

## ROLE OF TC-99M DISIDA SCINTIGRAPHY IN INFANTS WITH SUSPECTED OF BILIARY ATRESIA: A 6-YEAR EXPERIENCE

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### ABSTRACT

Hepatobiliary scintigraphy using Technetium-99m diisopropyl iminodiacetic acid (Tc-99m DISIDA scintigraphy) performed in 105 infants with predominantly conjugated hyperbilirubinemia and suspected of biliary atresia (BA) were reviewed. Radio-nuclide hepatobiliary scintigraphy is well recognized as the only noninvasive diagnostic method to demonstrate the patency of biliary system. All patients had the Tc-99m DISIDA scintigraphy performed after 5 days of phenobarbital therapy. Of the 55 infants with no evidence of radiotracer excretion into the biliary and/or gastrointestinal (GI) tract up to 24 hours after injection, 47 had a final diagnosis as BA proven by surgery. Whereas the remaining 8 patients, 2 were diagnosed as biliary hypoplasia, 2 were diagnosed as bile-plug syndrome, and 4 had a diagnosis as infectious neonatal hepatitis (NH). All of these were proven by laparotomy with intraoperative cholangiography and follow up clinical course. The remaining 50 patients demonstrated definite excretion of the radiotracer into the GI tract, thus entirely excluded the diagnosis of BA. Of these, 22 had a final diagnosis as idiopathic NH, 19 were diagnosed as infectious NH, and 9 had a diagnosis as having cholestatic jaundice of unknown cause. In our series, we found that the sensitivity, specificity and accuracy of Tc-99m DISIDA scintigraphy for the diagnosis of BA were 100%, 86% and 92%, respectively. The positive and negative predictive value were 85% and 100%. The results of our study indicate that Tc-99m DISIDA scintigraphy is a sensitive and highly accurate method in the diagnosis of BA. Therefore, it is highly recommended as a routine screening investigation of choice in evaluating infants with suspected of BA.

### INTRODUCTION

While there are several causes of conjugated hyperbilirubinemia in the neonatal period, the major differential diagnosis of these infants is between biliary atresia (BA) and neonatal hepatitis (NH), since majority of the non-surgical cholestasis are due to NH.<sup>1,2</sup> BA is one of the most common diseases of the biliary tree in infants. It is also a very important disease, due to its serious and potentially fatal if not treated.<sup>3</sup> Thus, an accurate and noninvasive investigation for

diagnosis of BA is essential. It is extremely important to distinguish between these two entities for proper treatment. The treatment of BA requires prompt surgical intervention, whereas NH needs only medical or conservative treatment.<sup>1,3,4</sup>

Early diagnosis of BA by a sensitive diagnostic test is essential, since the success of surgical treatment is primarily dependent on early intervention, and it is most successful when

performed before the age of 2 months.<sup>3,4</sup> The distinction between BA and NH by the clinical evidence, biochemical tests and histological features is very difficult and unreliable.<sup>5-7</sup> Therefore, many diagnostic techniques have been developed for the differential diagnosis of BA including ultrasonography,<sup>8</sup> duodenal fluid collection,<sup>9,10</sup> percutaneous transhepatic cholangiography,<sup>11</sup> endoscopic retrograde cholangiopancreatography,<sup>12</sup> laparoscopy,<sup>13</sup> laparotomy with intrahepatic cholangiography,<sup>14</sup> percutaneous liver biopsy<sup>15</sup> and radionuclide hepatobiliary scintigraphy.<sup>5-8, 16-19</sup> Among these modalities, radionuclide hepatobiliary imaging using Technetium-99m iminodiacetic acid (IDA) derivatives is well recognized as the only simple, safe and noninvasive investigation, which can demonstrate the hepatocyte function and the patency of biliary system.

The typical scintigraphic finding in BA is prompt hepatic uptake with no evidence of tracer excretion into the GI tract up to 24 hours after injection. Therefore, definite excretion of the radioactivity into the intestine excludes the diagnosis of BA, and avoids unnecessary laparotomy in these groups of patients.

The purpose of our study was to verify the reliability of the hepatobiliary scintigraphy using Technetium-99m diisopropyl iminodiacetic acid (Tc-99m DISIDA scintigraphy) in the differential diagnosis of patients with suspected of BA.

