The Diagnostic Accuracy of Hepatobiliary Scintigraphy and Ultrasonography in Cholestatic Jaundice Infants.

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บทคัดย่อ:
วัตถุประสงค์: โรคทางเดินน้ำาดีตีบตัน (biliary atresia) และกลุ่มอาการตับอักเสบในทารกแรกเกิด (neonatal hepatitis syndrome) เป็นสาเหตุส่วนใหญ่ของดีซ่านหรือน้ำาดีคั่งในทารก แต่ทั้งสองสาเหตุมีอาการแสดงที่คล้ายกันมากซึ่งทำให้การวินิจฉัยทั้งสองเป็นไปได้ยาก การศึกษามีวัตถุประสงค์เพื่อเปรียบเทียบความแม่นยำของการวินิจฉัยด้วยการตรวจทางเวชศาสตร์นิวเคลียร์ในระบบตับและทางเดินน้ำาดี (hepatobiliary scintigraphy) และความแม่นยำของ ultrasonography ในทารกที่มีดีซ่านจากโรคทางเดินน้ำาดีตีบตัน

วัสดุและวิธีการ: ทารกที่มีดีซ่าน 124 ราย ระหว่างเดือนมกราคม พ.ศ. 2539 ถึง มิถุนายน พ.ศ. 2550 มารับบริการในโรงพยาบาลสงขลานครินทร์ อ.ยะลา จ.ยะลา 95000 ได้รับการวินิจฉัยโดย ultrasonography และ hepatobiliary scintigraphy ผลจากการวินิจฉัยใน 81 ราย ได้แก่ การผ่าตัดช่องท้องแล้วพบถุงน้ำาดีตีบตัน ท่อน้ำาดีตีบตัน หรือ intraoperative cholangiography พบมีการอุดกั้นทางเดินน้ำาดี แล้วน่า
Abstract:

Objective: Biliary atresia (BA) and neonatal hepatitis syndrome (NHS) are major causes of cholestatic jaundice, but the two conditions are symptomatically very similar and it is difficult for pediatricians to distinguish between them when making a diagnosis. The aim of this study was to compare the diagnostic accuracy of hepatobiliary scintigraphy (HS) with ultrasonography (US) in cholestatic jaundice infants to exclude biliary atresia.

Material and Method: Of 124 patients suffering from cholestatic jaundice from January 1996 to June 2007 were seen in Songklanagarind Hospital; 68 patients underwent HS and 70 patients underwent US. A laparotomy finding of either atretic common bile duct or gallbladder, or evidence of bile duct obstruction from intraoperative cholangiography, was considered as the final diagnosis of BA, and the results were compared.

Results: Based on the operative noted above, 44 patients (54.3%) had BA. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of HS in the diagnosis of BA were 97.0%, 42.9%, 61.5%, and 93.75%, respectively. The overall accuracy of HS was 69.1%. The sensitivity, specificity, PPV and NPV of the US were 28.9%, 75.0%, 57.9%, and 47.1%, respectively. The overall accuracy of US evaluations was 50.0%.

Conclusion: HS is an important imaging technique in the diagnostic evaluation of infants with cholestatic jaundice. It is a convenient and reliable method of differentiating BA from NHS, with a diagnostic accuracy superior to that of US.

Keywords: biliary atresia, cholestatic jaundice, hepatobiliary scintigraphy, infants, ultrasound
Introduction

It is often a challenge for the pediatrician to accurately distinguish between biliary atresia (BA) and neonatal hepatitis syndrome (NHS), the two major causes of cholestatic jaundice in infancy. Because the best outcome depends on early surgical intervention in BA, being able to differentiate BA from other causes of neonatal jaundice is extremely important.¹⁻⁵

Until now, hepatobiliary scintigraphy (HS) has been thought to be the most sensitive modality (97–100%) to distinguish BA from other causes of neonatal cholestasis, but the specificity of HS varies from 67% to 93%, depending on the ⁹⁹mTc labeled radiopharmaceutical agent used.⁶

HS is a convenient and reliable method of differentiating BA from NHS, some studies have indicated that HS is superior to ultrasonography (US) in differentiating these conditions,⁷ but the evidence is still controversial. It has other advantages over other competing imaging modalities as well, in that HS evaluates fasting bile flow, is not invasive and is not operator dependent. This study was undertaken to evaluate the accuracy of HS in excluding BA as the cause of infantile cholestatic jaundice and comparing its diagnostic accuracy with US.

