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Comparison of different diagnostic methods for differentiating biliary atresia from idiopathic neonatal hepatitis

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Abstract

Aim: To retrospectively analyze different methods in differentiating biliary atresia from idiopathic neonatal hepatitis. **Methods:** Sixty-nine infants with cholestatic jaundice and final diagnosis of idiopathic neonatal hepatitis (INH) and biliary atresia (BA) were studied retroprospectively from January 2004 to December 2006. A thorough history and physical examination were undertaken. All cases underwent abdominal magnetic resonance cholangiography (MRCP), ultrasonography (US), hepatobiliary scintigraphy (HBS), HBS single-photon emission computer tomography (HBS SPECT), and operation or percutaneous liver biopsy. The accuracy, sensitivity, specificity, and predictive values of these various methods were compared. **Results:** There were 39 girls and 30 boys, among whom 35 had INH (age, 61±17 days) and 34 had BA (age, 64±18 days). The mean age at onset of jaundice was significantly lower in cases of BA when compared to INH cases (9±13 vs. 20±21 days; P=.032). The diagnostic accuracy of different methods was as follows: liver biopsy, 97.1%; HBS SPECT, 91.30%; MRCP, 71.01%; HBS, 66.67%; US, 65.22%. **Conclusion:** Our results indicate that biopsy of the liver is considered as the most reliable method to differentiate INH from BA. The accuracy of HBS SPECT is higher than that of MRCP, HBS, and US. There was no significant difference in diagnostic accuracy among MRCP, HBS, and US.

Keywords: Biliary atresia; Idiopathic neonatal hepatitis; Magnetic resonance cholangiography; Liver biopsy

1. Introduction

Cholestatic jaundice in early infancy is an important clinical condition that results from diminished bile flow and/or excretion, and can be caused by a number of disorders. Idiopathic neonatal hepatitis (INH) and biliary atresia (BA) are the two main causes [1,2]. It is important to distinguish INH from BA in an infant presenting with jaundice, as the former purely needs a medical management and the latter requires surgical intervention as soon as possible [3].

Magnetic resonance cholangiography (MRCP), ultrasonography (US), technetium 99m-iminodiacetic acid (EHIDA) hepatobiliary scintigraphy (HBS), and HBS single-photon emission computed tomography (HBS SPECT) are the major diagnostic tools used in the differential diagnosis of neonatal hepatitis and BA, which are common causes of conjugated hyperbilirubinemia in neonates and young infants [4–9]. Endoscopic retrograde cholangiopancreatography is the most useful diagnostic procedure available for direct observation of the extrahepatic bile duct, but it is an invasive procedure that requires infants to undergo general anesthesia, which must be performed by a well-trained endoscopist with the correct instrumentation and technique [10–12]. Therefore, a multidisciplinary approach to the evaluation of neonatal jaundice is needed to determine the cause of the condition. In this study, we

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Table 1
Comparison of various diagnostic methods for INH and BA

Method	Patients (*n*)	Results	Final diagnosis				
			BA (*n*=34)		INH (*n*=35)		
			n	%	*n*	%	*P*
MR	69	BA	29	85.29	15	42.86	<.05
		INH	5	14.71	20	57.14	
US	69	BA	17	50	6	17.14	<.05
		INH	17	50	29	82.86	
Hepatobiliary scintigraphy	69	BA	30	88.24	19	54.29	<.01
		INH	4	11.76	16	45.71	
SPECT	69	BA	32	94.12	4	11.43	<.01
		INH	2	5.88	31	88.57	
Liver biopsy	69	BA	34	100	2	5.71	<.01
		INH	0	0	33	94.29	

BA vs. INH, chi-square analysis.

evaluated and compared the different diagnostic methods for this differentiation.

