

Biliary Atresia: Color Doppler US Findings in Neonates and Infants¹

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Purpose:

To describe color Doppler ultrasonographic (US) findings in livers of neonates with biliary atresia (BA) and to compare them with US findings in livers of neonates with non-BA and control subjects.

Materials and Methods:

Institutional review board approval was obtained; acquisition of informed consent was exempted. US and color Doppler US findings were retrospectively reviewed in 64 patients with neonatal cholestasis and 19 control subjects. BA and non-BA were confirmed in 29 and 35 patients, respectively. Three pediatric radiologists assessed US and color Doppler US images, independently documented their findings, and resolved discrepancies by consensus. Triangular cord (TC) sign, gallbladder length, and hepatic artery and portal vein diameters were evaluated on US images. The presence of hepatic subcapsular flow was evaluated on color Doppler US images. Diagnostic value of TC sign and hepatic subcapsular flow in the diagnosis of BA were evaluated. Significance of hepatic artery and portal vein diameters in each group was assessed.

Results:

In the diagnosis of BA, sensitivity and specificity of the TC sign on US images were 62% and 100%, respectively. On color Doppler US images, hepatic subcapsular flow was detected in all patients with BA and in five patients with non-BA. At the first review, there was a discrepancy between radiologists in interpretation of hepatic subcapsular flow in patients with non-BA. However, consensus was reached at the second review. There was no hepatic subcapsular flow in control subjects. Sensitivity and specificity of hepatic subcapsular flow on color Doppler US images were 100% and 80%–86%, respectively, on the basis of individual interpretations of reviewers. Sensitivity and specificity of hepatic subcapsular flow on color Doppler US images were 100% and 86%, respectively, on the basis of consensus reading. Mean diameter of the hepatic artery in patients with BA ($2.1 \text{ mm} \pm 0.7$ [standard deviation]) was significantly larger than that in patients with non-BA ($1.5 \text{ mm} \pm 0.4$, $P < .001$) and control subjects ($1.5 \text{ mm} \pm 0.4$, $P = .001$).

Conclusion:

The presence of hepatic subcapsular flow is useful for differentiating between BA and other causes of neonatal jaundice.

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There are many causes of neonatal jaundice. Most cholestatic conditions can be classified as either obstructive or hepatocellular in origin. Biliary atresia (BA) accounts for more than 90% of obstructive cholestasis cases (1). Hepatocellular cholestasis results from impairment of bile formation and indicates defective functioning of most or all hepatocytes. Idiopathic neonatal hepatitis accounts for the majority of cases of hepatocellular cholestasis. When assessing neonatal cholestasis, it is important to differentiate between obstructive and hepatocellular cholestasis because the former requires surgical correction whereas the latter necessitates medication (1). However, it is difficult to distinguish between these diseases because they have similar clinical symptoms and biochemical and histologic findings (2). Therefore, Moyer et al (3) introduced general guidelines for the evaluation of cholestatic jaundice in infants.

In these patients, high-spatial-resolution real-time ultrasonography (US) serves as a first-line screening tool with which to determine the cause of jaundice. The presence of the triangular cord (TC) sign and an abnormal gallbladder (GB) on high-spatial-resolution real-time US images is widely accepted as the diagnostic criterion for BA (4). However, the TC sign cannot always be found in every patient, and its detection is largely dependent on the techniques used by the operator and his or her experience. Furthermore, it is difficult to see the TC sign in an infant with hepatic

maldevelopment or if the resolution of the US apparatus is poor (5).

Histologically speaking, BA is characterized by portal tract inflammation, a small cell infiltrate, and bile duct plugging and proliferation. In later stages of disease, bridging fibrosis gives way to features of overt biliary cirrhosis (6). Hyperplastic and hypertrophic changes in branches of the hepatic artery are observed in patients with BA (7). At US, the diameter of the hepatic artery is larger in patients with BA than in patients with non-BA and control subjects. The range of the diameters of the normal hepatic artery is 1.0–2.5 mm according to Kim et al (8) and 0.5–4.0 mm according to Humphrey and Stringer (9). However, there have been no reports on hepatic subcapsular flow in patients with BA.

The purpose of our study was to describe the color Doppler US findings in the livers of neonates with BA and to compare them with US findings in the livers of neonates with non-BA and control subjects.

Materials and Methods

Patients

Institutional review board approval was obtained, and acquisition of informed consent was exempted. From March 2003 to July 2007, we performed US and color Doppler US in 64 patients with neonatal cholestasis who had not been fed for at least 4 hours, and we retrospectively reviewed the US and color Doppler US findings. We did not include images obtained in four patients with BA who were uncooperative during color Doppler US. Among the 64 patients, 29 (17 boys, 12 girls; mean age, 51 days \pm 24 [standard deviation]) received a diagnosis of BA on the basis of surgical and

pathologic findings. The remaining 35 patients (26 boys, nine girls; mean age, 48 days \pm 32) received a diagnosis of BA on the basis of the results of clinical, imaging, and laboratory studies ($n = 25$) and pathologic examination ($n = 10$), as follows: idiopathic hyperbilirubinemia ($n = 13$), neonatal hepatitis ($n = 8$), total parenteral nutrition (TPN)-induced cholestasis ($n = 6$), nonsyndromic paucity of interlobular bile duct ($n = 5$), Alagille syndrome ($n = 2$), and portal vein thrombosis ($n = 1$).