## MATERIALS AND METHODS

Tc-99m DISIDA hepatobiliary scintigraphy in 105 consecutive infants with predominantly conjugated hyperbilirubinemia and suspected of BA obtained between January 1992 and December 1997, were reviewed retrospectively. The patients included 54 male and 51 female infants, who ranged in age from 17 days to 7 months. The average direct and total bilirubin levels of the pa-

tients were  $7.71 \pm 3.91$  mg/dl (range, 2.88 to 23.62), and  $14.26 \pm 6.95$  mg/dl (range, 5.3 to 34.3) respectively. The patients presented with either persistent jaundice with predominantly conjugated hyperbilirubinemia, acholic stools, hepatomegaly and/or splenomegaly. All patients had their Tc-99m DISIDA scintigraphy performed after phenobarbital premedication in a dose of 5 mg/kg/day orally, divided into two equal doses for 5 days.

The infants were fast for at least 2 hours before, and until 2 hours after injection of the radiopharmaceutical to prevent possible dilution of the excreted radiotracer in the bowel, and to minimize contraction of the gallbladder(GB). Tc-99m DISIDA scintigraphy was performed by intravenous injection of the Tc-99m labeled DISIDA with a dose of 100-200 microCi/Kg (3.7-7.4 MBq/Kg) of body weight, with a total dose of at least 1 mCi (37 MBq). The patients were placed in the supine position under a large-field-of-view gamma camera, equipped with a low-energy all-purpose collimator, using either ZLC Siemens or APEX SP-4 Elscint gamma camera. Sequential anterior abdominal imaging was obtained at 5, 15, 30, 45 minutes, and at 1, 2, 4 and 6 hours after injection. Each image was acquired for 300 Kcounts in 256 x 256 matrix. Other views, especially the right lateral view of the abdomen was also obtained in order to differentiate the right renal activity from the biliary and/or intestinal activity. The studies were terminated earlier if the images showed definite radiotracer excretion into the intestine. If no evidence of tracer excretion into the GI tract occurred at 6 hours, 24 hour image on the following day was routinely performed.

## RESULTS

Of the 105 infants evaluated with Tc-99m DISIDA scintigraphy, 55 patients (52.4%) revealed no evidence of tracer excretion into the biliary system and/or the GI tract up to 24 hours after injection. Of these, 47 patients had a final

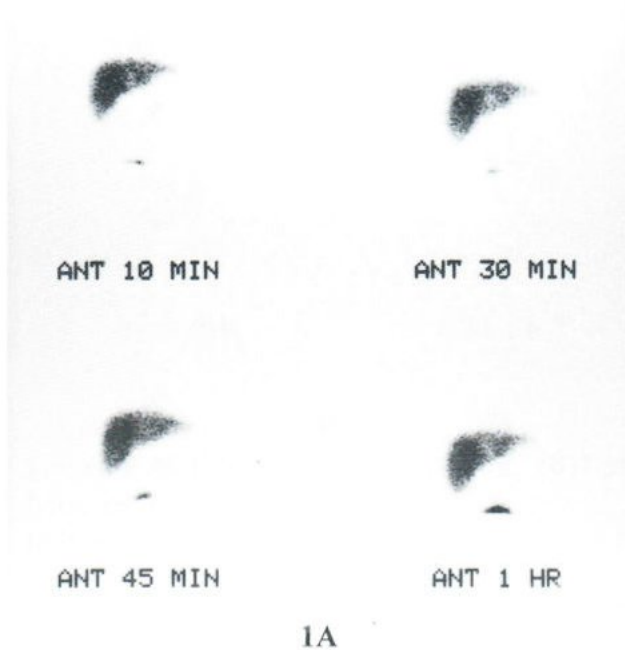
diagnosis as BA proven by surgery. Whereas the remaining 8 patients, 2 were diagnosed as biliary hypoplasia, 2 were diagnosed as bile-plug syndrome, and 4 had a diagnosis as having infectious NH from cytomegalovirus. Therefore, we have overall 47 true positive scans (85.5%), and 8 false positive scans (14.5%) in our study. All of these patients were proven by laparotomy with/without intraoperative cholangiography, and followed up the clinical course.

Regarding the hepatic uptake in these 8 patients with false positive scans for BA, 2 patients with biliary hypoplasia showed moderately decreased hepatic uptake. Two patients with bile-plug syndrome, one showed good hepatic uptake, and another one showed slightly decreased hepatic uptake. The remainder 4 patients with infectious NH, 2 revealed good hepatic uptake, one showed slightly decreased hepatic uptake, and the last one demonstrated markedly decreased hepatic uptake.

