Original Works

Optimal Diagnostic Strategy for Infantile Cholestasis in Pediatric Surgery

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Abstract

Introduction: The initial goal in treatment for infantile cholestasis is to exclude surgical cholestasis, especially biliary atresia (BA). In this study, we retrospectively reviewed the diagnostic course of infantile cholestasis.

Methods: Between 2000 and 2009, a total of 44 infants with cholestasis were referred to our department. The median age at admission was 54 days (range: 0-143 days). The medical charts of these infants were reviewed.

Results: The initial diagnostic approach was ultrasonography followed by the qualitative detection of bilirubin in stool. The 35 infants with acholic stool and/or a small or absent gallbladder on ultrasonography were subsequently examined by hepatobiliary scintigraphy (HBS). Twenty-nine infants with negative scintigraphy findings underwent intraoperative cholangiography (IOC), and BA was finally confirmed in 24 of 44. A choledochal cyst was noted in 2, Alagille syndrome in 2, cytomegalovirus infection in 2, panhypopituitarism in 2, multiple hemangiomas of the liver in 1, and cholecystolithiasis in 1. The remaining 10 infants were diagnosed as having neonatal hepatitis. The sensitivity and specificity of HBS for BA were 100% and 54.5%, respectively.

Conclusion: HBS is a useful modality for detection of BA with a sensitivity of 100%. The indication for IOC should depend on these scan results.

Key Words: Hepatobiliary scintigraphy, Neonatal hepatitis, Biliary atresia, Laparotomy, Infantile cholestasis.

Introduction

Infantile cholestasis is defined as an impaired canaliculi biliary flow resulting in the accumulation of biliary substances such as direct bilirubin and bile acids in blood and extrahepatic tissue[1-6]. The incidence of infantile cholestasis is estimated to be approximately one in 2,500 live births[5-7], and potentially leads to serious conditions such as hepatobiliary dysfunction. The causes of infantile

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cholestasis are diverse, including metabolic disease, immaturity, and surgical disorders. The initial goal of infantile cholestasis is to exclude surgical cholestasis as early as possible, especially biliary atresia (BA), because early surgical intervention for BA may improve outcomes[8-10].

In this study, we retrospectively reviewed the diagnostic course of infantile cholestasis and discussed the optimal screening program for BA.

Patients and Methods

This retrospective study included infants with significant direct hyperbilirubinemia who were referred to our surgical unit (Department of Pediatric Surgery, Kyoto Prefectural University of Medicine) with a potential diagnosis of surgical cholestasis between 2000 and 2009. All patients received liver function tests at presentation. Cholestasis was diagnosed in the presence of direct hyperbilirubinemia, defined as level greater than 1.0 mg/dL. Screening for the common viruses causing infantile cholestasis such as toxoplasmosis, rubella, cytomegalovirus (CMV), herpes virus, and hepatitis B and C was performed if needed. Specific biochemical tests, metabolic screening, or imaging studies were performed as required in individual patients for a confirmation of diagnosis.

The diagnostic algorithm for surgical jaundice was as follows. The initial approach included abdominal ultrasonography (USG) using the LOGIQ 7 ultrasound system (GE Medical Systems, Milwaukee, WI, USA). USG was performed after 3 hours of fasting and repeated after a feed. This allowed for the detection of structural abnormalities of the intra- and extrahepatic bile duct to exclude ductal dilatation causes such as a choledochal cyst. Next, we prioritized study of the gallbladder to evaluate for size, shape, stones, and sludge[11]. Following this, the qualitative detection of bilirubin in stool was performed. Cases with gallbladder abnormalities including absence, small, crooked, poor-contracting, or with wall irregularity, accompanied with acholic stool were highly suspected to be a diagnosis of BA. The cases with abnormal gallbladder and/or with acholic stool were subsequently examined by hepatobiliary scintigraphy (HBS) with ^{99m}Tc-PMT (pyridoxal-5-methly-triptophan). Serial static images were acquired for up to 6 hours on a dual-head gamma camera. Delayed anterior and posterior images were acquired at 24 hours. The cases with negative scintigraphy underwent intraoperative cholangiography with a liver biopsy in order to determine the diagnosis and exclude BA.