Routine chemical studies, including measurement of total and direct serum bilirubin levels, were performed in all patients. The reference ranges for the blood sample parameters provided by our institution were 0.2–1.2 mg/dL for total bilirubin and 0.1–0.4 mg/dL for direct bilirubin.

From January to July 2007, we performed US and color Doppler US in 19 neonates and infants (11 boys, eight girls; mean age, 41 days \pm 28) without jaundice or liver disease. These subjects served as the control group, and their clinical diagnoses were as follows: Gastrointestinal tract disease was diagnosed in eight patients, renal disease was diagnosed in eight patients, congenital heart disease was diagnosed in two patients, and cervical lymphadenitis was diagnosed in one

Advances in Knowledge

- Color Doppler US can be used to detect hepatic subcapsular flow in patients with biliary atresia (BA).
- Color Doppler US findings may indicate hyperplasia and hypertrophy of the hepatic artery in patients with BA; these are indicated by a significantly larger hepatic artery diameter in patients with BA than in patients with non-BA and control subjects.

Implication for Patient Care

- Hepatic subcapsular flow on color Doppler US images can be used to diagnose BA when triangular cord sign findings are negative.

Published online

10.1148/radiol.2522080923

Radiology 2009; 252:282–289

Abbreviations:

BA = biliary atresia
 CMV = cytomegalovirus
 EARPV = echogenic anterior wall of the right portal vein
 GB = gallbladder
 TC = triangular cord
 TPN = total parenteral nutrition

Author contributions:

Guarantors of integrity of entire study, M.S.L., M.J.K., Y.N.P.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, M.S.L., M.J.K., Y.N.P.; clinical studies, M.S.L., M.J.K., C.S.Y., S.J.H., J.T.O., Y.N.P.; statistical analysis, M.S.L., M.J.K.; and manuscript editing, M.S.L., M.J.K., M.J.L., C.S.Y.

Authors stated no financial relationship to disclose.

patient. Institutional review board approval and parental informed consent were obtained before US and color Doppler US were performed in control subjects. We did not check total or direct bilirubin levels in any neonate or infant in the control group because none of them had a biliary tree or liver disease. In the 19 neonates and infants in the control group, we checked both total and direct bilirubin levels in eight neonates and two infants.

US and Color Doppler US

One pediatric radiologist (M.J.K.) with more than 15 years of experience performed US by using 5–8-MHz curved linear and 5–12-MHz linear transducers (HDI 5000 and IU-22, respectively; Philips, Bothell, Wash) in all patients who had not been fed for at least 4 hours. US and color Doppler US images were assessed by three pediatric radiologists: One radiologist (M.J.K.) performed US and color Doppler US, while the other two (C.S.Y., M.J.L.) were unaware of the results of clinical and pathologic analyses. The radiologists independently documented the US and color Doppler US findings and resolved discrepancies in consensus. At longitudinal scanning, we measured the length of the GB and the thickness of the echogenic anterior wall of the right portal vein (EARPV) just proximal to the right portal vein bifurcation site. A GB length of at least 1.5 cm was considered normal (10). With US, the sole criterion for the TC sign was an EARPV that was thicker than 4 mm on longitudinal US images (11). We defined diffuse periportal echogenicity as an EARPV that was at least 1–4 mm thick on US images. We also evaluated the diameter of the portal vein at the level of the proximal portion of the main portal vein and the diameter of the proper hepatic artery, which runs parallel to the main portal vein. One observer (M.J.K.) measured the thickness of the EARPV, length of the GB, and diameters of the portal vein and hepatic artery more than twice and chose the largest ones. The other radiologists assessed these measurements and based their assessment on measurements obtained by the aforementioned radiologist (M.J.K.).

After completion of US, all patients underwent color Doppler US (pulse repetition frequency, 1200–1500 Hz; power gain percentage, 82%–92%; medium flow velocity; medium wall filter). For transverse scanning performed with the linear transducer, the color box was positioned on the anterior surface around the falciform ligament. The color box measured 1 cm in height and 3–4 cm in width. We considered hepatic subcapsular flow to be present when vascular structures continued to the liver capsular surface on color Doppler US images.

Surgical and Pathologic Evaluations

All patients with BA underwent the Kasai procedure, and one patient underwent liver transplantation after the Kasai procedure. Among the 35 patients with non-BA, 10 underwent a liver biopsy. Their diagnoses were as follows: nonsyndromic paucity of interlobular bile duct ($n = 5$), neonatal hepatitis ($n = 3$), Alagille syndrome ($n = 1$), and TPN-induced cholestasis ($n = 1$).