Material and Method

One hundred and twenty four patients suffering from cholestatic jaundice were seen in Songklanagarind Hospital, the largest tertiary care center and major referral center in southern Thailand, from January 1996 to June 2007. Forty three were referrals and were excluded from the study because incomplete medical records, although HS showed excretion in 27 patients and no excretion in 16 patients. The remaining 81 patients were included in this study. Conjugated hyperbilirubinemia–caused cholestatic jaundice was defined as a total serum bilirubin level of more than 3.0 mg/dL (51 μmol/L), with the direct form more than 40% of the total (normal values 0.2–1.0 mg/dL (3.4–17 μmol/L) and 0–0.2 mg/dL (0–3.4 μmol/L)).

Imaging

Sixty eight of the 81 patients underwent HS. Phenobarbital (5 mg/kg/day) was given to each patient at least 5–7 days before the HS, and all subjects were fasted for at least 4 hours before their procedure. Following the administration of technetium–⁹⁹m diisopropyl iminodiacetic acid (⁹⁹mTc–DISIDA) in a dose of 0.2 mCi/kg, HS sequential images of the anterior abdomen in the supine position were performed at 1, 2 and 6 hours. A further delayed image was obtained at 24 hours if there was still no visualization of bowel activity by 6 hours (Figure 1). The impression or diagnosis of radiologist was the final diagnosis for BA by used HS.

Seventy in 81 patients had an US focusing on the fibrous tissue at the porta hepatis and the triangular cord, which is the visualization of a triangular or tubular shaped echogenic density just cranial to the portal vein bifurcation on a transverse or longitudinal scan, to assess the presence or absence of the gallbladder (Figure 2) and/or other unusual characteristics of the liver resulting from BA. The hyperechogenicity or cirrhosis of the liver was assessed. All subjects were fasted for at least 4 hours before US. The impression or diagnosis of radiologist was the final diagnosis for BA by used US.
Figure 1  A. Showing of the NHS case, in which the anterior image of HS shows good hepatocyte uptake and gall bladder intestinal activity. 
B. Showing a BA case, in which the anterior image of HS shows no tracer excretion into the intestine. (Faint urinary tract excretion can be seen.)

Figure 2  US films from a patient with biliary atresia
A. Showing the triangular cord sign (↓) cranial to the portal vein, distant 2.8 mm 
B. Showing the atretic gallbladder (↓), 15.8 mm in length
Final diagnosis

The final diagnosis of BA was based on either operative findings of either atretic common bile duct or gallbladder (Figure 3), or on evidence of bile duct obstruction from the intraoperative cholangiography (IOC) (Figure 4). The results of the HS and US were compared with these definitive diagnoses.

Figure 3  Intraoperative findings in one of the BA cases
A. Liver, dark in color with irregular surface
B. Atretic gall bladder

Figure 4  Intraoperative cholangiography via a gallbladder catheter
A. Yellowish bile is detected upon aspiration of the gallbladder.
B. Intraoperative cholangiography shows outline the biliary tree.
Diagnosis of BA in the pathological reports was based on typical histopathological features, including bile duct proliferation, bile plugs, giant cell transformation, canalicular and cellular bile stasis, and periportal fibrosis. In patients showing giant cell transformation, inflammatory cell infiltration, and/or lobular disorganization on liver biopsy, the final diagnosis was hepatitis.

**Statistical analysis**

Data were recorded in Microsoft Excel® and analyzed using the R software (version 2.15.2). The results of each modality were analyzed for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy.

**Results**

Of the 81 subjects with cholestatic jaundice enrolled in the study, 44 (54.32%) were diagnosed as BA, based on the operative finding. Of these, 21 were male (47.72%) and 23 female (52.27%); 37/81 (45.68%) had NHS and neonatal jaundice from unspecified hepatocellular damage. HS was performed in 33 of the 44 patients who had a final diagnosis of BA.

Of the 68 patients undergoing HS, 52 had scintigraphic findings indicating BA, of which 32 (61.5%) were true positives and 20 (38.5%) were false positives. Sixteen patients had scintigraphic findings not indicative of BA, of which 15 (93.8%) were true negatives and 1 (6.25%) was a false negative. Based on the operative results, the sensitivity, specificity, PPV, and NPV of the HS in diagnosis of BA were thus 97.0%, 42.9%, 61.5%, and 93.75%. The overall accuracy of HS was 69.1%.

Of the 70 patients undergoing US, 19 patients were positive for BA, of which 11 (57.9%) were true positives and 8 (42.1%) were false positives. Of the 51 patients whose ultrasound evaluations were not indicative of BA, 24 (47%) were true negatives and 27 (52.9%) were false negatives. Based on the operative results, the sensitivity, specificity, PPV, and NPV of the US in the diagnosis of BA were thus 28.9%, 75.0%, 57.9%, and 47.1%. The overall accuracy of ultrasound evaluations was 50.0%. A receiver operating characteristic (ROC) curve was plotted for each test (Figure 5).

