2011			67.7	59.7 ± 19.4*,†	56.2 ± 16.5‡,§	59.8 ± 19.1§,¶
	(1994-2002)			(67.8)			
	(2003-2011)			(67.6)			
Median (range)	1987-1992[4]	65.5					
	1994-2011			64.0	58.5 (18-109)	56.5 (18-88)	59.0 (18-109)
	(1994-2002)			(63.0)			
	(2003-2011)			(65.0)			
Number, % (95% CI)							
≤45	1989-1994[17]		18.9				
	1994-2011			20.4	8, 23.5 (9.3-37.8)	8, 26.6 (10.8-42.5)	6, 24.0 (7.3-40.7)
≤60	1989-1991[18]	34.0					
	1989-1994[17]		40.5				
	1994-2011			45.1	19, 55.9 (39.2-72.6)	19, 63.3 (46.1-80.6)**	14, 56.0 (36.5-75.5)
>80	1989-1994[17]		23.1				
	1994-2011			25.3	4, 11.8 (0.9-22.6)**,††	1, 3.4 (2.3-15.6)**,††	2, 8.0 (2.6-18.6)**,††
>90	1989-1991[18]	13.0					
	1989-1994[17]		15.1				
	1994-2011			16.2	2, 5.9 (2.0-13.8)**,††	0, 0.0**,††,‡‡	1, 4.0 (3.7-11.7)**,††,‡‡

*P = .023; ‡P = .001; ¶P = .000 vs JBAR data during screening (1994-2011), 1-sample t test.
†P = .003; §P = .000 vs Tochigi data before screening (1987-1992), 1-sample t test.
**P < .05 vs JBAR data during screening (1994-2011), ††P < .05 vs JBAR data before screening (1989-1994), and ‡‡P < .05 vs Tochigi data before screening (1987-1992).

not show abnormality at the 1-month health checkup. At 1.5 months of age, the patient's guardian noticed pale-pigmented stool and jaundice. The patient received Kasai procedure at 76 days of age and did not undergo liver transplantations. One patient (Patient 8) was not on our list but was later identified through the medical aid list. The patient received Kasai procedure at 66 days of age and did not undergo liver transplantations until October 2013. Therefore, with the exception of Patients 1, 2, 6, and 8, in which the usage of stool color card failed, 30 of the total 34 patients showed stool color changes around the time of the 1-month health checkup.

Demographic Data of Patients with Biliary Atresia

Among the 34 patients with biliary atresia, 11 (32.4%) were male and 23 (67.6%) were female. The numbers of patients who had type I, II, and III biliary atresia were 5 (14.7%), 1 (2.9%), and 25 (73.5%), respectively. The type of biliary atresia in 3 patients was unknown (8.8%). All patients with biliary atresia received Kasai procedure (1 patient with type I biliary atresia received hepaticojejunostomy, and all others received hepatoportoenterostomy).

Age at the Time of Kasai Procedure

The mean age at the time of Kasai procedure was 59.7 days in the 34 patients with biliary atresia (**Table I**). The percentage of Kasai procedure performed before 60 days of age was greater in patients with biliary atresia who were referred promptly after reporting of positive colors. The percentage of Kasai procedure performed after 80 days of age was significantly lower in the Tochigi cohort (**Table I**). The mean age ± SD of Kasai procedure for the 8 patients with biliary atresia who were missed at the 1-month checkup was significantly later compared with the other patients with biliary atresia (n = 26; 77.5 ± 20.4 days vs 54.3 ± 15.8 days; P = .002).

Long-Term Native Liver Survival Probabilities of Patients with Biliary Atresia

As of October 2013, 17 patients received liver transplants and 17 did not. One female patient died at 13 months without receiving a liver transplant. Kaplan-Meier survival analysis with the end point defined as liver transplant, death, or alive as of October 31, 2013, showed the native liver survival probability at 5, 10, and 15 years to be 87.6%, 76.9%, and 48.5%, respectively (**Table II**). The median survival estimated by Kaplan-Meier analysis is the earliest time at when the cumulative survival probability reached 50% or lower. In this study, the median native liver survival was 197.2 (95% CI 136.0-258.4), 207.9 (95% CI 184.6-231.3), and 212.5 (95% CI 146.7-278.4) months in all patients, patients who were referred promptly upon reporting of positive color, and patients with type III biliary atresia, respectively. There was no significant

Table II. Kaplan-Meier analysis of native liver survival at 5, 10, 15, and 20 years in the present study and previous reports

Countries	No. teams/ medical centers	Stool color card	Period	Study design	No. patients	Rate of native liver survival % (SE), y			
						5	10	15	20
Yokohama, Japan[19]	1	No	1970-1986	RCR	80	63.0	54.0	-	44.0
Sendai, Japan[20]	1	No	1975-1980	RCR	60	60.0	60.0	58.0	-
			1981-1986		50	68.0	60.0	51.0	-
US[21]	2	No	1972-1996	RCR	266	49.0	-	-	-
UK[22]	3	No	1999-2009	RCR	443	46.0 (95% CI 41-51)	40.0 (95% CI 34-46)	-	-
France[23]	45	No	1986-2009	RCR	1044	40.0 (1.6)	35.8 (1.6)	32.1 (1.7)	29.6 (2.0)
France[10]	27/45	No	1986-2002	RCR	695	37.9 (2.0)	32.4 (2.0)	28.5 (2.3)	-
Present study	8	Yes	1994-2011	Cohort study					
All patients with biliary atresia					34	87.6 (0.06)	76.9 (0.08)	48.5 (0.11)	-
Patients identified using the stool color card and referred promptly					30	89.6 (0.06)	77.6 (0.08)	55.5 (11.1)	-
Patients with type III biliary atresia					25	86.8 (0.07)	70.5 (0.10)	50.4 (0.12)	-

RCR, retrospective chart review in medical center(s).
In this study, the period of native liver survival was from the point of Kasai procedure until liver transplantation, death, or October 31, 2013, whichever occurred sooner.

difference across the 3 aforementioned groups mentioned on the basis of the log-rank test ($P > .05$).