When the Kasai procedure or liver biopsy was performed, the surgeon examined the liver surface carefully and noted the presence of hepatic subcapsular telangiectasia when enlarged, tangled plump vessels were seen on the liver surface. During the histopathologic examination, the hepatic subcapsular telangiectatic vessels confirmed at gross inspection were evaluated with a microscope when the hepatic surface was well preserved on the prepared tissue.

Statistical Analyses

The two-sample t test was used to compare age and total bilirubin and direct bilirubin levels between the patients with BA and those with non-BA. The two-sample t test was used to compare age between patients with BA and control subjects. The Pearson χ^2 test was used to compare male-to-female ratio among patients with BA, those with non-BA, and control subjects. We could not compare levels of total and direct bilirubin in patients with BA with those in control subjects because the numbers of neonates and infants in whom bilirubin levels were checked were too small.

Sensitivity, specificity, and positive

and negative predictive values were calculated for the TC sign on US images and the hepatic subcapsular flow on color Doppler US images in patients with BA and those with non-BA. Individual readings were used first; consensus readings were used thereafter.

The Mann-Whitney test was used to evaluate differences in GB length and mean diameters of the portal vein and hepatic artery among patients with BA, those with non-BA, and control subjects. For all tests, a two-tailed P value of less than .05 was considered to indicate a significant difference.

Multivariate logistic regression analysis was used to determine whether the presence of the TC sign, GB length, diameters of the portal vein and hepatic artery, and presence of hepatic subcapsular flow were useful in predicting the presence or absence of BA. Data analyses were performed with statistical software (SPSS, version 12; SPSS, Chicago, Ill).

Results

In the 64 patients with neonatal jaundice, we did not find any significant differences in age, male-to-female ratio, or levels of total or direct serum bilirubin between patients with BA and those with non-BA. Furthermore, we did not find any significant difference in age or male-to-female ratio between patients with BA and control subjects. We could not compare the levels of total and direct bilirubin between patients with BA and control subjects because the numbers of neonates and infants in whom the bilirubin level was checked were too small (Table 1).

US Findings

Eighteen patients with BA had a positive TC sign (mean EARPV thickness, 4.5 mm \pm 0.6 [standard deviation]), and 11 patients with BA had diffuse periportal echogenicity (mean EARPV thickness, 3.5 mm \pm 0.3). Neither the patients with non-BA nor the control subjects had the TC sign (Table 2). Detection of the TC sign resulted in sensitivity, specificity, and positive and negative predictive values of 62%, 100%, 100%, and 76%, respectively (Table 3).

The mean GB length was 1.5 cm \pm

0.8 in patients with BA, 2.1 cm ± 0.6 in patients with non-BA, and 2.3 cm ± 0.7 in control subjects. The GB was significantly shorter in patients with BA than in patients with non-BA ($P = .03$) and control

subjects ($P < .001$). The GB was shorter than 1.5 cm (10) in 19 patients with BA and nine patients with non-BA. A normal or elongated (≥ 1.5 cm) GB was seen in 10 patients with BA, 26 patients with non-

BA, and all neonates and infants in the control group. There was no significant difference in the mean diameter of the portal vein between patients with BA (4.3 mm ± 0.8) and those with non-BA (3.9

Table 1

Clinical Characteristics of Patients with BA, Patients with non-BA, and Control Subjects at US

| Characteristic | Patients with BA ($n = 29$) | Patients with Non-BA ($n = 35$) | P Value | Control Subjects ($n = 19$) | P Value |
|--------------------------------|-------------------------------|-----------------------------------|-----------|-------------------------------|-----------|
| Age (d) | 51 ± 24 (3–91) | 48 ± 32 (3–150) | .62 | 41 ± 28 (2–90) | .19 |
| Male-to-female ratio | 17:12 | 26:9 | .18 | 11:8 | .28 |
| Total bilirubin level (mg/dL) | 8.7 ± 2.1 (4.1–12.6) | 8.3 ± 4.6 (2.7–28.3) | .73 | 0.3 ± 0.1 (0.2–0.7) | ... |
| Direct bilirubin level (mg/dL) | 6.3 ± 2.3 (1.5–9.5) | 5.1 ± 4.3 (0.6–21.7) | .24 | 0.3 ± 0.2 (0.1–0.5) | ... |

Note.—Unless otherwise indicated, data are means ± standard deviations, with ranges in parentheses.