2. Materials and methods

In a retroprospective study from January 2004 to December 2006, the differential diagnosis and etiologic work-up of cholestasis in infancy were carried out. Sixty-nine consecutive cholestatic infants (39 girls, 30 boys) with a final diagnosis of INH or BA were entered in our study. Cases with etiologies other than INH and BA were excluded from the study. These patients were all referred to the Department of Pediatric Gastroenterology in Beijing Children's Hospital of Capital Medical University, which is the biggest children's hospital in China and Asia.

For all patients, a complete blood count, urinalysis, urine reducing substances, thyroid function tests, bacterial culture of both urine and blood, serum alpha-1-antitrypsin, and screening for cystic fibrosis (sweat chloride test) were performed. Acid–base status was determined as an initial step to evaluate the metabolic disorders. For all patients, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were checked, and all underwent MRCP, US, HBS, HBS-SPECT, and percutaneous liver biopsy. Cases suspicious for BA underwent laparatomy and intraoperative cholangiography.

The mean time between US and ^{99m}Tc-EHIDA HBS was 2 days (range, 0–4 days). The mean times between MRCP and US and ^{99m}Tc-EHIDA HBS were 2.6 days (range, 0–14 days) and 2.3 days (range, 0–13 days), respectively.

After a minimum 4-h fast, all patients underwent US with the use of 5- to 10-MHz and 4- to 7-MHz transducers. US was performed by one pediatric radiologist. We evaluated the hepatic parenchymal echoes, gallbladder size and shape, and presence or absence of a triangular cord in the porta hepatis. We measured the width and depth of the cord when possible. When abnormal hypoechoic or cystic lesions were noted on the anterior side of the portal venous bifurcation, power Doppler US (pulse repetition frequency, 700–1000 Hz; persistence setting, high; power gain percentage, 75–80%) was used to exclude vascular structures.

HBS was performed in all patients with the use of a gamma camera (Macroni IRIX 3). Patients were not fed for at least 6 h prior to ^{99m}Tc-EHIDA imaging. Approximately 5 mCi (185 MBq) of a ^{99m}Tc-EHIDA compound was injected intravenously. Images of the liver, biliary tree, and abdomen were obtained in the anterior projection at 5-, 10-, 15-, 20-, 30-, and 60-min intervals, and at 6 and 24 h. HBS SPECT was performed with the collection of images with 30 s/frame, for 40 frames, 64×64 matrix, 1.78 zoom, and circular orbit.

Hepatic extraction of the radiotracer, depiction of the gallbladder, and presence of activity in the small bowel were observed on the serial images obtained within 6 h and on the 24-h-delay image obtained by an experienced nuclear

Table 2
Accuracy of various diagnostic methods for BA and INH

Diagnostic method	*n*	BA (%)	*n*	INH (%)	*n*	INH vs. BA (%)
MR	29/34	85.29	20/35	57.14	49/69	71.01
Ultrasonography	17/34	50	29/35	82.85	45/69	65.22
Hepatobiliary scintigraphy	30/34	88.24	16/35	45.71	46/69	66.67
SPECT	32/34	94.12	31/35	88.57	63/69	91.30
Liver biopsy	34/34	100	33/35	94.29	67/69	97.10

[1]Accurately diagnosed cases/performed cases [7].