Discussion

We have conducted a 19-year Japanese cohort study for screening of biliary atresia using the stool color card. The high stool color card sensitivity and specificity achieved are likely to have contributed to more patients with biliary atresia being diagnosed earlier, leading to a timely Kasai procedure. Accordingly, long-term native liver survival probabilities were improved. Serinet et al[10] reported that if every patient with biliary atresia were to undergo the Kasai procedure before 46 days of age, 5.7% of all liver transplantations performed annually in France in patients younger than 16 years could be spared.

In our cohort, the 5-, 10-, and 15-year native liver survival probabilities (**Table II**) were greater compared with studies conducted in US,[21] the UK,[22] and France,[10,23] where stool color card was not used. Notably, the 5- and 10-year native liver survival probabilities increased by more than 20% during 1994-2011 compared with studies conducted in the Japanese cities of Yokohama and Sendai where stool color card was not used (**Table II**).[19,20] The 15-year native liver survival probability estimated by Kaplan-Meier analysis in the Sendai patients was 51%-58% between 1975 and 1986[20] (**Table II**), which is greater than what we found in this study. It might be attributable to the data being collected from a single, highly specialized center, whereas our data were collected from 8 centers.

There are 2 other reports of long-term native liver survival rates in Japanese patients with biliary atresia. Notably, the method for the calculation of native liver survival and/or subjects selected in those studies was different from this study. In our case, we did not consider whether jaundice appeared or not after Kasai procedure. On the basis of JBAR data of 1989, Nio et al[24] reported the 5-year native liver survival rate was 62.0% in 735 patients who did not undergo liver transplantations, and 19 (2.6%) of patients were lost to follow-up. The 10-year native liver survival rate was 52.8% (57/108). The authors also found that when the Kasai procedure was performed at age of <60, 61-90, 91-120, and >120 days among patients with type III biliary atresia registered between 1953 and 2009 whose jaundice disappeared after Kasai procedure, the 10-year native liver survival rate was 74.4% (32/43), 74.5% (41/55), 100.0% (6/6), and 33.3% (1/3), respectively.[11]

Although the stool color card has been adopted and used in Taiwan,[14] Argentina,[25] and Switzerland,[26] the outcome was only reported in Taiwan, where the 5-year native liver survival rate (without jaundice) was 64.3% (18/28).[27]

According to JBAR data, the mean and median age at Kasai procedure was not significantly different between the periods of 1994-2002 and 2003-2011 (**Table I**), suggesting that the management of patients with biliary atresia did not change drastically over the years. Hence, the improvement of the probability of native liver survival revealed in this study is likely to be attributable to the younger age at Kasai procedure as a result of stool color card usage.

Although data of patients who did not use stool color card were available in JBAR, we could not access them because of the restriction imposed by the Act on the Protection of Personal Information. As such, the associations between stool color card usage/early Kasai procedure and the probability of long-term native liver survival cannot be statistically analyzed.

On the basis of our results in Tochigi Prefecture, the stool color card was gradually introduced to 16 other autonomous administrative divisions in Japan between 1999 and 2010. However, only patients from 2 of the regions were followed up. Nonetheless, the mean age of Kasai procedure after the introduction of stool color card was found to be significantly younger in those regions,[28,29] demonstrating excellent reproducibility and effectiveness of the stool color card.

In April 2012, a nationwide biliary atresia screening using an updated edition of the stool color card was initiated. In addition, a pilot study was launched in October 2013 in Beijing, China. The new edition of stool color card consists of digital photographic images to ensure quality control and

greater reproducibility. A modified screening protocol has also been devised. Instead of a single inspection point, the stool color card is now being inspected at 3 intervals; 2 weeks, 1 month, and 1-4 months after birth, allowing us to identify more patients with biliary atresia.

On the basis of our 19-year experience of stool color card usage in the Tochigi Prefecture cohort, the effectiveness of the stool color card, a non-invasive technique, was demonstrated. In particular, the stool color card was beneficial for patients with biliary atresia whose jaundice was not obvious. However, we are aware that the distribution of the stool color card in the community alone is not sufficient to achieve earlier detection of biliary atresia. Proper usage of the stool color card by guardians coupled with a sound knowledge of biliary atresia among healthcare personnel is essential. ■