Table 2

US and Color Doppler US Findings in Patients with BA, Patients with non-BA, and Control Subjects

| Findings | Patients with BA ($n = 29$)* | Patients with Non-BA ($n = 35$)* | P Value† | Control Subjects ($n = 19$)* | P Value‡ | P Value§ |
|----------------------------------|--------------------------------|------------------------------------|------------|--------------------------------|------------|------------|
| TC sign | | | | | | |
| Positive (EARPV ≥ 4 mm) | 18 (62) | 0 (0) | NA | 0 (0) | NA | NA |
| Negative (EARPV < 4 mm) | 11 (38) | 35 (100) | NA | 19 (100) | NA | NA |
| GB length | | | | | | |
| <1.5 cm | 19 (66) | 9 (26) | .03 | 0 (0) | <.001 | .223 |
| ≥1.5 cm | 10 (34) | 26 (74) | NA | 19 (100) | NA | NA |
| Diameter of portal vein (mm)¶ | 4.3 ± 0.8 (3.0–6.0) | 3.9 ± 0.8 (2.3–5.0) | .085 | 3.9 ± 0.6 (2.7–4.7) | .057 | .573 |
| Diameter of hepatic artery (mm)¶ | 2.1 ± 0.7 (1.3–3.3) | 1.5 ± 0.4 (0.7–2.1) | <.001 | 1.5 ± 0.4 (0.8–2.1) | .001 | .993 |
| Hepatic subcapsular flow | | | | | | |
| Present | 29 (100) | 5 (14) | NA | 0 (0) | NA | NA |
| Absent | 0 (0) | 30 (86) | NA | 19 (100) | NA | NA |

Note.—NA = not applicable.

* Unless otherwise noted, data are numbers of patients, with percentages in parentheses.

† P values for comparing patients who had BA with patients who had non-BA.

‡ P values for comparing control subjects with patients who had BA.

§ P values for comparing control subjects with patients who had non-BA.

¶ Data are mean values ± standard deviations, with ranges in parentheses.

Table 3

Diagnostic Value of TC Sign and Hepatic Subcapsular Flow in First and Consensus Reviews by Three Reviewers

| Imaging Features | First Review | | | | | | | | Consensus Review | | | |
|--------------------------|--------------------|-----------------|---------|---------|-----------------|-----------------|---------|---------|------------------|-----------------|---------|---------|
| | Observers 1 and 2* | | | | Observer 3† | | | | | | | |
| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
| TC sign | 62 | 100 | 100 | 76 | 62 | 100 | 100 | 76 | 62 | 100 | 100 | 76 |
| Hepatic subcapsular flow | 100 | 86 | 85 | 100 | 100 | 80 | 81 | 100 | 100 | 86 | 85 | 100 |

Note.—NPV = negative predictive value, PPV = positive predictive value.

* Observers 1 and 2 = M.J.K. and C.S.Y., respectively.

† Observer 3 = M.J.L.

Figure 1

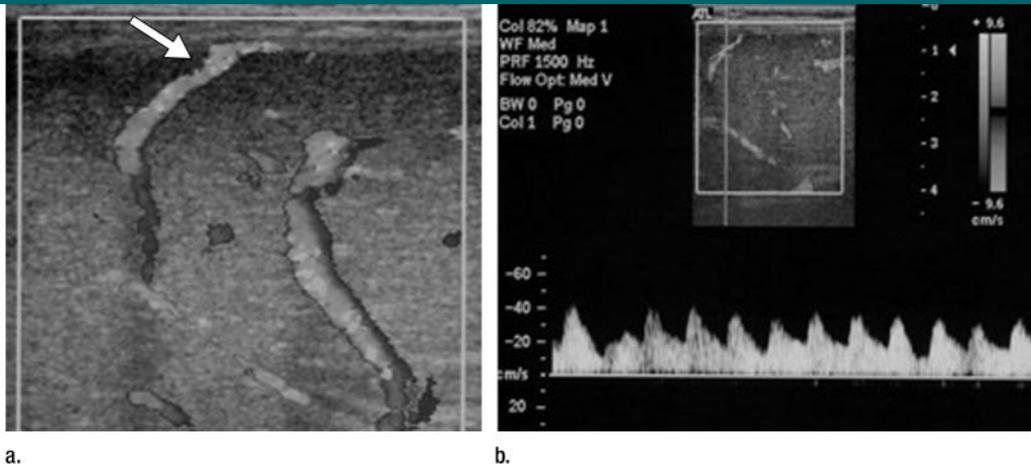


Figure 1: Color Doppler US images in a 32-day-old girl with BA. (a) The presence of hepatic arterial flow (arrow) extended to the hepatic surface. (b) An arterial waveform was seen in the enlarged vessel at the hepatic surface.

