ULTRASOUND AND NUCLEAR SCAN IN THE DIAGNOSIS OF BILIARY ATRESIA IN PERSISTENTLY JAUNDICED INFANTS

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ABSTRACT

This review of cases aims to evaluate the sensitivity and specificity of ultrasonography (US) and hepatobiliary scintigraphy (HBS) in the diagnosis of biliary atresia in persistently jaundiced infants. Thirty-four (34) patients (age 1 to 11 months, 11 females and 23 males) underwent surgery for correction of biliary atresia diagnosed by ultrasound and/or hepatobiliary scintigraphy between January 1981 to December 1995 at the Clinical Division of Santo Tomas University Hospital. All patients had tissue sent for histopathological examination. There were 26 patients with both ultrasound and scintigraphic studies, six (6) with scintigraphic studies only, and one (1) with ultrasound only. Using Fisher's Exact Probability Test, hepatobiliary scintigraphy showed a better sensitivity (83.3%) than ultrasound (68.8%) ($p < 0.05$). However, ultrasound has a better positive predictive value (84.6%) compared to hepatobiliary scintigraphy (75%) in the diagnosis of biliary atresia in persistently jaundiced infants. The study recommends that ultrasound should be used as the initial imaging modality of choice in evaluating biliary atresia in persistently jaundiced infants.

INTRODUCTION

Biliary atresia (BA) is a serious disease of very young infants. It is an obstructive condition of the bile ducts causing neonatal jaundice. The obstruction is of unknown etiology but results from a progressive obliterative process of variable extent. In the majority of patients, the entire extrahepatic biliary tree is obliterated. However, others may have only partial obliteration. The symptoms are evident between 2 to 6 weeks after birth. A slight female predominance is noted but there is no racial predilection.[1] The typical patient is a few months old with intractable jaundice, acholic stools, and deep yellow urine.

BA has to be differentiated from neonatal hepatitis which presents with similar clinical features, laboratory findings and histopathological characteristics. The pathogenesis of BA and neonatal hepatitis may be the same. It has been suggested that an initial insult leads to an inflammatory process at any level of the hepatobiliary tract. If it is the hepatocyte, it results in neonatal hepatitis and if it is at the extrahepatic bile ducts, it results in BA.[2]

The two most important tests in the evaluation of BA are ultrasound (US) and hepatobiliary scintigraphy (HBS). These diagnostic tests aim to provide an early and accurate answer to a specific question: Is the patient's cholestasis due to

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neonatal hepatitis or BA? Is the patient a surgical (biliary atresia) or a medical (neonatal hepatitis) case ?

Ultrasound is always utilized as the initial diagnostic modality in the evaluation of children with jaundice.[3] The advantages of US include low cost, ease of use, versatility and availability. Limitations include presence of bowel gas, obesity, and the necessity for fasting for four to six hours prior to the procedure.

Absent or small gallbladder is a frequent finding in BA; therefore, nonvisualization of the gallbladder or a small gallbladder on sonography favors this diagnosis.[4] The ultrasonic demonstration of a normal gallbladder (normal length > or = 1.5 cm) supports the diagnosis of neonatal hepatitis and is less commonly seen in BA. The presence of the gallbladder , however, does not necessarily rule out the diagnosis of BA. Contraction of the gallbladder after a fatty meal militates against BA.[5] In addition, some researchers claim that the visualization of triangular or tubular echogenic density in the vicinity of the portal vein (triangular cord sign) is specific for BA.[6]

Majority of patients with BA will not have sonographically depictable bile ducts. But occasionally there will be atresia of only portions of the bile ducts with dilatation of the segments proximal to the atretic area.[4] In these cases, it is possible to demonstrate the biliary tree.

HBS is the other modality usually requested to differentiate between BA and neonatal hepatitis. The technetium-99m iminodiacetic acid derivatives (Tc99m-IDA) are rapidly extracted from the blood by the hepatocytes and are excreted into the bowel through the biliary ducts.[7] Most of the intravenously injected tracer is seen in the liver within 30 minutes. When there is hepatocellular disease there is delayed uptake; with biliary obstruction , the materiai accumulates in the liver, but none appears in the bowel. Complete biliary tract obstruction is diagnosed when the gallbladder and intestines are not visualized plus the presence of a "liver scan"-appearing liver.[8]

A delay in management of the obstructed neonate may result in cirrhosis, portal hypertension and pancreatitis. Previous reports showed better prognosis when surgery is done before ten weeks of age.[9]

This study aims to evaluate the sensitivity and specificity of US and hepatobiliary scintigraphy and their predictive values in the diagnosis of BA in persistently jaundiced infants.