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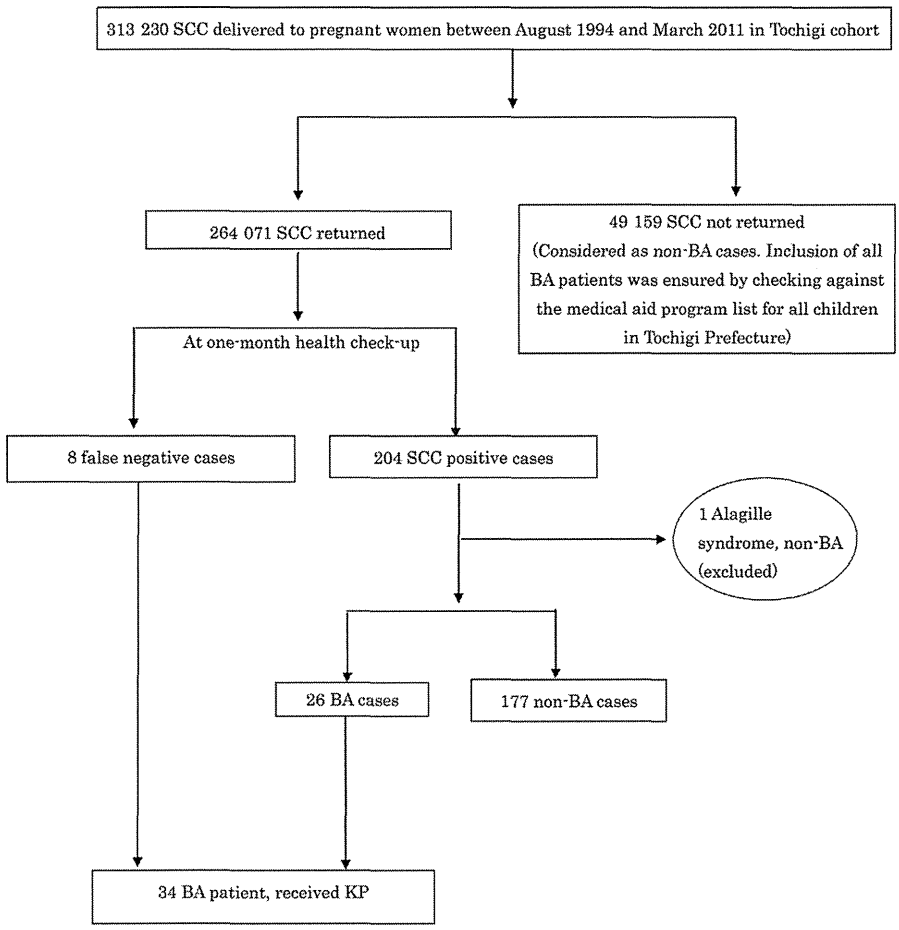

Figure 1. The flowchart for stool color chart screening. The numbers of participants, positive cases, false-negative cases, patients with biliary atresia in the Tochigi cohort from August 1994 to March 2011. *BA*, biliary atresia; *KP*, Kasai procedure; *SCC*, stool color card.

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Original Articles

Postnatal management of prenatally diagnosed biliary cystic malformation

Hiromu Tanaka, Hideyuki Sasaki, Motoshi Wada, Tomoyuki Sato, Takuro Kazama, Kotaro Nishi, Hironori Kudo, Megumi Nakamura, Masaki Nio *

Department of Pediatric Surgery, Graduate School of Medicine, Tohoku University, Sendai, Japan

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ABSTRACT

Purpose: Recent advances in ultrasonography have increased prenatal diagnosis of biliary atresia (BA) and choledochal cyst (CC). These conditions are not easy to distinguish before or just after birth. This study investigated diagnostic and therapeutic problems in prenatal diagnosis of BA and CC.

Methods: We retrospectively studied clinical characteristics and progression of hepatobiliary cysts in 10 patients (4 cases of BA, 6 cases of CC) from the time of diagnosis. Chronological changes in cyst size and gallbladder morphology were assessed and measured sequentially by ultrasonography.

Results: Three cases of BA were type I cyst and 1 case was type III-d. All cases of CC were type Ia. Cyst size decreased between birth and surgery in BA but increased in CC. The gallbladder appeared atrophic in BA. There was no significant difference in gestational age or cyst size at prenatal diagnosis, changes in cyst size between birth and surgery, and degree of liver fibrosis.

Conclusions: BA should be suspected if cyst size decreases before and after birth and the gallbladder atrophies after birth. Cholangiography is the only reliable method to differentiate BA from CC. Neonatal surgery is indicated for CC with icterus and liver dysfunction.

Recent advances in ultrasonography have increased prenatal diagnoses of biliary atresia (BA) and choledochal cyst (CC). The Japanese Biliary Atresia Society classifies biliary cystic malformations in BA as either type I cyst (correctable) or type III-d [1]. In type I cysts, atresia of the distal common bile duct accompanies cystic dilatation. Type III-d BA shows atresia of the bile duct at the porta hepatis, with a solitary cyst in the fibrous remnant. Patients with untreated BA progress to irreversible cirrhosis and death. In contrast, the optimal time for prenatal diagnosis and treatment of CC has not been established. A previous study reported that delayed surgery results in liver fibrosis [2–4]. It is important to distinguish between prenatally diagnosed BA and CC as soon as possible and to institute appropriate treatment in response to each pathological condition, after birth. In this study, we analyzed prenatally diagnosed biliary cystic malformations and investigated the postnatal management and points of differential diagnosis.

1. Materials and methods

Hepatobiliary cysts were prenatally detected in 10 cases with biliary cystic malformation (4 cases of BA and 6 cases of CC) from 1991 to 2012. All patients were female. BA and CC were eventually distinguished and the type of BA was determined based on surgical findings and intraoperative cholangiography. We retrospectively investigated and analyzed gestational age (GA) at prenatal diagnosis, cyst size at prenatal diagnosis, chronological change in cyst size, GA and body weight at birth, gallbladder morphology, direct bilirubin (D-bil), γ-glutamyltransferase (G-GTP) level, stool color, disease type, age at surgery, degree of liver fibrosis, progression of disease, and outcome.