The continuous variables were expressed each as a median and range or as mean±SD and the proportions were expressed in absolute values and percentages.

Results

A total of 44 early infants with cholestasis were managed during the study period. There were 25 girls and 19 boys with a median age at admission of 54 days (range: 0-143 days). The median weight at admission was 4,265 g (range: 2,027-7,140 g). The median onset of jaundice was at 22 days (range: 0-131) and the median value of total bilirubin at admission was 9.2 mg/dL (range: 4.1-31.0 mg/dL).

The diagnostic outcomes are depicted in Fig. 1. Bile duct screening by USG revealed a choledochal cyst in two infants. One underwent definitive surgery for the choledochal cyst at the age of 50 days. The other patient developed liver failure in spite of external drainage, resulting in the necessity of a living liver transplantation. The remaining 42 cases were examined by the qualitative detection of stool bilirubin and USG exploration of the gallbladder. BA was excluded from seven infants with a normal gallbladder on USG and positive stool bilirubin. One of these patients had bile inspissated bile syndrome

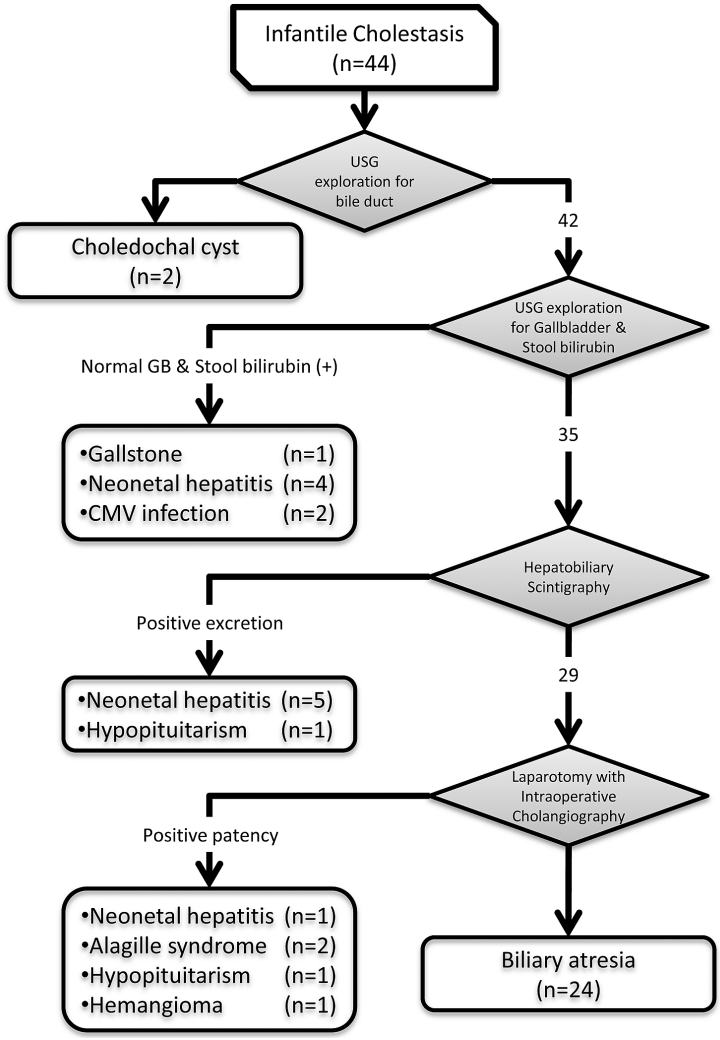

Fig. 1. Chart of the diagnostic course of the patients with infantile cholestasis.

due to choledocolithiasis, and responded to medical treatment. Two of the seven had CMV infection revealed by virus antibody tests, and the remaining five infants were diagnosed as having neonatal hepatitis, resolving spontaneously. The remaining 35 infants were subsequently examined by HBS. In six of these patients excretion to the duodenum was noted. In the infants with positive scintigraphy, five were found to have neonatal hepatitis and one had panhypopituitarism with anterior pituitary hypoplasia and optic nerve hypoplasia revealed by MR imaging.