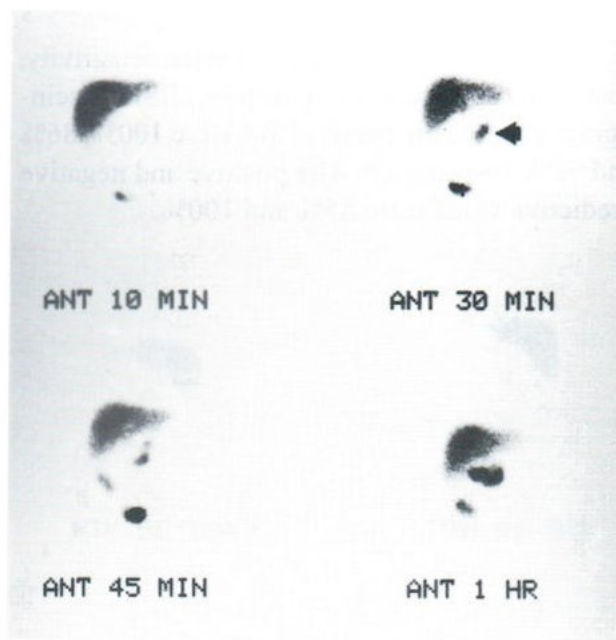
The remaining 50 patients (47.6%) demonstrated definite excretion of the radiotracer into the intestinal tract, which indicated the patency of biliary system. Thus, a diagnosis of BA was entirely excluded in these patients. Therefore, we can avoid unnecessary laparotomy in these groups of patients. Of these, 22 had a final diagnosis as idiopathic NH, 19 were diagnosed as infectious NH (cytomegalovirus 15, rubella virus 2, syphilis 1, and human immunodeficiency virus 1), and 9 had a diagnosis as having cholestatic jaundice of unknown cause.

Moreover, of the 50 patients who did show tracer excretion into the intestine, 22 (44%) demonstrated bowel activity within 1 hour, 27 (54%) showed tracer excretion during 1-4 hours, and the remaining one patient (2%) revealed intestinal activity at 6 hours after injection.

In our study, we found that the sensitivity, specificity and accuracy of Tc-99m DISIDA scintigraphy for the diagnosis of BA were 100%, 86% and 92%, respectively. The positive and negative predictive value were 85% and 100%.

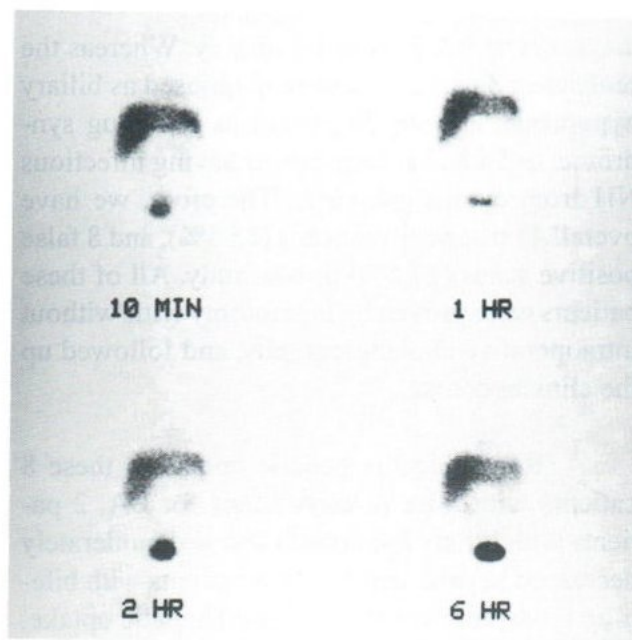


**Fig.1(A) Biliary atresia.** A 2-month-old infant presented with persistent conjugated hyperbilirubinemia and acholic stools. The Tc-99m DISIDA hepatobiliary scintigraphy reveals prompt hepatic uptake with no evidence of tracer excretion into the biliary and/or GI tract up to 6 hours after injection. The 24 hour image (not shown) also fails to demonstrate the GI activity. The patient had a final diagnosis as BA proven by surgery.