Cyst size was assessed and sequentially measured by ultrasonography (US). Patients were classified into 3 groups according to the degree of change in cyst size from baseline (at diagnosis or birth) to assessment (at birth or operation): reduction group (<90% of baseline cyst size, D group), the no change group (<110% but >90% of baseline cyst size, NC group), and the expansion group (>110% of the baseline cyst size, U group).

Gallbladder findings were classified into 2 groups: atrophic, where the gallbladder was either absent or small, and normal, where the lumen of gallbladder was detectable by postnatal sonography.

We measured D-bil (mg/dl) and G-GTP (U/l) from birth to operation. G-GTP levels vary with age, sex, and assay methods. In this study, we defined a normal G-GTP level as 100 U/l, which is twice the upper range for adults.

Intraoperative cholangiography was performed, via the gallbladder and common bile duct, to distinguish BA from CC. Patients diagnosed with BA were classified according to the classification of the

* Corresponding author at: Department of Pediatric Surgery, Graduate School of Medicine, Tohoku University, 1–1 Seiryo-machi, Aoba-ku, Sendai 980–8574, Japan. Tel.: +81 22 717 7237; fax: +81 22 717 7240.
E-mail address: mnio@ped-surg.med.tohoku.ac.jp (M. Nio).

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Japanese Biliary Atresia Society [1]. Patients with CC were classified according to the classification reported by Todani et al. [5].

Liver biopsies were performed intraoperatively. Specimens were fixed in formalin and stained with hematoxylin-eosin and elastica-Goldner stains, and the degree of liver fibrosis was assessed. We scored the degree of liver fibrosis according to the new Inuyama classification as F0 (no fibrosis), F1 (fibrous portal expansion), F2 (bridging fibrosis), F3 (bridging fibrosis with architectural distortion), and F4 (liver cirrhosis) [6]. This classification is used to define the underlying liver status and can separately assess the degree of fibrosis and the grade of necroinflammatory activity [6,7].

Change in cyst size, GA, body weight at birth, and age at surgery were expressed as means ± SD. The Mann–Whitney *U* test was used for statistical analysis of continuous data, and the chi-square test was used for categorical data. A value of $P < 0.05$ was considered statistically significant.

The institutional review committee approved this study. Informed consent was obtained in all cases.

2. Results

2.1. GA at prenatal diagnosis

The 4 cases of BA were diagnosed between 21 and 28 weeks (median, 25 weeks), and the 6 cases of CC were diagnosed between 20 and 37 weeks (median, 32 weeks). The mean GA, at the time of prenatal diagnosis, was less in the BA patients than in the CC patients, but the difference was not statistically significant (Table 1).

2.2. Sonographic cyst morphology

2.2.1. Prenatal cyst morphology

Mean cyst size at prenatal diagnosis was 19.5 ± 7.9 mm (median, 20 mm) in the BA group and 13.0 ± 5.4 mm (median, 12 mm) in the CC group. This difference was not statistically significant.

In 7 cases (4 BA and 3 CC), the chronological change in prenatal cyst size was examined at birth and the prenatal stage. In the BA group, 2 cases were NC, 2 cases were D, and none were U (Table 2). In contrast, in the CC group, 2 cases were U and 1 case was NC (Table 2). Cyst size appeared to decrease or remain unchanged between prenatal diagnosis and birth in BA patients, but expanded in CC patients. However, this difference was not statistically significant.

2.2.2. Postnatal cyst morphology

Mean cyst size at birth was 18.8 ± 10.1 mm (median, 17.5 mm) in the BA group and 26.0 ± 6.3 mm (median, 24 mm) in the CC group. The difference was not statistically significant.

In 9 cases (4 BA and 5 CC), the chronological change in prenatal cyst size was examined both at surgery and at birth. In the BA group, 2 cases were D, 2 cases were NC, and none were U (Table 2). In contrast, in the CC group, 4 cases were U and 1 case was NC (Table 2). Cyst size between birth and surgery decreased in BA patients and expanded in CC patients, a statistically significant difference ($P = 0.043$).

Table 1
Patient characteristics.

Case	Type	Gestational age at prenatal diagnosis (weeks)	Cyst size at prenatal diagnosis (mm)	Gestational age at birth (weeks)	Birth weight (g)
BA 1	I cyst	26	18	37	2610
BA 2	I cyst	24	22	37	2900
BA 3	III-d	21	8	39	3243
BA 4	I cyst	28	30	38	3194
CC 1	Ia	34	NA	39	2942
CC 2	Ia	30	12	41	2760
CC 3	Ia	29	NA	40	2754
CC 4	Ia	35	NA	37	2276
CC 5	Ia	37	20	39	2890
CC 6	Ia	20	7	38	2666

NA, not available.

Table 2
Preoperative findings.

Case	Change in cyst size (%)		Stool color	Gallbladder
	At birth*	At surgery**		
BA 1	79.4	93.3	Yellow	Atrophic
BA 2	90.9	105.0	Yellow	Atrophic
BA 3	75.0	1.6	Yellow → gray	Atrophic
BA 4	100.0	76.5	Yellow → gray	Normal
CC 1	NA	137.1	Yellow	Normal
CC 2	150.0	145.0	Yellow	Normal
CC 3	NA	129.6	Yellow → gray	Normal
CC 4	NA	NA	Yellow	Normal
CC 5	100.0	100.0	Yellow	NA
CC 6	175.2	170.8	Yellow	Normal

NA: not available.
* Size % compared to the size at prenatal diagnosis.
** Size % compared to the size at birth.

