Hepatobiliary scintigraphy in persistent direct hyperbilirubinemia in the neonate

Mahmoud El-Desouki, MD FRCP(C), Moh'd Mohamadiyeh, MD ABNM, Abdullah Al-Rabeah, MBBS FRCS(C), Saleh Othman, Nasser Al-Jurayyan, MD ABNM, Abdullah Asaad, MBBS DTCH, Mohammad Al-Mouzan, Abdulbaset Bashir, Zafer Skiff, Assal Y. Al-Samarrai, FRCS

ABSTRACT

Objectives: To present the value and usefulness of hepatobiliary scintigraphy in the investigation of infants with persistent hyperbilirubinemia through our experience in King Khaled University Hospital at King Saud University, Riyadh. **Setting:** King Khalid University Hospital, Departments of Nuclear Medicine, Pediatrics and Pediatric Surgery. Patients and methods: Seventy-seven patients aged between 5 days and 6 months (average 62 days), 43 females and 34 males, 65 Saudi and 12 non-Saudi were investigated. Laboratory tests, abdominal ultrasound, hepatobiliary scintigraphy, liver biopsy, explorative laparatomy and intraoperative cholangiography were performed whenever indicated. The findings on hepatobiliary scintigraphy of non-visualization of the gallbladder and no activity in the bowel up to 24 hours post injection (p.i.) were considered consistent with the diagnosis of biliary atresia. **Results:** Thirty four infants were diagnosed by hepatobiliary scintigraphy as having biliary atresia. Only 3 of the 34 were false positives as compared to liver biopsy results. Twenty-nine of the other 43 patients showed bowel activity sometime between 6 and 8 hours p.i. whereas the other 14 showed it at 24 hours p.i. Fourteen cases of the 19 with hepatitis showed decreased and delayed liver uptake in an irregular pattern. The other 5 cases of hepatitis showed good liver uptake similar to that seen in cases with biliary atresia. **Conclusions:** Hepatobiliary scintigraphy has become an essential part of the investigational work-up plan of infants with persistent hyperbilirubinemia before and after surgery because it is a simple and noninvasive technique.

Saudi Medical Journal 1997; Vol. 18 (3)

Keywords: *Hepatobiliary scintigraphy, biliary atresia, neonatal jaundice, neonatal hepatitis, biliary hypoplasia.*

Disorders of the biliary tree are an important cause of neonatal hyperbilirubinemia (HB). The most frequent diagnoses are biliary atresia (BA) and neonatal hepatitis (NH). In BA the bile flow is obstructed due to obliteration of the extrahepatic ducts.[1] Distinction between the surgically correctable causes of HB, such as BA and non-correctable ones is vital and important. Hepatobiliary scintigraphy (HBS) using 99mTc-Imino diacetic acids (IDA) has been shown to be both useful and valuable in the investigation of infants with persistent neonatal HB.[2-6] In this work we present our experience at the King Khaled University Hospital, Riyadh, investigating persistent HB in Saudi and non-Saudi infants.

Patients and methods. Seventy-seven patients aged between 5 days and 6 months (average 62 days), 43 females and 34 males, 65 Saudi and 12 non-Saudi were investigated as follows:

Hepatobiliary scintigraphy. After 5 days administration of 5 mg/kg/day of phenobarbitol, 1-2 mCi of 99mTc-disisopropyl (disofenin) was administered intravenously to infants after 3 - 4 hours of fasting. Imaging of the abdomen started immediately after injection with flow (16 frame/2 sec each) on 64 matrix, followed by sequential static images of 3 - 5 minutes each for 60 minutes in anterior projection until visualization of gallbladder (GB) and/or bile ducts was observed, after which views in the right anterior oblique, right lateral and posterior projections were taken. If activity in the bowel was not identified, delayed images of the abdomen were obtained at 2 - 3, 4 - 8 and 20 - 24 hours post injection.