Figure 2

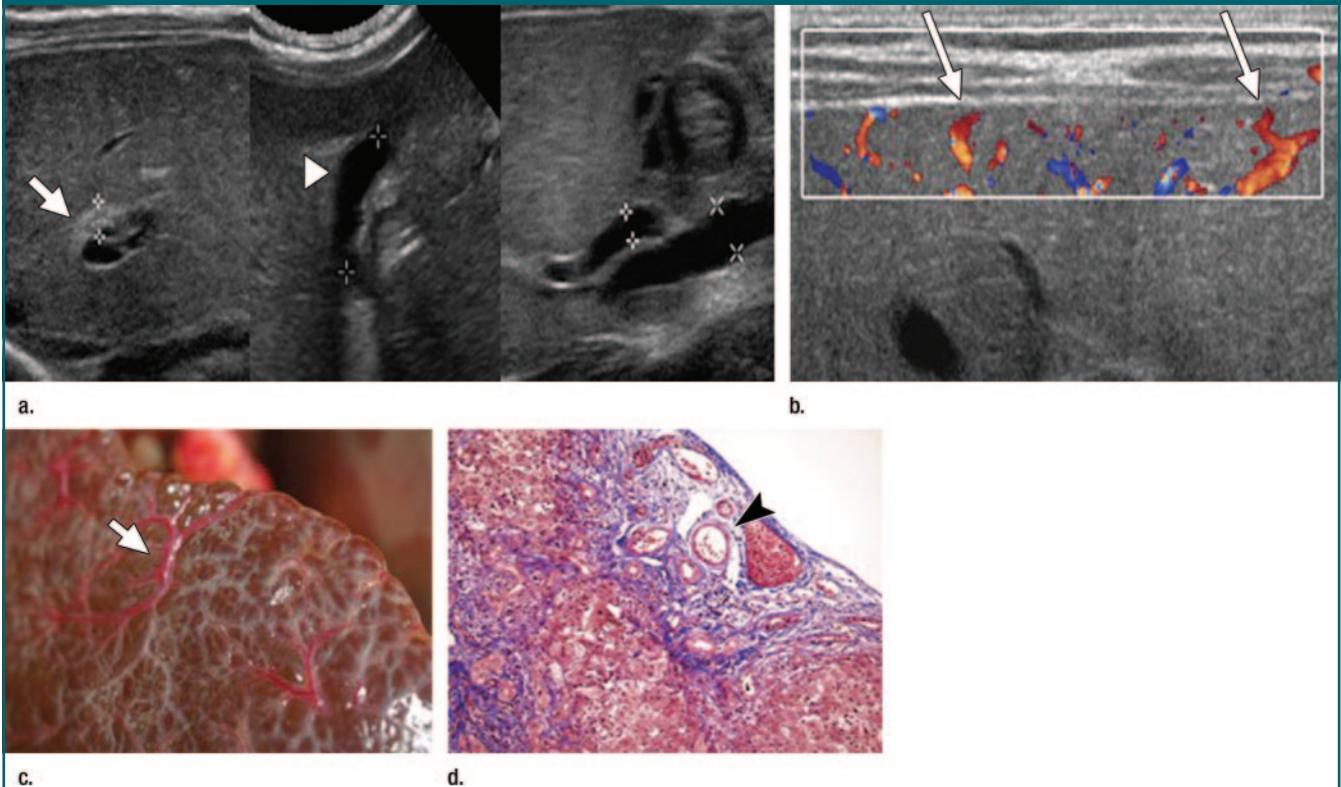


Figure 2: Images in a 65-day-old boy with BA. (a) US images. Left: The EARPV (arrow) (+) is 4 mm thick. This is regarded as a positive TC sign. Middle: The GB length (arrowhead) (+) is 1.6 cm. Right: Diameters of the proximal hepatic artery (+) and portal vein (x) are 3.0 and 5.0 mm, respectively. (b) Hepatic subcapsular flow (arrows) is seen on this color Doppler US image. The rectangle indicates the color box. Red areas indicate blood flow toward the transducer. Blue areas indicate blood flow away from the transducer. (c) At surgery, the liver has a nodular and cirrhotic surface and telangiectatic vessels (arrow). (d) Photomicrograph reveals dilated hepatic arteries (arrowhead) in the hepatic subcapsular area. (Trichrome stain; original magnification, $\times 100$.)

mm \pm 0.8) or between patients with BA and control subjects (3.9 mm \pm 0.6) ($P = .057$). However, the diameter of the hepatic artery was significantly larger in patients with BA (2.1 mm \pm 0.7) than in patients with non-BA (1.5 mm \pm 0.4) ($P < .001$) and control subjects (1.5 mm \pm 0.4) ($P = .001$) (Table 2).

There was no significant difference between patients with non-BA and control subjects in terms of diameter of the hepatic artery ($P = .868$), diameter of the portal vein ($P = .771$), and GB length ($P = .102$).

There were no discrepancies among the three reviewers in their interpretation of the TC sign, GB length, and diameters of the portal vein and hepatic artery.

Color Doppler US Findings

Color Doppler US revealed hepatic arterial flow extending to the hepatic surface

in all patients with BA (Figs 1, 2). Of the 35 patients with non-BA, 30 did not have hepatic subcapsular flow (Fig 3). Five patients with non-BA had hepatic subcapsular flow, four had a history of TPN for more than 6 weeks, and one was confirmed to have cytomegalovirus (CMV) hepatitis with a high CMV immunoglobulin M antibody titer (Fig 4). There was no hepatic subcapsular flow in control subjects. There was no discrepancy in the interpretation of hepatic subcapsular flow on color Doppler US images obtained in patients with BA among the three reviewers. At first review, two observers (M.J.K., C.S.Y.) determined that five of 35 patients with non-BA had hepatic subcapsular flow, and one observer (M.J.L.) determined that seven patients with non-BA had hepatic subcapsular flow. At the second review, a consensus was reached that five of 35 patients with non-BA had hepatic subcapsular flow.