Finally, 29 of 44 cases (66.0%) with negative scintigraphy underwent a laparotomy with intraoperative cholangiography and liver biopsy. BA was confirmed in 24 infants and these patients simultaneously underwent a Kasai portoenterostomy at an average of 74.4 days of age (range: 48-153). The remaining five infants with an intact bile duct had diagnoses including Alagille syndrome (2 patients), panhypopituitarism (1 patient), multiple hemangiomas of the liver (1 patient), and neonatal

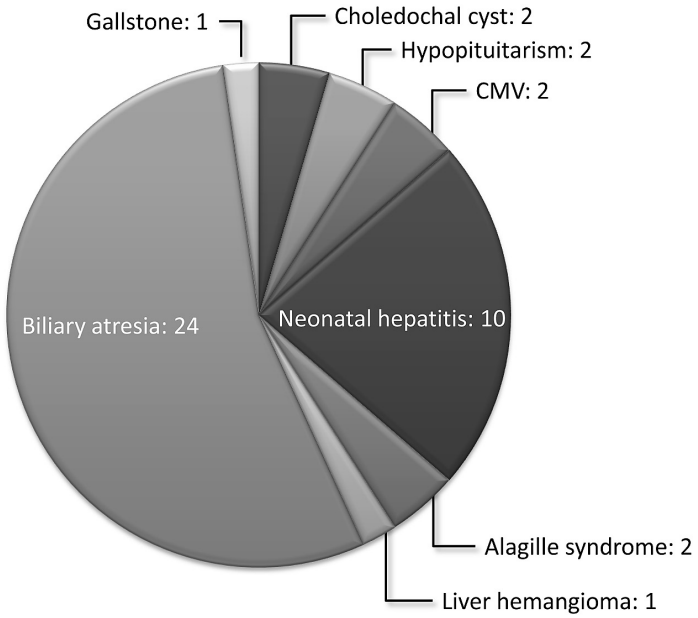

Fig. 2. Etiological spectrum of infantile cholestasis (n=44).

hepatitis (1 patient). The etiological spectrum of infantile cholestasis in this study is shown in Fig. 2. The diagnostic sensitivity and specificity of HBS in this study for BA was 100% and 54.5%, respectively.

Discussion

BA is a unique pediatric liver disease characterized by an idiopathic, progressive, fibrosclerosing obliteration of large bile ducts with an incidence of 0.8-1.0 per 10,000 live births throughout the world[8)12)]. While early diagnosis and surgical intervention are essential as BA is the most frequent cause of liver-related death in children, early detection has been hampered by the lack of an effective screening strategy. The current diagnostic and therapeutic standard for BA is open cholangiography with a Kasai procedure. This entails resection of the obstructed extrahepatic bile duct with placement of a loop of bowel to the porta hepatis in an effort to restore bile flow, even in the liver transplantation era. The Kasai procedure appears to provide the greatest likelihood of the re-establishment of bile flow and the longest term survival of the native liver when performed before the age of 45 to 60 days[8-10)14)]. Therefore, an optimal diagnostic strategy includes a screening program to distinguish patients needing intraoperative cholangiography from infants with cholestasis.

The differential diagnosis of infantile cholestasis was limited. BA accounted for approximately 25% of the cases, and a small percentage of cases were considered to be caused by viral infections, metabolic, genetic, inherited, or developmental diseases (i.e., galactosemia, tyrosinemia, cystic fibrosis, Alagille syndrome). The vast majority were designated as idiopathic neonatal hepatitis, clearly a default diagnosis due to an unknown underlying pathophysiology[3)]. The etiological spectrum of infantile cholestasis in our setting features female preponderance and a high proportion of surgical cholestasis.

This included cholecystolithiasis, choledochal cyst, BA, and liver hemangiomas, up to 63.6% of cases in this series. This is explained by our extensive referral base from pediatric clinics or neonatal intensive care units directly to our surgical unit. Most of patients referred to our center had been excluded from diagnoses such as indirect hyperbilirubinemia and the common neonatal metabolic disorders such as galactosemia and hypothyroidism. In our series, almost half of the cases (54.5%) were due to BA. Idiopathic neonatal hepatitis was the second major cause. In four of the 10 cases of neonatal hepatitis, meconium peritonitis with jejunoileal atresia was antecedent to the onset of jaundice[13].