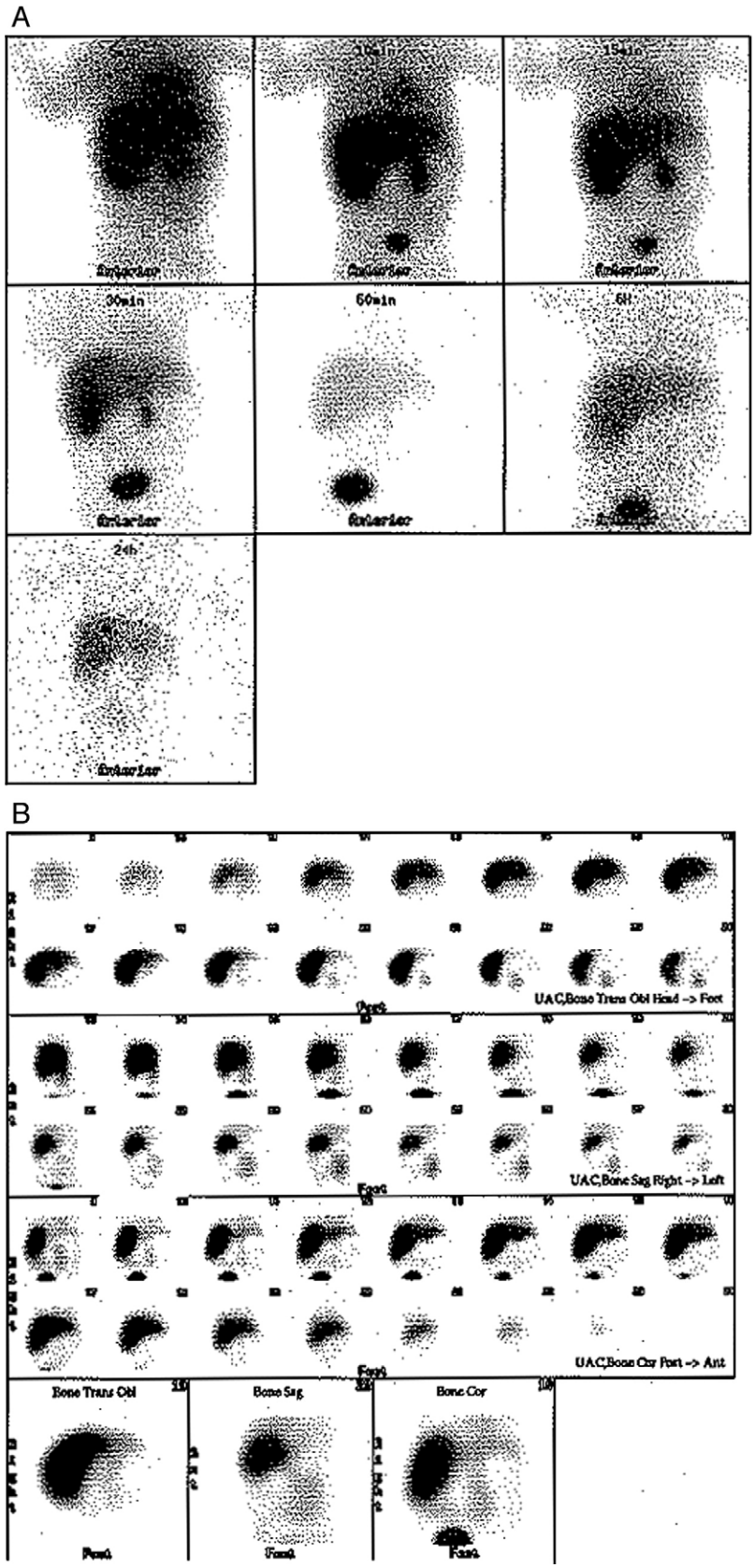


Fig. 1. Biliary atresia. (A) SPECT image from a 10-week-old female infant showing good extraction of tracer in the initial 1-h images, no gastrointestinal tract activity at 6 h, or 24-h planar imaging. (B) The SPECT study shows no gastrointestinal tract activity. (SPECT images: upper row transverse, middle coronal, lower sagittal.)

medicine physician. Poor hepatic extraction was defined as decreased hepatic activity and persistence of cardiac blood-pool activity over 60 min. Good hepatic extraction was defined as prompt diffuse hepatic activity with no cardiac blood-pool activity on images obtained at 5–10 min.

One hour before the MRCP imaging examination, patients were sedated with orally administered chloral hydrate (50 mg/kg). We did not use a negative contrast medium for the suppression of upper gastrointestinal signals. All MR images were obtained with a 1.5-T unit with the use of head or knee coils. Before MRCP, we obtained transverse T1-weighted fast multiplanar spoiled gradient-recalled-echo images [repetition time (ms)/echo time (ms), 180/4.2; flip angle, 90°; section thickness, 5 mm; section gap, 1 mm; matrix, 256×3×128; imaging time, 25 s] to localize the hepatobiliary system.