The scintigraphic images were reinterpreted by three nuclear medicine physicians (MD,MM,SO), without knowledge of the final diagnosis. The degree and pattern of radioactive tracer uptake (RATU) by the liver, GB visualization and time of

From the Departments of Nuclear Medicine (El-Desouki, Mohamadiyeh, Othman), Pediatric Surgery (Al-Rabeah, Al-Samarrai), King Saud University, Riyadh and Pediatric (Al-Jurayyan, Asaad, El-Mouzan), King Saud University, Riyadh and Pediatric Surgery Department, (Bashir, Skiff), Security Forces Hospital, Riyadh, Saudi Arabia.

Received July 1996. Accepted for publication in final form September 1996.

Address correspondence and reprint request to: Dr. Mahmoud El-Desouki, Associate Professor and Head, Nuclear Medicine Division, King Khalid University Hospital, King Saud University, PO Box 7805-46, Riyadh 11742, Kingdom of Saudi Arabia. Fax no: (966)-1-467-2393.

Table 1 - Distribution of neonatal jaundice cases.

Diagnosis	Number
Biliary atresia	34
Intrahepatic cholestasis	43
Hepatitis: 19	
Other : 24	
(e.g. TPN, PHP, HTh)	
Total	77

TPN: total parenteral nutrition
PHP: panhypopituitarism
HTh: hypothyroidism

appearance of activity in the bowel, if occurred, were recorded. Nonvisualization of the GB and bowel was considered a positive indicator of BA. Poor RATU and/or inhomogenous uptake pattern by the liver was considered suggestive of NH. Conclusions were reached by consensus.

Diagnostic laboratory tests. Serial liver function tests were carried out including total bilirubin and the percent direct fraction in addition to the investigation of infectious microorganisms (i.e. TORCH) and metabolic causes.

Ultrasound. All patients underwent abdominal ultrasounds. Images were obtained using a variety of real-time ultrasound machines with 5.0 - 7.5 Mhz sector transducers. All studies were performed after adequate time of fasting in relation to expected time of feeding. Ultrasound evaluation included the gallbladder; size, shape and wall thickness and the intra- and extra-hepatic biliary trees; dilatation, filling defect and presence of associated congenital malformation (i.e. choledocal cyst).

Liver Biopsy Percutaneous liver biopsy was performed to confirm clinical suspicions. The findings of fibrosis, bile duct proliferation and fibrosis and canalicular bile stasis were looked for in each patient.

Explorative laparotomy and operative cholangiogram Exploration of the porta hepatis region was performed under general anesthesia and endotracheal intubation in each case in which biliary atresia was still highly considered. Liver gross appearance; size, color, surface and consistency were evaluated. The gallbladder and the extrahepatic ducts were also evaluated for size, fibrosis and connections. Intraoperative cholangiogram was performed by inserting a small catheter to evaluate the patency and size of the extra- and intra-heptic biliary ducts.

Results Liver biopsy was performed in 58 patients. The diagnosis of BA (Table 1) was concluded when the section of wedge biopsy showed disturbed hepatic architecture, bile duct proliferation and fibrosis. Diagnostic findings of hepatitis were considered based on biopsy findings consistent with giant cell hepatitis, isolation of microorganisms (i.e. CMV) in culture media (i.e. urine), or clinical follow up.

Hepatobiliary scintigraphy. All 34 patients with BA showed prompt and homogenous hepatic uptake (Fig. 1) and no bowel activity throughout the study which lasted between 20 and 24 hours. Only 3 patients had different diagnoses, 2 hepatitis and 1 total parenteral nutrition with sensitivity, specificity, positive predictive value, negative predictive value and accuracy rates of 100%, 88.9%. 91%, 100% and 94.8%, respectively (Table 2). Sixteen cases of BA had both pre- and postoperative HBS (Fig. 2) to evaluate the outcome of the reconstructive surgery. Twenty-nine of the other 43 patients showed bowel activity sometime between 6 and 8 hours p.i. whereas the other 14 at 24 hours p.i. Fourteen cases of the 19 with hepatitis showed decreased and delayed liver uptake in an irregular pattern (Fig. 3) representing compromised hepatocyte function. The other 5 cases of hepatitis showed good liver uptake similar to that seen in cases with BA, therefore distinction between these two entities could not be made based on this finding alone.