Making a definite diagnosis before subjecting a child to a laparotomy is not an easy task. No single test is 100% accurate. Laboratory parameters that have been used to differentiate BA from cholestasis are the presence of acholic stool along with hyperbilirubinemia (significantly elevated direct bilirubin). Such parameters can be used as screening tests. However, a test with better accuracy is essential in the diagnosis of BA. In infants with conjugated hyperbilirubinemia, performing USG is still the first step because of its accessibility, affordability and noninvasiveness[11]. USG is sensitive in detecting anatomic abnormalities such as a choledochal cyst and gallbladder morphology. However, it is highly operator dependent and poorly reproducible. Although gallbladder abnormalities including absence, small, poor-contracting and wall irregularities may suggest BA, gallbladders with neonatal hepatitis could show the same findings. In personal communication, the diagnostic sensitivity and specificity of USG for BA is 76.9% and 88.9% , respectively (data not shown). Despite these limitations, we recommend USG as the first step in the evaluation of infantile cholestasis.

In this study, ^{99m}Tc-PMT scintigraphy had a sensitivity of 100% and specificity of 54.5%. Injected radioactive material is normally excreted into the intestine within a predictable period of time. Nonvisualization of radioactivity within the intestine 24 hours after injection indicates biliary obstruction or hepatocellular dysfunction including both neonatal hepatitis and BA[15]. The literature reports 91% accuracy, 97% sensitivity, and 82% specificity for HBS in diagnosing BA. The problem with this modality is that too many children may be subjected to laparotomy due to its low sensitivity. To avoid unnecessary laparotomy in this study, we combined USG, stool testing and HBS, and repeated these studies to confirm results. As a result, the negative laparotomy rate in this series was 17.2% as low as other studies (18.1-28.0%)[16-18].

Although pre-laparotomy liver biopsy has been a tool for diagnosing BA with an accuracy of 60-95%[7)19)], there is still controversy regarding the value of liver histology. This is because morphological alterations in BA are similar to and often indistinguishable from those of neonatal hepatitis. There are also no strict histopathological criteria to diagnose BA. We did not perform routine liver biopsy because it is time-consuming, and most of our patients were referred at the age of nearly 60 days, therefore too advanced to wait for pathological results. Moreover, we considered laparotomy with intraoperative cholangiography as a gold standard for the definitive diagnosis of infantile cholestasis. A simultaneous Kasai hepatoportoenterostomy procedure is crucial to improve outcomes in BA. In conclusion, infantile cholestasis demands a diagnostic, systematic approach. HBS is a very useful modality for the early detection of BA with a sensitivity of 100%. Therefore, the indication for laparotomy with intraoperative cholangiography should depend on these scan results.

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〈和文抄録〉

小児外科における乳児黄疸の診断治療戦略

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乳児閉塞性黄疸では，まず胆道閉鎖症を除外することが優先される．本研究では，当科で治療を行った乳児黄疸例の診断に至る過程と診断群の臨床的特徴について検討した．対象症例は，2000 年から 2009 年までに乳児黄疸に対して外科的疾患の診断のため当科に紹介となった 44 例を対象とした．入院時日齢の中央値は 54 日（0 日～143 日）であった．診断はまず腹部超音波検査から行い，さらに便中ビリルビン定性検査を行った．35 例において，無胆汁便および胆嚢萎縮あるいは欠損が認められ，これらには次いで肝胆道排泄シンチグラフィが施行された．その結果，胆道シンチにおいて核種の排泄を認めなかった 29 例において，開腹胆道造影が施行された．最終的に胆道閉鎖症は 44 例中 24 例（54.5％）において確定診断された．それ以外の診断としては，先天性胆道拡張症，アラジール症候群，サイトメガロウィルス感染，汎下垂体機能低下症がそれぞれ 2 例，肝血管腫，胆石症がそれぞれ 1 例であった．残る 10 例は新生児肝炎と診断された．胆道シンチの胆道閉鎖症に対する感受性と特異度はそれぞれ 100％と 54.5％であった．したがって，乳児黄疸に対する開腹術の適応は，胆道シンチの結果により決定するのが妥当であると考えられた．

キーワード：肝胆道シンチグラフィ，新生児肝炎，胆道閉鎖症，開腹術，乳児黄疸．