One observer (M.J.L.) thought that two patients with neonatal hepatitis had hepatic subcapsular flow; at consensus reading, this was determined to be negative hepatic subcapsular flow. Hepatic subcapsular flow had sensitivity, specificity, and positive and negative predictive values of 100%, 80%–86%, 81%–85%, and 100%, respectively, on the basis of individual readings of three reviewers. Hepatic subcapsular flow had sensitivity, specificity, and positive and negative predictive values of 100%, 86%, 85%, and 100%, respectively, on the basis of consensus reading (Table 3).

Multivariate logistic regression analysis showed that the presence of hepatic subcapsular flow on color Doppler US images was a significant predictor of BA ($P = .006$). However, presence of the TC sign ($P = .282$), GB length ($P = .644$), and diameters of the portal vein ($P = .868$) and hepatic artery ($P = .288$) were

Figure 3

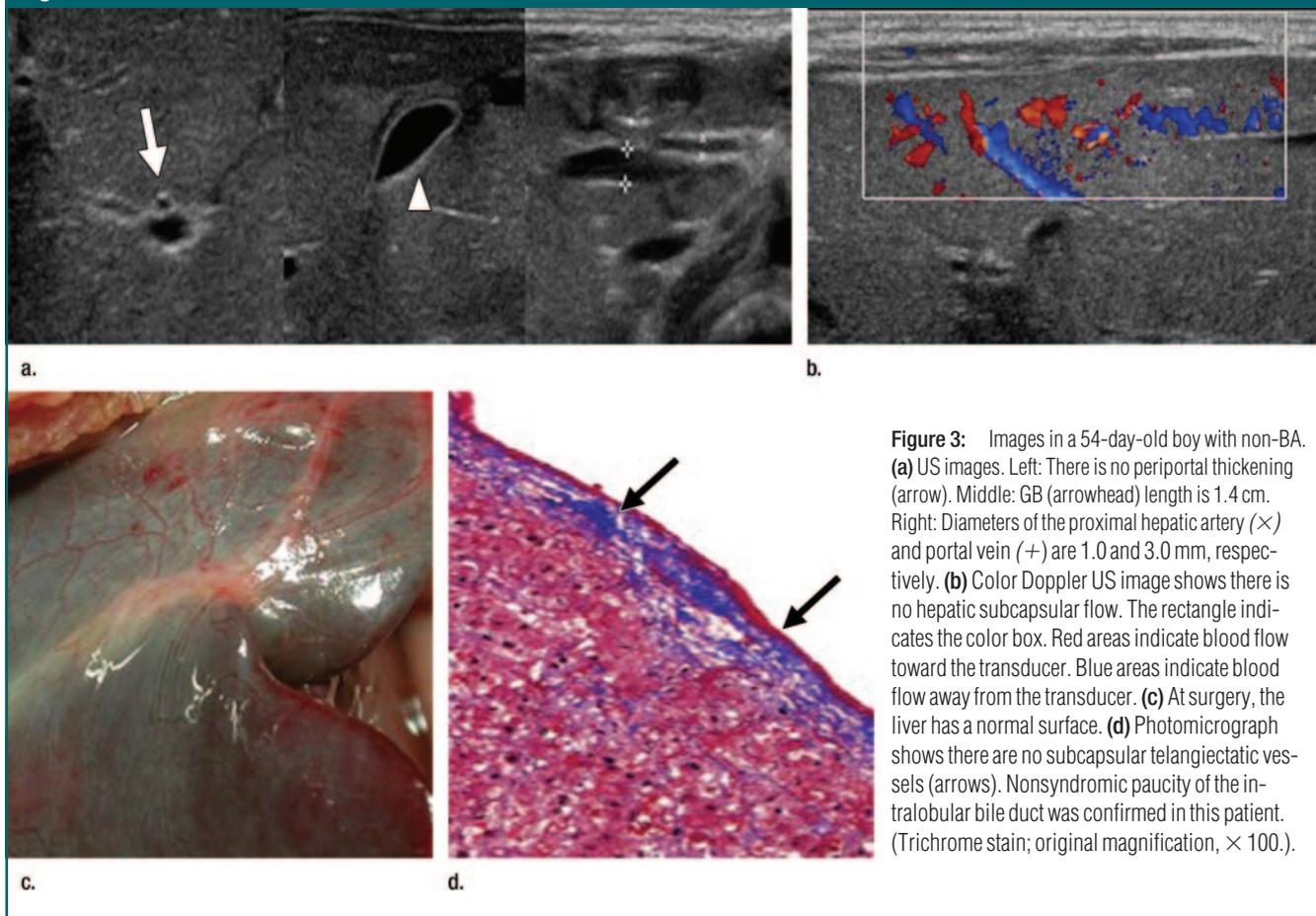


Figure 3: Images in a 54-day-old boy with non-BA. (a) US images. Left: There is no periportal thickening (arrow). Middle: GB (arrowhead) length is 1.4 cm. Right: Diameters of the proximal hepatic artery (X) and portal vein (+) are 1.0 and 3.0 mm, respectively. (b) Color Doppler US image shows there is no hepatic subcapsular flow. The rectangle indicates the color box. Red areas indicate blood flow toward the transducer. Blue areas indicate blood flow away from the transducer. (c) At surgery, the liver has a normal surface. (d) Photomicrograph shows there are no subcapsular telangiectatic vessels (arrows). Nonsyndromic paucity of the intralobular bile duct was confirmed in this patient. (Trichrome stain; original magnification, \times 100.).

not. The predicted sensitivity and specificity of hepatic subcapsular flow on color Doppler US images based on multivariate logistic regression analysis were 92% and 82%, respectively.

Surgical and Pathologic Findings

During surgery, subcapsular telangiectasia was seen in all patients with BA (Fig 2). We were unable to find hepatic subcapsular telangiectasia in any of the 10 patients with non-BA who underwent liver biopsy (Fig 3). Microscopic examination revealed dilated hepatic arteries in the hepatic subcapsular area in all patients with BA (Fig 2). Histopathologic analysis of the liver biopsy specimen obtained in one patient who received TPN for 10 weeks revealed ductular and hepatocyte cholestasis with portal fibrosis and ductular proliferation.

Discussion