MRCP was performed with a T2-weighted single-shot fast SE sequence with thin-section and thickslab acquisitions. To cover the entire biliary tree, transverse multisection single-shot fast SE images were acquired with the following parameters: ∞/80–100 (effective); echo train length, 128; matrix, 256×3×192; section thickness, 3–4 mm; bandwidth, 31.3 kHz; field of view, 16–20 cm; and mean acquisition time, 36 s. When there was an area of abnormal signal intensity anterior to the bifurcation of the main portal vein, limited sagittal single-shot fast SE images of the porta hepatis were obtained to further define the relationship with surrounding structures. In all patients, coronal and oblique coronal (245°, 230°, 130°, 145° to the axis) images were acquired.

MRCP was assessed by two pediatric radiologists who were unaware of the US and ^{99m}Tc-EHIDA imaging results. Multisection and thickslab single-shot MRCP were analyzed, with an emphasis on the visualization of the extrahepatic bile duct and gallbladder. When the extrahepatic bile duct was indistinct or invisible, specific attention was paid to periportal thickening and to the presence or absence of high signal intensity in the porta hepatis on T2-weighted images. The radiologists independently documented the single-shot MR cholangiographic findings and then resolved discrepancies by consensus.

At routine histopathologic examination of the specimens obtained when the Kasai procedure was performed, the portal mass was examined carefully for evidence of cystic changes in the fibrotic mass, and the diameter of bile duct at the porta