2.3. GA and body weight at birth

Mean GA at birth was 37.8 ± 0.8 weeks (median, 37.5 weeks) in the BA group and 39.0 ± 1.3 weeks (median, 39.0 weeks) in the CC group. The mean GA at birth was less in the BA patients than in the CC patients, but the difference was not statistically significant. Mean body weight at birth was 2986 ± 254 g (median, 3047 g) in the BA group and 2714 ± 216 g (median, 2757 g) for the CC group (Table 1), but the difference was not statistically significant.

2.4. Postnatal gallbladder morphology

Among BA patients, the gallbladder was atrophic in 3 cases (absent in 1 and no lumen detected in 2) and normal in 1 case. In contrast, the gallbladder morphology was normal in 5 cases of CC (Table 2). The difference between groups was statistically significant ($P = 0.018$).

2.5. Change in stool color

Stool color at birth was yellow in all cases. In 2 BA cases (50%) and 1 CC case (16.6%), the stool turned gray before surgery (Table 2). This difference was not statistically significant. Stool color gradually became gray in 2 cases of BA. One CC patient developed acholic stool and icterus suddenly at the age of 47 days and underwent surgery at 63 days of age.

2.6. Laboratory data

Mean value of D-bil was measured from birth until the fifth week. Mean value of D-bil was persistently increased in BA but not in CC (Fig. 1). Of the 4 BA patients, cases 3 and 4 showed preoperative elevation of D-bil, whereas cases 1 and 2 showed no elevation (Fig. 2).

Chronological changes in G-GTP levels were measured in 9 cases (4 BA and 5 CC) between birth and surgery. All BA cases had elevated G-GTP at birth, but the level of G-GTP decreased until surgery ($P = 0.034$) (Fig. 3). In contrast, case 3 in the CC group was icteric during follow-up, with G-GTP exceeding 1700 U/l, whereas other CC cases showed various inconsistent patterns (Fig. 3).

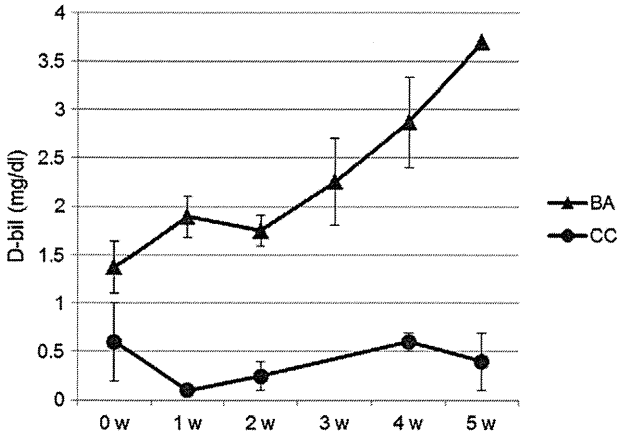

Fig. 1. Change in D-bil level. Comparison of mean D-bil in BA and CC groups over first 5 postnatal weeks. Mean Dbil increased continuously between birth and 5 weeks of age in BA patients. D-bil was not increased in CC patients.

2.7. Intraoperative findings

Mean age at surgery was 35.0 ± 14.9 days (median, 38 days) in the BA group and 99.8 ± 48.7 days (median, 86.5 days) in the CC group (Table 3). The difference was not statistically significant.

In the BA group, 3 cases were type I cysts, and 1 case was type III-d according to the classification of the Japanese Biliary Atresia Society [1]. Hepatic portojejunostomy (HP-J) was performed in 3 BA cases (type I cyst in 2, type III-d in 1), and hepaticojejunostomy (H-J) was performed in 1 BA case (type I cyst). In the CC group, all cases were type Ia according to the classification reported by Todani et al. [5]. H-J was performed in all CC cases (Table 3). In case 3 in the BA group, the cyst size gradually decreased during gestation and the intrahepatic and extrahepatic bile duct were visualized on cholangiography at 21 days after birth. When cholangiography was repeated at 48 days after birth, the cyst had become type III-d.

2.8. Degree of liver fibrosis

In the BA group, 2 cases (50%) were F1, and 2 (50%) were F2. In contrast, in the CC group, 4 cases were F0 (66.7%), and 2 were F1 (33.3%) (Table 3). The degree and occurrence of liver fibrosis were higher in BA patients than in CC patients, but the difference was not statistically significant.

2.9. Postoperative course and outcome

Cholangitis occurred in the early postoperative period or the fifth month after surgery in 2 cases of BA. In the CC group, cholangitis did not occur within 1 year after surgery. However, case 4 in the CC group experienced cholangitis twice during the extended postoperative period (Table 3). The difference in the occurrence of cholangitis was not statistically significant.

At the time of writing, the average patient age was 2 years 8 months ± 2 years 3 months (median, 2 years 2 months) in the BA group and 15 years 1 month ± 6 years 9 months (median, 18 years 3 months) in the CC group. All patients were alive and were not icteric.