Detection of the TC sign with US is a widely accepted criterion with which to diagnose BA (4). According to Lee et al (11), use of an EARPV with 4-mm thickness as a criterion for identifying the TC sign in the diagnosis of BA resulted in sensitivity, specificity, accuracy, and positive and negative predictive values of 80%, 98%, 94%, and 94%, respectively. However, in recent articles, Kim et al (8) and Humphrey and Stringer (9) reported that the TC sign had a sensitivity of only 58% and 73%, respectively, in the diagnosis of BA. According to a report by Tan Kendrick et al (12), the fibrotic cord can be easily masked by diffuse periportal echogenicity when there is nonspecific inflammation or cirrhosis. Thus, the TC sign is supportive but not as sensitive when either cirrhosis or widespread periportal inflammation is present. In our study, only 18 of 29 patients with pathologically confirmed BA had positive TC signs (sensitivity, 62%; specificity, 100%). Our results are consistent with the findings of Kim et al (8) and show that the TC sign has low sensitivity in the diagnosis of BA.

After Stowens (13) described hyperplastic and hypertrophic changes in the branches of the hepatic artery in the intrahepatic portal areas of patients with BA, there were several reports on the

hepatic arterial changes in patients with BA (7,14). According to Kim et al (8) and Humphrey and Stringer (9), the diameter of the hepatic artery is significantly larger in patients with BA than in patients with non-BA and control subjects. Our results show that the diameter of the hepatic artery was significantly larger in patients with BA than in patients with non-BA ($P < .001$) and control subjects ($P = .001$). Our results also show that the diameter of the portal vein in patients with BA was not significantly different from that in patients with non-BA ($P = .085$); however, the small sample size might not have allowed us to detect a significant difference between the groups.

Uflacker and Pariente (15) reported the presence of angiographically demonstrable perivascular arterial tufts in the periphery of the hepatic arterial circulation in patients with BA and suggested that these findings might be useful in the diagnosis of BA. However, angiographic evaluation is not routinely performed for the diagnosis of BA. We used color Doppler US instead of angiography to evaluate hepatic arterial changes. On color Doppler US images, an enlarged hepatic artery and hepatic arterial flow that extended to the hepatic surface were seen in all patients with BA.

Hepatic subcapsular flow had sensitivity, specificity, and positive and negative predictive values of 100%, 86%, 85%, and 100%, respectively, on the basis of consensus reading. All patients with BA who had hepatic subcapsular flow on color Doppler US images had subcapsular telangiectatic vessels at the time of the Kasai procedure. The microscopic examination enabled us to confirm the presence of dilated vessels, which seemed to be hypertrophic hepatic arteries, in the hepatic subcapsular area. The pathogenesis of hepatic arteriopathy in patients with BA is unknown.