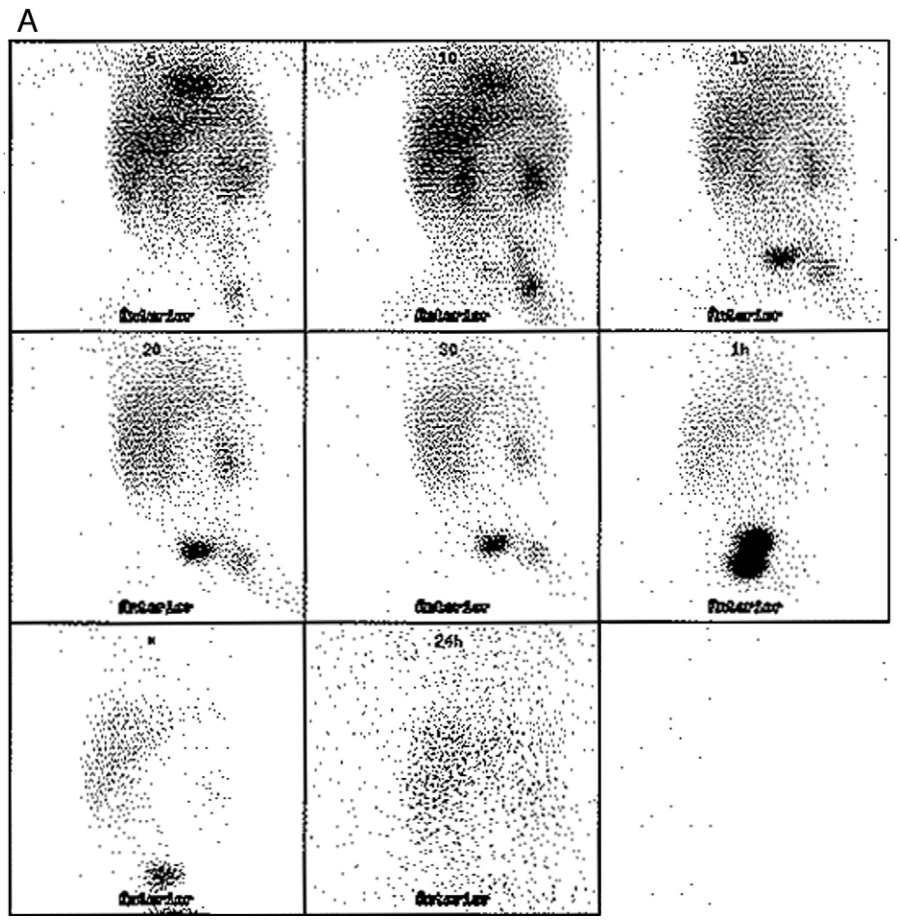
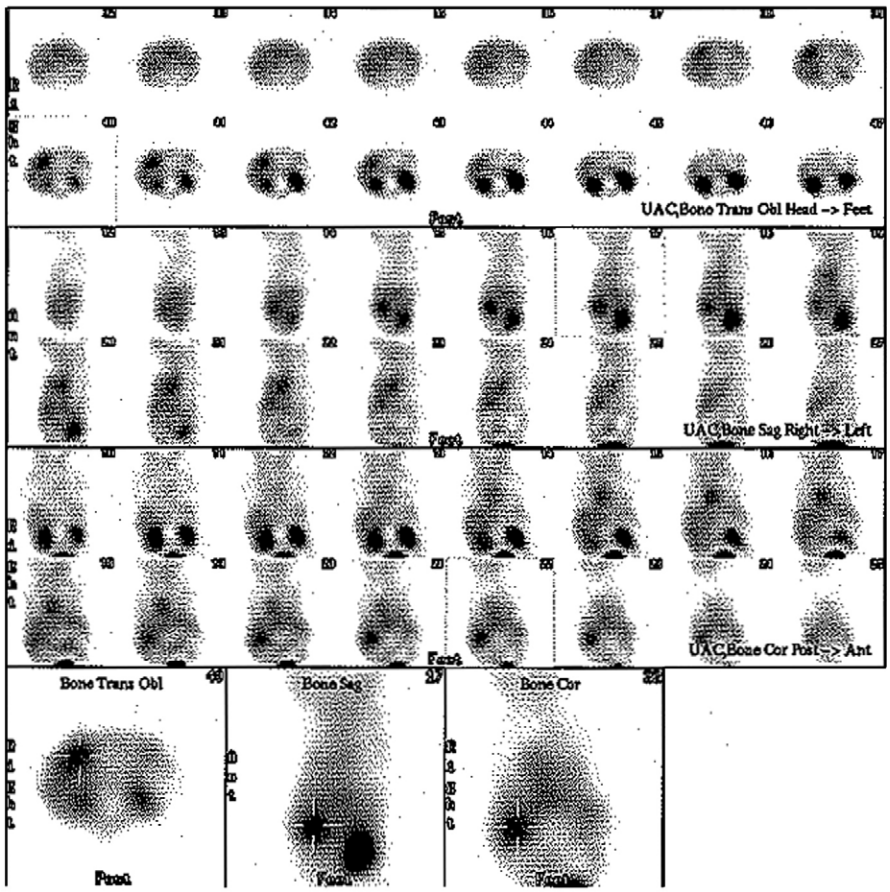


Fig. 2. Severe INH. (A) SPECT image from a 9-week-old male infant showing very poor extraction of tracer by the liver. No obvious gastrointestinal tract excretion was seen at 6 and 24 h on planar imaging. (B) SPECT imaging at 6 h shows obvious activity in the gastrointestinal tract (arrows) excluding BA. (SPECT images: upper row transverse, middle coronal, lower sagittal.) (C) Coronal heavily T2-weighted single-shot fast spin-echo MRCP images were acquired. Gallbladder, hepatic, or common ducts are not identified on MRCP images.

B



C

Fig. 2. (*continued*).

Table 3
Sensitivity and specificity of various diagnostic methods for BA and INH

Diagnostic method	Sensitivity for BA		Specificity for BA	
	%	*n*	%	*n*
MR	85.29	29/34	57.14	20/35
Ultrasonography	50	17/34	82.85	29/35
Hepatobiliary scintigraphy	88.24	30/34	45.71	16/35
SPECT	94.12	32/34	88.57	31/35
Liver biopsy	100	34/34	94.29	33/35

Sensitivity for BA was equivalent to specificity for INH, and specificity for BA was identical to sensitivity for INH.

hepatis was measured. When a cystic space was noted in the fibrotic mass, immunohistochemical staining for cytokeratin was performed to identify remnants of the ductal epithelium.