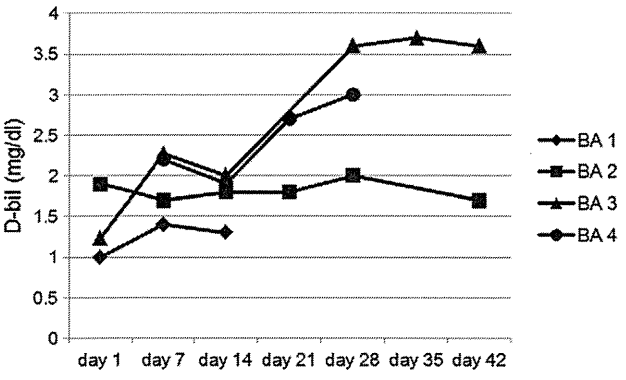

Fig. 2. Change in D-bil in the BA group. Changes in preoperative D-bil in 4 BA patients. D-bil level increased in cases 3 and 4, but remained unchanged in cases 1 and 2.

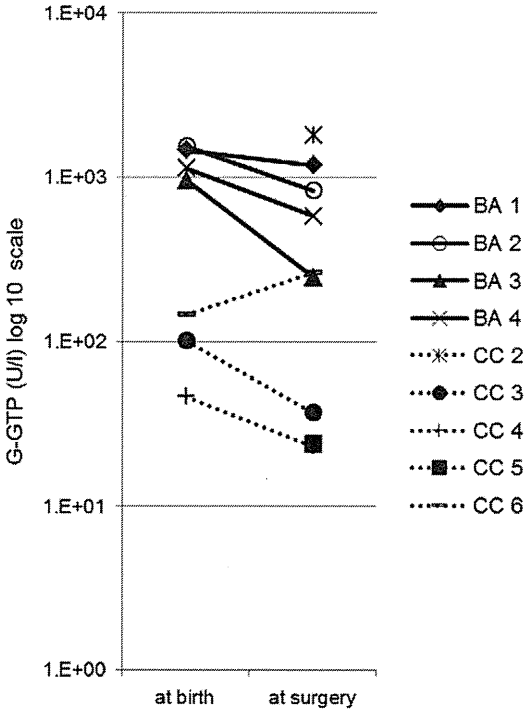

Fig. 3. Change in G-GTP in the BA and CC group. Chronological changes in G-GTP level in 9 cases (4 cases of BA and 5 cases of CC) between birth and surgery, expressed as common logarithms. In the BA group, elevated levels of G-GTP at birth decreased significantly between birth and surgery ($P = 0.034$). Case 3 in the CC group was icteric during follow-up with G-GTP exceeding 1700 U/l. Other CC cases showed inconsistent variations.

3. Discussion

Recent advances in ultrasonography enable prenatal identification of BA and CC with increasing frequency [8,2]. It is not easy to distinguish BA from CC before or just after birth [9]. Some cases are often treated as CC, although the actual diagnosis is BA. Although surgery was performed within 2 months after birth in all 4 BA cases

Table 3
Intraoperative findings and postoperative courses.

Case	Age at surgery (days)	Procedure	Liver fibrosis	Episodes of cholangitis
BA 1	14	HP-J	F1	Yes
BA 2	50	HP-J	F1	No
BA 3	48	HP-J	F2	Yes
BA 4	28	H-J	F2	No
CC 1	42	H-J	F0	No
CC 2	105	H-J	F0	No
CC 3	63	H-J	F1	No
CC 4	137	H-J	F0	Yes*
CC 5	184	H-J	F0	No
CC 6	68	H-J	F1	No

HP-J, hepatic portojejunostomy.
H-J, hepaticojejunostomy.
* Cholangitis as a late complication.

presented here, we believe that surgery should be performed during the neonatal period and treatment started as soon as possible.

Prenatal differential diagnosis of BA and CC has been achieved on the basis of changes in cyst size [10], chronological changes in cyst size, cyst patterns [11], or timing of expression [12], but no definitive index exists. Because we assessed chronological changes in prenatal cyst size in a small number of cases, the difference was not statistically significant. Cyst size appeared to decrease between prenatal diagnosis and birth in BA patients, but did not change in CC patients. Our results support those of Matsubara et al. and Casaccia et al. [10,11]. They observed that between birth and surgery, cyst size decreased in BA patients, but increased in CC patients; the difference was statistically significant. This measurement may also be useful for making differential diagnoses between the groups.

In this study, case 3 in the BA group underwent HP-J at 48 days after birth; cyst size decreased before surgery. Intrahepatic and extrahepatic bile ducts could be visualized by cholangiography at 21 days of age, but cholestasis did not subsequently improve. When cholangiography was repeated at 48 days of age, the cyst had become type III-d. We believe that bile duct atresia at the porta hepatis had developed gradually during the neonatal period. The findings of this case are extremely valuable because they may help elucidate the mechanism underlying BA.

Examination of postnatal gall bladder morphology showed atrophy in 3 of 4 BA cases, whereas all 5 CC cases were normal, a statistically significant difference. This finding suggests that gallbladder morphology is an important parameter for distinguishing between BA and CC.

Our results demonstrate that US is a useful diagnostic tool for differential diagnosis of BA and CC. In contrast, stool color was not a reliable diagnostic tool in the early postnatal period because stool color was normal, at birth, in all patients with either BA or CC.

The level of D-bil is generally an important and essential measure of cholestasis. We observed an increase in D-bil levels in 2 cases in the BA group. In an additional 2 BA cases, the level of D-bil exceeded normal values, but interestingly did not tend to increase. The BA and CC groups showed differences with respect to G-GTP. Specifically, the level of G-GTP was elevated at birth in all BA patients, with a characteristic tendency to decrease postnatally, prior to surgery.