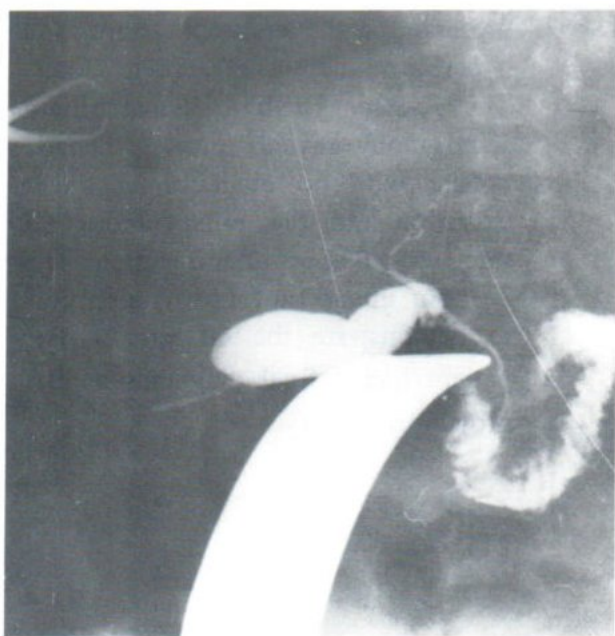
1B

**Fig.1(B)** Follow up Tc-99m DISIDA imaging after Kasai's operation reveals good hepatic uptake with biliary excretion of the radiotracer into the intestine (arrow).



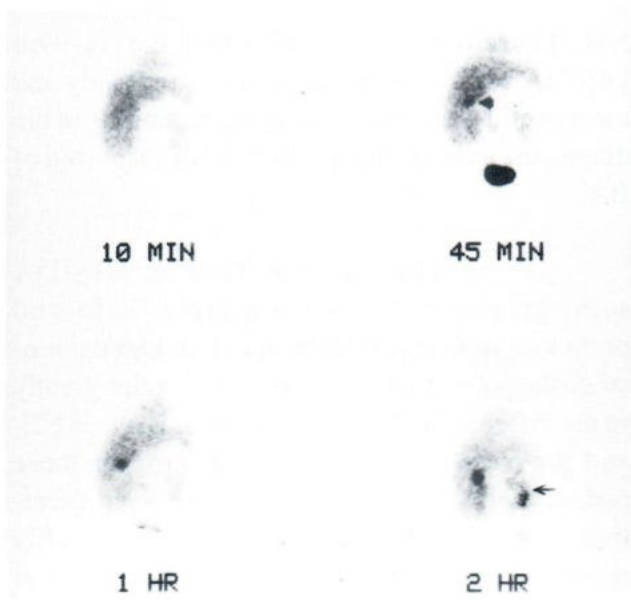
2A

**Fig.2 (A)** **Bile-plug syndrome.** A 3-month-old infant with persistent jaundice and conjugated hyperbilirubinemia. Sequential anterior abdominal imaging with Tc-99m DISIDA shows rather good hepatic uptake with no definite tracer excretion into the intestine up to 24 hours after injection. The patient was diagnosed as bile-plug syndrome proven by laparotomy with intraoperative cholangiography.



2B

**Fig.2(B)** Intraoperative cholangiography demonstrates the patency of biliary system.



**Fig.3 Neonatal hepatitis.** A 2-month-old infant with positive cytomegalovirus titers and conjugated hyperbilirubinemia. The hepatobiliary scan reveals moderately decreased hepatic uptake with evidence of tracer excretion into the gallbladder since 45 minutes after injection (arrow head). Decreased and delayed tracer excretion into the intestine is observed (thin arrow). There is still persistent cardiac blood-pool activity.

## DISCUSSION

In infants with conjugated hyperbilirubinemia, the main clinical problem usually arises in distinguishing BA from NH.<sup>1,2,7</sup> Hepatobiliary imaging using Tc-99m IDA derivatives is a useful imaging technique in the diagnostic evaluation of these groups of patients.<sup>16-19</sup>

The IDA derivatives undergo the same metabolism as bilirubin and organic anions. After hepatocyte uptake, it is excreted into the biliary tree and eliminated in the intestine.<sup>20</sup> Hepatobiliary scintigraphy with Tc-99m IDA derivatives is well recognized as the only noninvasive diagnostic method to demonstrate the

patency of biliary system, and it is the only technique which provides the real-time assessment of bile flow from the liver to the intestine.<sup>20,21</sup> Moreover, it is useful not only in the diagnosis of BA, but also plays role in the postoperative assessment after surgical treatment as well.<sup>7</sup>