Finally, the accuracy of the four diagnostic methods (MRCP, US, HBS, HBS-SPECT, and liver biopsy) was evaluated for differential diagnosis of INH and BA. The sensitivity, specificity, positive predictive value, and negative predictive value of each method were also calculated.

3. Results

There were 69 cholestatic infants, including 39 (56.52%) girls and 30 (43.48%) boys with a mean age of 60±19 days (range, 31–121 days). There were 35 (50.72%) cases (19 girls, 16 boys) of INH and 34 (49.28%) cases (20 girls, 14 boys) of BA. The mean age of INH patients was 59±16 days (range, 33–86 days) and that of BA patients was 62±14 days (range, 31–121 days), and the difference was not statistically significant. Age at onset of jaundice in INH was 22±19 days (range, 2–59 days) and in BA was 12±11 days (range, 2–42 days), and the difference was significant (P=.032). Forty-eight (69.57%) cases had clay-colored stools, among which 16 had INH and 32 had BA; and 21 (30.43%) cases had normal-colored stools, among which 19 had INH and 2 had BA (P=.003). The difference in mean ALT, AST, and ALP values between INH and BA patients was not significant.

Table 1 shows a comparison of the various methods used in diagnosing the 69 infants with cholestasis. Table 2 shows the diagnostic accuracy of each method in order of accuracy. Liver biopsy had 100% diagnostic accuracy for BA and 95.2% for INH, respectively (Figs. 1 and 2). Table 3 shows the sensitivity and specificity, and Table 4 demonstrates the positive and negative predictive values of each method in differentiating BA and INH. Liver biopsy had the highest sensitivity and specificity for differentiating BA and INH.

4. Discussion

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guideline for the evaluation of cholestatic jaundice in infants recommends that any infant noted to be jaundiced at the 2-week well-child visit should be evaluated for cholestasis [1]. Evaluation of breast-fed infants may be delayed until 3 weeks of age if they have a normal physical examination, no history of dark urine or light stools, and can be reliably monitored [1,13,14]. Neonatal hepatitis and BA, which typically occur in term infants, account for 70–80% of cases [15].

Evaluation should be undertaken in a staged approach [16]. The initial step is rapid diagnosis and early initiation of therapy of treatable disorders. Conditions, such as sepsis, hypothyroidism, panhypopituitarism, and inborn errors of metabolism (e.g., galactosemia), must be recognized and treated promptly to avoid significant progression of the illness. Extrahepatic BA must be differentiated from neonatal hepatitis because early surgical intervention (i.e., before 2 months of age) results in a better outcome.

The development of a half-Fourier acquisition single-shot fast SE or turbo SE sequence means that the use of MRCP for the investigation of biliary tract diseases in adults has increased [17–20]. Authors of published articles have described the feasibility of MR cholangiography in children. Matos et al. [21] stated that BA could be ruled out if the extrahepatic bile duct is completely identified at MRCP. Guibaud et al. [22] reported that because of the small bile duct and the low rate of bile excretion in neonates and young infants with cholestatic jaundice, MRCP should not be relied on for the demonstration of the bile duct. Both Matos et al. and Guibaud et al. used a two-dimensional turbo SE sequence with spatial resolutions that ranged from 0.78 to 2.3 mm. Both source images and maximum intensity projections were reviewed. Chan et al. [23] used a half-Fourier acquisition single-shot turbo SE sequence with spatial resolutions that ranged from 0.63 to 1.04 mm. They reported that MRCP showed both the first branch of the intrahepatic bile duct and the common bile duct in most children without structural abnormalities. In five patients with BA, neither the common hepatic duct nor the common bile duct could be seen at MRCP; only a focal rudimentary extrahepatic bile duct was found.