This study shows that BA cannot be excluded even if stool color is not abnormal, the level of D-bil does not increase early during the postnatal period, or the level of G-GTP decreases. Therefore, in the case of these, we should be performed a positive diagnosis.

We found that postnatal advancement of disease in early BA is not uncommon, even if the stool color is yellow and laboratory data remain unchanged, as in the specific case of patient 3 in the BA group in which the stool color and laboratory data changed in early day of life. These results may provide important insights into the pathological mechanism of BA.

The optimal time to treat prenatally diagnosed CC patients has been discussed but not established [9]. Some reports suggest that it is imperative to treat CC patients as soon as possible, because delayed surgery may advance liver fibrosis [2–4]. However, other reports suggest that elective surgery is indicated to minimize surgical complications and ensure surgical safety [13,14]. In the present study, the degree of liver fibrosis in CC patients was milder than that in BA patients, but some patients without D-bil level increases progressed to fibrosis, irrespective of age. In 2 cases of CC with liver fibrosis, the G-GTP level persistently exceeded 100 U/l for more than 1 month. On the basis of our findings, we propose some guidelines for early surgery in CC patients with icterus. Specifically, we suggest that both elevation of D-bil and changes in G-GTP levels should be considered, and early surgery should be performed if there is a persistent increase in G-GTP levels.

Cholangiography is the only reliable method for differentiating BA from CC. The only early postsurgical complications in the 10 cases were occurrences of cholangitis in 2 BA patients. We recommend neonatal surgery in cases of CC with icterus, liver dysfunction and where the possibility of BA cannot be excluded. Cases of asymptomatic CC should be treated surgically within the first 2 months because there is a risk that liver fibrosis may progress if treatment is delayed.

In a single institution, there are very few cases of prenatally diagnosed biliary atresia and choledochal cyst. This small size is a limitation of our study as well as other articles. Advances in ultrasonography may increase the prenatal diagnosis of biliary atresia and choledochal cyst. We expect to be able to amass additional data from our institution, as well as nationwide data, and wish to analyze them in greater detail in the future.

In conclusion, BA should be strongly suspected when cyst size tends to decrease before and after birth and when postnatal gallbladder atrophy is observed. Stool color and postnatal laboratory data are not useful for early differential diagnoses, and definitive diagnosis of BA or CC can be obtained only by cholangiography. In some patients, for example case 3 in the BA group, atresia of the bile duct at the porta hepatis can develop gradually, even if the stool color is not abnormal, the level of D-bil does not increase during the early postnatal period, or the level of G-GTP decreases. These patients should be carefully followed until surgery. Cases of CC with icterus and liver dysfunction should be treated surgically during the neonatal period.

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ORIGINAL ARTICLE

Does hepatic hilum morphology influence long-term prognosis in type I/I cyst biliary atresia?

Masaki Nio[1] · Motoshi Wada[1] · Hideyuki Sasaki[1] · Hiromu Tanaka[1]

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Abstract
Purpose Some patients with cystic biliary atresia (BA) achieve exceptionally good postoperative courses. Early differentiation of pediatric patients with the favorable-type disease can lead to beneficial long-term postoperative management. We examined whether the hepatic hilum morphology affects long-term prognosis in type I/I cyst BA, atresia of the common bile duct with/without a cyst.
Methods Of 253 BA patients identified since 1972, 40 were classified as having type I/I cysts and were divided into two subtypes according to hepatic duct size (subtype α: $n = 18$; duct diameter, ≥1 mm and subtype β: $n = 22$; duct diameter, <1 mm) to compare postoperative clinical courses.
Results In subtypes α and β, jaundice disappeared in 16 (89 %) and 19 (86 %) patients, respectively ($p = 0.81$), and 13 (72 %) and 12 (55 %) survived with native livers ($p = 0.18$) at a mean age of 23.3 and 25.5 years, respectively ($p = 0.42$).
Conclusions There were no significant differences in long-term outcomes between subtypes α and β, although approximately 40 % developed liver failure during the postoperative course. Thus, close long-term follow-up is essential in type I/I cysts, regardless of the hepatic hilum morphology.

Keywords Biliary atresia · Hepatic hilum morphology · Hepatic duct size · Long-term prognosis

✉ Masaki Nio
mnio@ped-surg.med.tohoku.ac.jp

[1] Department of Pediatric Surgery, Tohoku University Graduate School of Medicine, 1-1, Seiryomachi, Aobaku, Sendai 980-8574, Japan

Introduction

Some patients with cystic biliary atresia, particularly those with choledochal cysts rather than biliary atresia, have favorable prognoses and show exceptionally good postoperative courses. The so-called "correctable types" of biliary atresia include choledochal cyst-like disease that should be distinguished from biliary atresia in which the hepatobiliary system is universally involved in severe inflammatory processes. However, these two disease categories have not been strictly distinguished between neonates and younger infants. Early differentiation of pediatric patients with the favorable-type disease can lead to beneficial long-term postoperative management. To address this issue, we focused on the morphological variations at the porta hepatis in biliary atresia.