Ultrasound. In patients with BA, the most common ultrasonographic findings (32 of 34) were non-dilated bile ducts and a tiny and contracted gallbladder (29 of 34). In the other patients with no BA (43), the gallbladder was visualized in 38 patients.

Discussion Extrahepatic biliary atresia (BA) is a disease of the infant, in which all or part of the extrahepatic bile duct is destroyed or absent.[7] It is the single, most frequent cause of death from liver disease and indication for liver transplantation in children.[8] Diagnosis of BA is very difficult and cumbersome. The clinical presentations of hyperbilirubinemia (HB) caused by BA and neonatal hepatitis (NH) are very similar.[9] Laboratory studies are not diagnostic and values in BA overlap with those found in patients with intrahepatic cholestasis.[7] Pathological findings

Table 2 - The diagnostic acuracy of HBS in BA.

Test	Bx +ve	Bx +ve	Total
HBS +ve	31	31	34
HBS -ve	0	0	24
Total	31	31	58

Bx: liver biopsy
+ve: positive
-ve: negative

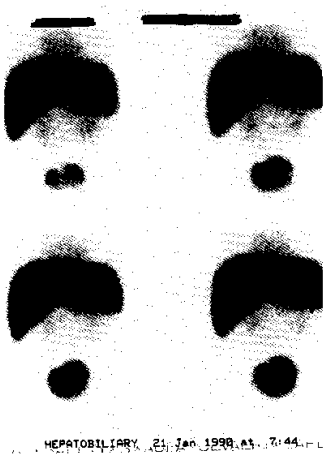

Figure 1 - Billary atresia. Note the good up take of the radioactive tracer by the liver and no activity in the bowel.

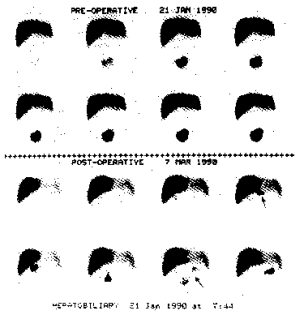

Figure 2 - Biliary atresia. The upper two rows show images before surgery. The lower two rows show images 2 months after surgery. Note the activity in the anastomosis (arrows).

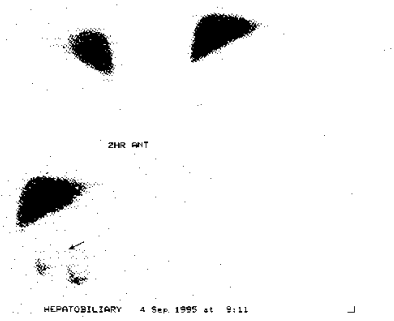

Figure 3 - Neonatal hepatitis. Irregular uptake pattern in the liver and activity in the bowel (arrow).

may overlap between BA and NH. Persistent HB beyond 2 weeks in the term infant should be investigated in order to establish its cause. Early diagnosis of correctable cause of HB, such as BA type I and IIa and b, is vital because it implicates the success of the surgical intervention.[10] Type III atresia, involving obstruction of ducts at or above the porta hepatis, is observed in more than 90% of patients and referred to as surgically noncorrectable.[11] The value and usefulness of the hepatobiliary scintigraphy (HBS) in the investigation of neonates with HB has been proved.[2-6] Appearance of activity in the bowel indicates patency of the bile ducts and thus excludes the possibility of BA. However, non-visualization of the bowel is not exclusively pathognomonic of the diagnosis of BA because other clinical conditions may as well not show activity in the bowel even at 24 hours p.i. Three of our patients who did not show activity were non BA cases despite the 5-day course of 5 mg/kg/day of phenobarbitol which was administered before HBS. Eight of 24 patients without BA, studied by Cox et al,[2] failed to show bowel activity after 5 days of phenobarbitol induction. Majd et al,[4] reported bowel activity in 6 out of 16 patients in repeated studies after phenobarbitol administration. Therefore, both the negative and positive predictive values of the HBS are clinically useful but the negative predictive value is more useful than the positive one. Pediatric surgeons may obtain from HBS valuable information on the performance of their patients postoperatively, as Fig. 2 shows activity in the bowel indicating success of the reconstructive surgery of hepatoportoenterostomy.