METHODOLOGY

The records of patients *who underwent biliary surgery from January 1981 to December 1995* at the Clinical Division of Santo Tomas University Hospital (STUH) were reviewed. Patients who satisfied the following criteria were entered into the study: 1. those who had radionuclide hepatobiliary imaging and/or ultrasonography before the surgery; and, 2. those who were not more than 12 months of age. Thirty-four subjects met the above criteria and were included in the study. The age ranged from 1 - to 11 months old. There were 11 females and 23 males. All patients had tissue sent for histopathological examination. There were 26 patients who had both US and scintigraphic studies, six with scintigraphic studies only and one with US only. A short history and physical examination were obtained from the chart. Pertinent laboratory and imaging procedures were noted. The histopathological report was also documented.

Non-visualization of the gallbladder and biliary tree was considered as positive US findings suggestive of BA. The presence of a normal gallbladder was considered as a negative US finding.

Positive scintigraphic findings were noted

in those cases which had no gallbladder visualization and no radioactive tracer excreted into the intestines up to 24 hours after the administration of the radiopharmaceutical. In addition, the liver had to be well-visualized with intense tracer uptake.

Data was tabulated using Microsoft Excel program. Statistical analysis with Fisher's exact probability test was done using Kwikstat (Texasoft, Texas, USA).

RESULTS

The 34 patients included in the study were typical. The cases were a few months old with recognized jaundice since birth. Acholic stools were frequent but not seen in all. Abdominal enlargement was seen infrequently. The initial workup of a jaundiced infant included a complete blood count and liver function tests. Bilirubin levels were also obtained.

Table 1 shows the laboratory exam results of the subjects. There were 11 females and 23 males. Worthy of note were the elevated values for SGOT, SGPT, total, indirect and direct bilirubin.

Table 2 shows the US, HBS, and histopathological diagnosis of the 34 subjects. Histopathological diagnosis was done by the pathologists of STUH. Worth mentioning was the one case diagnosed to have choledochal cyst by US which was later proved correct by histopathologic exam.

US and HBS versus histopathological diagnosis were analyzed via a 2 x 2 contingency table as seen in **Table 3 and 4.** Hepatobiliary scintigraphy was correct in 25 out of 33 patients (76%). The sensitivity and specificity of HBS were 83.3% and 66.7%, respectively. The positive predictive value was 75% and the negative predictive value was 76.9% ($p<0.005$). Ultrasonography was correct in 20 out of 27 patients (74%). The sensitivity and specificity of US were 68.8% and 81.8%, respectively. The positive predictive value was 84.6% and the negative predictive value was 64.3% ($p<.05$).

Table 5 shows the distribution of the 26 patients with both US and HBS and whether they have BA or not by pathology ($p<0.05$). In eight patients who were diagnosed to have BA by US and HBS, all of them (100%) had BA by histopathology. However, 2 out of 7 patients (28%) who had negative findings by both US and HBS had positive histopathologic result for biliary atresia; 5 out of these 7 patients (72%) who had negative findings by both US and HBS had no BA. On the other hand, 3 out of 7 patients (43%) who had positive HBS and negative US findings were correctly diagnosed to have BA; hence, 4 out of these 7 patients (57%) were incorrectly diagnosed to have BA. In 4 patients who had negative HBS and positive US findings 2 of these patients (50%) had BA and also 2 of these patients (50%) had no BA on histopathology. Out of these 26 patients who had both HBS and US examinations, 13 patients (50%) were correctly diagnosed to have biliary atresia. A cause of concern were the 2 patients (7.7%) with negative US and HBS findings but have biliary atresia on histopathology; both had no GB by US although the biliary ducts were seen in one. With HBS the liver was faintly visualized in both which makes nuclear physicians wary of diagnosing biliary obstruction since extensive liver damage could cause the same picture and is admittedly one of the causes of false positive exams.