When comparing the results of patients who had had both tests, there were 31 indicated BA, 21 patients who had both a HS and an US. Considering either or both tests being positive, to indicated BA of which 14 (66.7%) were true positives and 7 (33.3%) were false positives. Of 10 patients in which neither test indicated BA, 9 patients (90%) were true negatives and 1 (10%) was a false negative. Based on the operative results, the sensitivity, specificity, PPV, and NPV of both HS and US together in the diagnosis of BA were 93.3%, 56.25%, 66.7%, and 90.0%. The overall accuracy of both methods together was 74.2%.

**Discussion**

Both BA and NHS are major causes of cholestatic jaundice in infants. Perinatal obliteration of the extrahepatic bile ducts requires immediate surgery, whereas other causes of persistent jaundice may be treated medically and/or conservatively. Therefore, considerable effort has been made to facilitate the definite diagnosis of these conditions, to which HS has made a major contribution.
In the majority of previous trials, the finding of a tracer in the intestine has been considered as pathognomonic for the permeability of the extrahepatic biliary ducts, thus ruling out BA. However, the absence of an intestinal tracer had not been definitely associated with BA. Some authors have suggested that HS could be a straightforward and noninvasive diagnostic method which enables the permeability of the biliary tract to be assessed in infants with jaundice. Spivak et al. also confirmed these data; in their study, the absence of gut excretion on the first DISIDA study was 100% sensitive but only 43% specific for BA and the authors concluded that the absence of gut excretion on a first DISIDA study does not necessarily indicate extrahepatic obstruction; the study should be repeated if the diagnosis is not clear.

In our study a similar finding was obtained; the PPV of 61.5% shows that the absence of radioactive tracer entrance into the gut is not specific for BA and therefore if any doubt in diagnosis is present, further evaluation is warranted. This fact could be explained by the fact that neonatal hepatitis may be accompanied by biliary excretion ranging from zero to normal. Nonvisualization of the gallbladder has also been considered to be nonspecific in the discrimination of medical from surgical causes of jaundice.

Nevertheless, in some of the previous trials, disappointing results were obtained. A study by Cox et al. found that an absence of the gallbladder on US, and a lack of detectable radioisotope in the gastrointestinal and/or extrahepatic biliary tract on HS, lacked sensitivity and/or specificity when

![Figure 5](image-url)

**Figure 5** The ROC curve of the diagnostic BA, with the cut–point of “1” showing DISIDA negative and US negative, “2” showing DISIDA negative and US positive, and “3” showing DISIDA positive and US negative.
compared to liver biopsy. However, HS required more time, 6-8 days, and was less specific than US and liver biopsy together. The authors recommended that HS should not be routinely used in evaluating infantile cholestasis, especially if it delays surgical intervention.

In previous studies, it has been believed that the US features of neonatal hepatitis are nonspecific. However, Choi et al. concluded that the ultrasonographic triangular cord sign is a very specific finding representing the fibrous cone at the porta hepatis and is a quick, simple, and definitive tool in the noninvasive diagnosis of BA. They concluded that if a triangular cord sign is visualized, no further studies are necessary and an exploratory laparotomy can be done. If the triangular cord sign is not visualized, HS is recommended to evaluate bile duct patency. Also, Tan Kendrick et al. showed that the triangular cord sign and gallbladder length together are noninvasive, inexpensive, and very useful markers for BA. It is also considered in many institutions that US is the cheapest diagnostic tool in the management of these patients. In another study, by Park et al., US showed a diagnostic accuracy of 95% with 85% sensitivity and 100% specificity, while 99mTc-DISIDA HS showed a diagnostic accuracy of 56% with 96% sensitivity and 35% specificity.

The common feature of all previous studies is that they all recommended US as the initial imaging procedure of choice in patients presenting with jaundice to rule out anatomic anomalies such as a choledochal cyst or BA. In this study, disappointing results were obtained from the US, with a diagnostic accuracy of 50% with 29% sensitivity and 75% specificity, which contrasts with the other studies. In our data, there were only a few cases in which the radiologist reported the ultrasonographic finding of the triangular cord sign; in most cases the finding showed only the indirect evidence of the biliary atresia such as a collapsed gall bladder.

**Limitations**

The study was based on medical record. The US diagnosis was reported by multiple radiologists. The name of ultrasound machine was not recorded in that time of US.

**Conclusion**

HS is an important imaging technique in the diagnostic evaluation of infants with cholestatic jaundice. In a comparison of the diagnostic accuracy of HS and US in cholestatic jaundice infants to exclude biliary atresia, HS is a convenient and reliable method of differentiating BA from NHS, with a diagnostic accuracy superior to that of US. This study agrees with the growing concensus that US is less sensitive than HS in the diagnosis of BA, but has the advantage of being more specific. In our institute we recommend that neither HS nor US should be done if they will delay surgical intervention.

**References**


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