The onset of BA may start antenatally with continuous proliferation of primitive bile ducts at the level of the porta hepatis and progress beyond the 25th week of gestation.[12] In the majority of cases, obstructive obliteration of the biliary tract occurs postnatally.[13] Prognosis is highly dependent on timely diagnosis and treatment.[14] It is influenced by several factors.[15] Surgery performed before 60 days after birth produces better results.[16-18] Other factors are the severity of intrahepatic biliary cholangiopathy and the extent of hepatocyte injury and recurrent bouts of ascending cholangitis during the first 2 years after surgery.[15]

Conclusion Infants with persistent hyperbilirubinemia due to extrahepatic surgically correctable causes, such as biliary atresia, have to be diagnosed early in order to have a better prognosis for the course of their illness. Hepatobiliary scintigraphy is a valuable and quite useful diagnostic test as part of the work-up plan to investigate these infants and to follow them up after surgery.

References

1. Houwen RH, Bax NM. Anatomic anomalies in neonatal cholestatic jaundice. Tijdschr Kindergeneeskd 1993; 61: 151.
2. Cox KL, Standalnik RC, McGahan JP, et al. Hepatobiliary scintigraphy with Technetium-99m-disofenin in the evaluation of neonatal cholestasis. J Pediatr Gastroenterol Nutr 1987; 6: 885.
3. Kirks DR, Coleman RE, Filston HC, et al. An imaging approach to persistent neonatal jaundice. AJR 1984; 142: 467.
4. Majd M, Reba RC, Altman RP. Effect of Phenobarbitol on 99mTc-IDA in the evaluation of neonatal jaundice. Semin Nucl Med 1981; 11: 194.
5. Majd M, Reba RC, Altman RP. Hepatobiliary scintigraphy with 99mTc-PIPIDA in the evaluation of neonatal jaundice. Pediatrics 1981; 67: 140.
6. Hitch DC, Leonard JC, Pysher TJ, et al. Differentiation of cholestatic jaundice in infants: Utility of diethyl-IDA. Am J Surg 1981;142: 671.
7. Howard ER. Extrahepatic biliary atresia: a review of current management. Br J Surg 1983; 70: 193.
8. Whitington PF, Balisteri WF. Liver transplantation in pediatrics: indications, contraindications and pretransplant management. J Pediatr 1991; 118: 169.
9. Lai MW, Chang MH, Hsu HC, et al. Differential diagnosis of extrahepatic biliary atresia from neonatal hepatitis: a prospective study. J Pediatr Gastroenterol Nutr 1994; 18: 121-127.
10. Ohi R, Nio M, Chiba T, et al. Long-term follow-up after surgery for patients with biliary atresia. J Pediatr Surg 1990; 25: 442.
11. Kasai M. Treatment of biliary atresia with special reference to hepatic portoenterostomy and its modifications. Prog Pediatr Surg 1974; 6: 5.
12. Tan CE, Moscoso GJ. The developing human biliary system at the porta hepatis level between 11 and 25 weeks of gestation: a way to understanding biliary atresia. Pathol Int. 1994; 44: 600-610.
13. Landing BH. Considerations of the pathogenesis of neonatal hepatitis, biliary atresia and choledochal cyst: the concept of infantile obstructive cholangiopathy. Prog Pediatr Surg 1975; 6: 113.
14. Ho CW, Shioda K, Takahashi S, et al. The pathogenesis of biliary atresia: a morphological study of the hepatobiliary system and the hepatic artery. J Pediatr Gastroenterol Nutr 1993; 16: 53.
15. Suchy FJ. Extrahepatic biliary atresia. Saudi J Gastroenterol 1996; 2: 44.
16. Miyano T, Fujimoto T, Ohya T, et al. Current concept of treatment of biliary atresia. World J Surg 1993; 17:332.
17. Vasquez-Esteves J, Stewart B, Shikes RH, et al. Biliary atresia: early determination of prognosis. J Pediatr Surg 1989; 24: 48.
18. Grosfeld JL, Fitzgerald JF, Predaina R, et al. The efficacy of hepatoportoenterostomy in biliary atresia. Surgery 1989; 106: 692.