In our study, MRCP had a sensitivity and a specificity of 85.29% and 57.14% for BA, respectively. Accuracy of MRCP for differentiation between BA and INH in our series was 71.01%, which was lower than that reported by Norton

Table 4
Positive and negative predictive values of various diagnostic methods in BA and INH

Diagnostic method	Positive PV for BA and negative PV for INH		Negative PV for BA and positive PV for INH	
	%	*n*	%	*n*
MR	65.91	29/44	80	20/25
Ultrasonography	73.91	17/23	63.04	29/46
Hepatobiliary scintigraphy	61.22	30/49	80	16/20
SPECT	88.89	32/36	93.94	31/33
Liver biopsy	94.44	34/36	100	33/33

PV indicates predictive value.

et al. [24] (sensitivity, specificity, and accuracy were 90%, 77%, and 82%, respectively). This lower accuracy may be due to the lower experience of our sonographer for detection of triangular cord sign. Contrary to previous reports, false-positive and false-negative findings occur at MRCP.

Abdominal US is more helpful in the diagnosis of choledochal cysts but can also suggest the diagnosis of BA. Findings suggestive for the latter are nonvisualized gall bladder and the presence of the triangular cord sign [25–27]. The sensitivity and specificity of a small or absent gall bladder in detecting obstruction range from 73% to 100% and from 67% to 100%, respectively, when correlated with pathologic, surgical, and subsequent clinical examinations [1].

In our study, abdominal US had a sensitivity and a specificity of 50% and 82.86% for BA, respectively. Accuracy of US for differentiation between BA and INH in our series was 65.22%, which was lower than that reported by Lin et al. [28] (sensitivity, specificity, and accuracy were 86.7%, 77.1%, and 79.4%, respectively) and by Park et al. [9] (85%, 100%, and 95%, respectively). This lower accuracy may be due to the lower experience of our sonographer for detection of triangular cord sign.

HBS with technetium-labeled iminodiacetic acid analogs can be helpful in distinguishing BA from neonatal hepatitis and other causes of cholestasis. The sensitivity and specificity of scintigraphy in detecting obstruction range from 83% to 100% and from 33% to 100%, respectively [1]. In the present study, scintigraphy had a sensitivity and a specificity of 88.24% and 45.71% for detecting BA, respectively. Scintigraphy adds little to the routine evaluation of the cholestatic infant, but may be of value in determining patency of the biliary tract, thereby excluding BA [1].

HBS had an accuracy of 66.67% in this study, which is comparable to the data reported by Lin et al. [28] and Nadel [29], but higher than that by Park et al. [9] and Gupta et al. [3]. HBS SPECT had an accuracy of 91.30% in this study, which is comparable to the data reported by Sevilla et al. [30]. Sevilla et al. reported that HBS SPECT improves the diagnostic accuracy to a level compatible to the planar study when performed with phenobarbitone premedication.

Percutaneous liver biopsy is generally employed in the evaluation of neonatal cholestasis, particularly when biliary tract obstruction is high on the differential diagnosis [31]. The NASPGHAN guideline recommends that a percutaneous liver biopsy should be performed in most infants with undiagnosed cholestasis [1]. The biopsy should be interpreted by a pathologist with expertise in pediatric liver disease. Biopsy is recommended before performing a surgical procedure to diagnose BA. If the results are equivocal and biopsy was performed when the infant was <6 weeks of age, a repeated biopsy may be necessary.

Liver needle biopsy is the most invasive method among the various tests, but it is also the most accurate one. Our study found that liver needle biopsy was the most reliable method with the highest accuracy rate of 96.9%, which is similar to those in previous reports [2,12,15].

In conclusion, our results indicate that biopsy of the liver is considered as the most reliable method to differentiate INH from BA. The accuracy of HBS SPECT is higher than that of MRCP, HBS, and US. There was no significant difference in diagnostic accuracy among MRCP, HBS, and US.

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