Kasai's classification for biliary atresia [1] (Table 1) is fairly complicated and categorizes cases cyclopedically. This classification system consists of main types, distal subtypes, and proximal subtypes. Eighty-five percent of cases are type III, characterized by atresia at the porta hepatis, and 15 % of cases are type I, characterized by common bile duct atresia. Type I cyst is associated with cystic dilatation of the atretic common bile duct (Fig. 1). Type II is very rare. Type I/I cyst is further classified into two proximal subtypes, namely subtype α, characterized by a patent hepatic duct with a diameter of ≥1 mm, and subtype β, characterized by a hepatic duct diameter of <1 mm (Fig. 2). A report by the 2011 Japanese Biliary Atresia Registry (JBAR) [2] indicated that the jaundice clearance rate was significantly better in subtype α than in subtype β. We hypothesized that more patients with the favorable choledochal cyst-like character are included in subtype α than in subtype β and compared the short- and long-term outcomes between the two subtypes.

Table 1 Classification of extrahepatic biliary atresia

1. Main types
   - Type I: atresia of common bile duct
   - Type I cyst: atresia of common bile duct with cystic dilatation
   - Type II: atresia of hepatic duct
   - Type III: atresia of bile duct at the porta hepatis
2. Distal subtypes according to the patterns of distal bile ducts
   - a: patent common bile duct
     - a1: patent common bile duct and atretic hepatic duct
     - a2: patent common bile duct and aplasia of hepatic duct
   - b: fibrous common bile duct
     - b1: fibrous common bile duct and patent or atretic hepatic duct
     - b2: fibrous common bile duct and aplasia of hepatic duct
   - c: aplasia of common bile duct
     - c1: aplasia of common bile duct and patent or atretic hepatic duct
     - c2: aplasia of common bile duct and hepatic duct
   - d: miscellaneous
3. Proximal subtypes according to the patterns of hepatic radicles at the porta hepatis
   - α: dilated hepatic radicles (internal diameter >1 mm)
   - β: hypoplastic hepatic radicles (internal diameter <1 mm)
   - γ: bile lake
   - μ: fibrous hepatic radicles
   - ν: fibrous mass
   - o: aplasia of hepatic radicles

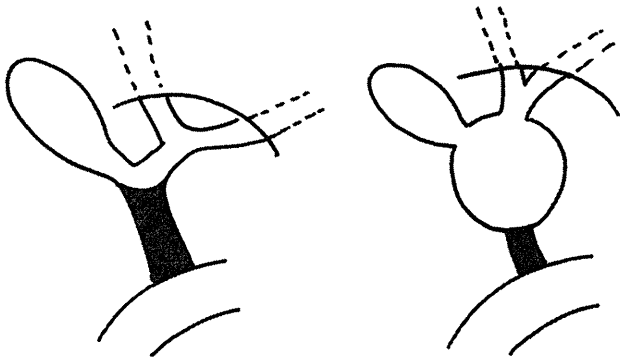

Fig. 1 Types of obstruction: type I atresia and type I cyst. Type I, atresia of the common bile duct (*left*); type I cyst, atresia of the common bile duct with cystic dilatation (*right*)

Materials and methods

Of 253 patients with biliary atresia who underwent corrective operation in Tohoku University Hospital between 1972 and 2013, 40 (12 males and 28 females) had type I biliary atresia including 30 with type I cyst. Among the 40 patients with type I biliary atresia, 18 (5 males and 13 females) were classified as having subtype α and 22 (7 males and 15 females) were classified as having subtype β. The patients were classified into subtypes α and β according to the findings of cholangiography (Figs. 3, 4), direct vision of the surgical field, and measurement of the diameter of the hepatic duct after removing the extrahepatic biliary tissue including a cystic structure if it exists. Clinical parameters including age at the time of surgery, surgical procedure, jaundice clearance rate, incidence of early cholangitis and severe portal hypertension, need for transplantation, and outcomes were compared between subtypes α and β. Jaundice clearance was defined as a total serum bilirubin level of <2.0 mg/dL. The study protocol was approved by the Clinical Research Ethics Board of our institution.

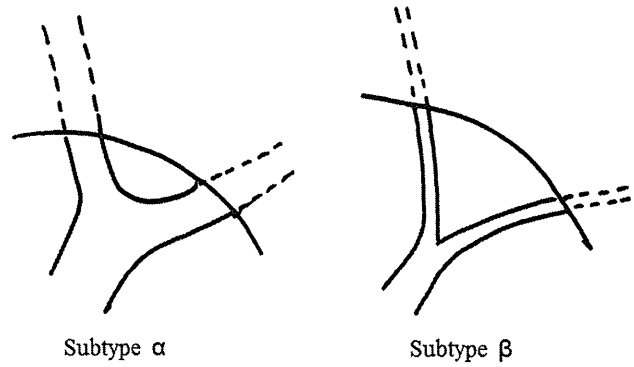

Fig. 2 Proximal subtypes α and β. Subtype α, dilated hepatic radicles (internal diameter ≥1 mm) (*left*); subtype β, hypoplastic hepatic radicles (internal diameter <1 mm) (*right*)

Statistical analysis was performed using the Chi-squared test or Student's *t* test, where appropriate. Cumulative survival rates were analyzed using Kaplan–Meier survival curves, and the statistical difference was assessed using the log-rank test. A probability (*p*) value of <0.05 was considered statistically significant.

Results (Table 2)

Age at surgery

The mean patient age at surgery was 61.2 days (range 14–104 days), and the mean patient age in subtypes α and β was 59.6 days (range 14–140 days). There was no significant difference between subtypes ($p = 0.77$).

Surgical procedures

Of the 18 patients in subtype α, 14 and 4 underwent hepaticojejunostomy and Kasai portojejunostomy, respectively. Of the 14 patients who initially underwent