Among a variety of Tc-99m IDA derivatives, Tc-99m DISIDA is most commonly used in hepatobiliary scintigraphy.<sup>22,23</sup> It has rather high hepatic extraction, and low urinary excretion. Tc-99m DISIDA scintigraphy can be successfully performed even though in patients with high bilirubin levels up to 20-30 mg/dl.<sup>21,22</sup> Normally the radiotracer is accumulated in the liver within 5 minutes, and the tracer excretion should be seen in the biliary tract within 10-15 minutes, with maximum activity at 40-45 minutes after injection. The small bowel activity should be seen within 30-60 minutes, and the GB should be seen within 1 hour after injection.<sup>20,21</sup> Therefore, it is most useful when definite tracer excretion into the GI tract occurs, which indicates evidence of biliary patency, and excludes the diagnosis of BA. In our series, we could avoid unnecessary laparotomy in 50 patients who revealed definite tracer excretion into the GI tract.

The classical scintigraphic finding in BA is good hepatic uptake with no definite tracer excretion into the intestine up to 24 hours.<sup>1,20,21</sup> When this finding occurs, the diagnosis of BA can be made with an extremely high degree of accuracy. However, nonvisualization of the tracer in the bowel does not always indicate BA, since other causes of neonatal jaundice such as NH and bile-plug syndrome may reveal no biliary excretion throughout the study as well.<sup>5,6,18,23</sup> In our study, we also found that 4 patients with infectious NH, 2 patients with biliary hypoplasia, and 2 patients with bile-plug syndrome, revealed no definite tracer excretion into the intestine up to 24 hours.

It is of interest that we found 6 NH patients (idiopathic NH 5, NH from cytomegalovirus 1) with serum bilirubin levels more than 30 mg/dl, who still demonstrated evidence of tracer excretion into the intestine. The average direct and total bilirubin levels of these patients were  $15.13 \pm 6.44$  mg/dl (range, 9.08 to 23.62), and  $32.91 \pm 1.27$  mg/dl (range, 31.02 to 34.3) respectively. This finding confirms that Tc-99m DISIDA scintigraphy is a reliable and useful imaging in differentiating BA from other causes of neonatal cholestasis, even in patients with serum bilirubin levels as high as 30 mg/dl.

Concerning the patients with positive GI activity, we found that 49 out of 50 patients (98%) demonstrated intestinal activity within 4 hours, and all (100%) showed bowel activity within 6 hours after injection. Whereas the 55 patients with no definite biliary excretion, all showed no evidence of tracer excretion at 6 hours, and at 24 hours after injection. Therefore, we wonder whether if no evidence of tracer excretion into the GI tract occurs at 6 hours, the 24 hour images should still be routinely performed or not.

Majd et al demonstrated that the specificity and accuracy of Tc-99m IDA scintigraphy in differentiating BA from NH increased significantly when performed after phenobarbital treatment.<sup>1</sup> Phenobarbital will enhance the biliary excretion of Tc-99m IDA agents by inducing the hepatic microsomal enzymes.<sup>1,2,3</sup> So, we routinely performed our study after 5 days of phenobarbital therapy. In our series, the Tc-99m DISIDA scintigraphy had a 100% sensitivity, 86% specificity and 92% accuracy for the diagnosis of BA. The positive and negative predictive value were 85%, and 100% respectively. The predictive accuracy of a negative imaging is therefore high enough to clinically exclude the diagnosis of BA. The results of our study indicate that the Tc-99m DISIDA scintigraphy is a sensitive and highly accurate method for the differentiation of BA from

NH. Therefore, we consider that the Tc-99m DISIDA hepatobiliary imaging is probably the most useful noninvasive imaging technique in the diagnostic evaluation of infants with suspected of BA.

In conclusion, the Tc-99m DISIDA scintigraphy is the only simple, safe and noninvasive imaging technique that can demonstrate the patency of biliary system. It helps greatly in the differential diagnosis between BA and NH, and prevents unnecessary laparotomy in those patients who demonstrate definite tracer excretion into the intestine. Therefore, it is highly recommended as a routine screening investigation of choice in infants with suspected of BA.

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