Burgener et al (16) performed angiographic, hemodynamic, and histologic examinations of portal hypertension and periportal fibrosis induced in a dog by means of intraperitoneal polyvinyl alcohol injection and found increased hepatic arterial flow; the increased number and diameter of hepatic arterial branches were late findings observed only after the de-

Figure 4

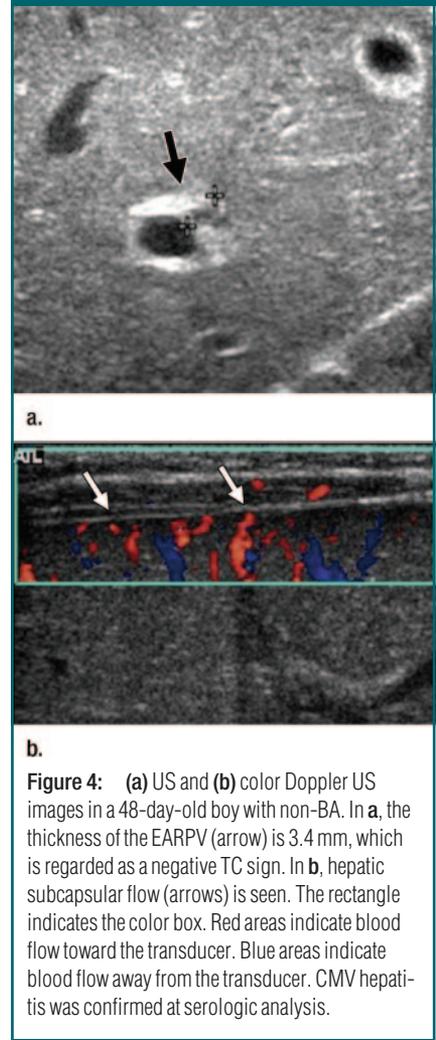


Figure 4: (a) US and (b) color Doppler US images in a 48-day-old boy with non-BA. In a, the thickness of the EARPV (arrow) is 3.4 mm, which is regarded as a negative TC sign. In b, hepatic subcapsular flow (arrows) is seen. The rectangle indicates the color box. Red areas indicate blood flow toward the transducer. Blue areas indicate blood flow away from the transducer. CMV hepatitis was confirmed at serologic analysis.

velopment of hepatic fibrosis. Ramm et al (17) reported that activated hepatic stellate cells are responsible for the increased production of type I collagen, which leads to hepatic fibrosis in patients with BA. In addition, their results showed that the hyperplastic bile duct epithelium is the predominant source of the profibrogenic cytokine transforming growth factor β within the portal tract that forms the fibrotic scar leading to cirrhosis. Thus, when we consider the histopathologic findings of BA (6), color Doppler US findings may reflect hypertrophy and hyperplasia of the hepatic artery in patients with BA, and we postulate that the pathogenesis of hepatic arteriopathy in BA involves fibrosis. However, in considering the role of ductal plate malformation in

the pathogenesis of BA, Desmet and Leuven (18) suggested that ductal plate malformation is often associated with abnormalities in the ramification of the portal vein and in the hyperplasia and hypertrophy of the hepatic artery branches in the portal tract.

Five of the 35 patients with non-BA had hepatic subcapsular flow on color Doppler US images. Of these five patients, four were thought to have TPN-induced cholestasis. In the remaining patient, CMV hepatitis was confirmed at serologic analysis. Histopathologic findings of TPN-induced cholestasis have been reported (19). In our study, these findings were also seen at pathologic analysis of specimens from the patients who received TPN. When we consider the findings of Burgener et al (16), these pathologic findings could explain why the four patients who received TPN for more than 6 weeks had hepatic subcapsular flow on color Doppler US images.

Lurie et al (20) reported that the histopathologic findings in the livers of patients with infantile CMV infection included cholestasis, portal fibrosis, and bile duct proliferation. Also, there have been several other studies in which the relationship between neonatal CMV infection and hepatic fibrosis was demonstrated (21,22). In consideration of the aforementioned reports, we presume that hepatic subcapsular flow in a patient with CMV hepatitis might be related to hepatic fibrosis; however, we could not confirm this at histopathologic analysis.

Our results show that although five patients with non-BA had hepatic subcapsular flow on color Doppler US images, we could exclude the possibility of BA because they had undergone TPN or had a high CMV immunoglobulin M titer.

Our study had limitations. We could not perform color Doppler US in all of the neonates and infants with hyperbilirubinemia during the study period. In some patients, reliable color flow on the hepatic surface could not be seen. Moreover, only one operator performed all US and color Doppler US examinations. This could have biased our results. Another limitation was that a small number of patients had TPN-induced cholestasis, and one pa-

tient had CMV hepatitis. Furthermore, in most of these patients, we were unable to confirm the presence of TPN-induced cholestasis or CMV hepatitis at pathologic analysis. An additional limitation was that US contrast material was not used in any patient. Hepatic subcapsular flow may have been amplified and easier to detect on color Doppler US images if we had used US contrast materials.

In conclusion, hepatic arterial flow extending to the hepatic surface on color Doppler US images had high sensitivity and relatively low specificity for the diagnosis of BA. The TC sign showed low sensitivity and high specificity for the diagnosis of BA. BA was confirmed at pathologic analysis in most patients who had negative findings for the TC sign but positive findings for hepatic subcapsular flow. The detection of BA can be supplemented by performing color Doppler US in addition to routine US when evaluating hepatic subcapsular flow; by using color Doppler US, we can potentially prevent delayed diagnosis of BA.

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