Table 1
Laboratory Data of the 35 Cases in the Study

Name	Sex	Age	SGOT	SGPT	TB	b1	b2
		months	u/l	u/l	mg/dl	mg/dl	md/dl
			8 to 33	5 to 40	.1 to 1.2	.1 to 1	.1 to 1
J.P	f	3		83			
E.C.	m	2		326	7	1.76	5.1
A.D	f	9	143	62		0.76	9.6
J.A.	m	3	136	95	6.4	2.6	3.76
K.O.	f	3			17	2.1	14.7
R.D.	m	2		125	7.2	3.4	7.36
J.B.	m	3					
J.C.	m	4					
J.T	m	2.5					
BH	m	2					
RB	f	4	500	300	15	1.7	14
BR	m	2	29		12	4	8
CL	f	9			18	6.58	12
CD	f	4.5		47.5	6.4	6.8	6.1
ML	f	2.5			5.7		4.8
KC	m	3.5		30.5	1.3	4.1	1.3
W.B.	f	3			11.7	5	6.2
C.J.	f	1.5	41	23	5	0.4	4.7
R.B	m	11			29.5	7.3	22.1
W.M.	m	3	600	350	7.7	5.2	2.5
B.Q.	m	2	100	58	7.6	5.2	2.4
R.D.	m	5	380	250	7.2	5	2.2
V.C.	m	2.5	210	300	8.7	6.1	2.6
M.S.	m	3	800	250	6.6	5.8	0.8
R.M.	m	3	680	580	10.8	6.8	4
K.V.	f	3	120	98	7.5	4.8	2.7
R.F.	m	4	580	460	8.6	6.6	2
K.S.	f	6	540	290	16.8	3.9	12.9
D.L.	m	4	400	350	5.8	3.9	1.9
J.C.	m	2	720	600	12	10.2	1.8
J.K.	m	2	580	340	16.3	12.7	3.6
R.B.	m	1	600	400	23.6	20.4	3.2
R.C.	m	1.5	110	80	23.4	15	8.4
A.R.	m	3	250	200	11.8	8.4	3.4
mean		3.56	375.95	237.42	11.31	5.95	6.00

Table 2
Imaging Results and Histopathological Findings

PATIENT	ULTRASOUND	SCINTIGRAPHY	HISTOPATHOLOGY
J.P	n gb, n bt	gb, si not seen	biliary atresia
E.C		gb, si not seen	neonatal hepatitis
A.D	n gb, n bt		biliary atresia, chronic cholecysitis, portal fibrosis
J.A		gb, si not seen, hepatitis	neonatal hepatitis
K.O	gb not seen, intrahep duct not dilated	gb, si not seen, hepatomegaly	biliary atresia
R.D		gb, si not seen	biliary atresia, portal , central fibrosis
J.B		gb, si not seen	biliary atresia
J.C		gb ,si not seen	biliary atresia,chronic cholecystitis, portal fibrosis
J.T		gb, si not seen, hepatitis	biliary atresia with fibrosis
BH	gb not seen	gb si not seen	biliary cirrhosis, stenotic, fibrotic cbd
RB	gb not seen, diffuse liver disease	gb, si not seen, liver not seen	biliary atresia
BR	gb not seen, diffuse liver disease	gb, si not seen, hepatomegaly	biliary atresia
CL	n gb, n liver	gb,si not seen, hepatomegaly	biliary atresia
CD	n gb, n liver	gb, si not seen, faint liver	biliary atresia, chronic cholecystitis
ML	n gb, n liver	gb, si not seen	biliary atresia, chronic inflammation of the liver
KC	gb not seen	gb, si not seen	biliary atresia, chronic inflammation of the bt
W.B	gb not seen	gb, si not seen	biliary atresia, chronic cholecystitis
C.J	gb not seen, diffuse liver disease	gb not seen, si seen	biliary atresia, liver cirrhosis, chronic inflammation of gb
R.B		gb, si not seen	neonatal hepatitis
W.M	n gb, n liver	gb,si seen	neonatal hepatitis
D.Q	n gb, n liver	gb,si seen	neonatal hepatitis
R.D	n gb, n liver	gb,si seen	neonatal hepatitis
S.D	gb, bt not seen	gb,si seen	neonatal hepatitis
M.S	gb, bt not seen	gb,si seen	neonatal hepatitis
R.M	gb, bt not seen	gb,si not seen	biliary atresia
K.J	gb, bt not seen	gb,si not seen, faint liver, hepatomegaly	biliary atresia
R.F	gb, bt not seen	gb,si not seen	biliary atresia
K.S	gb, bt not seen	gb,si not seen	biliary atresia
D.L	choleduchal cyst	gb, si not seen	choledochal cyst
J.C	n gb, bt seen	gb, si not seen, intense liver tracer uptake,hepatomegaly	neonatal hepatitis
J.K	n gb, bt seen	gb,si not seen	neonatal hepatitis
R.B	n gb, bt seen	gb, si not seen	neonatal hepatitis
R.C	n gb, bt seen	gb, si not seen, faint liver	neonatal hepatitis
A.R	n gb, bt seen	gb, si not seen, faint liver	neonatal hepatitis

gb=gallbladder; **bt**=biliary tract; **si**=small intestine; **n**=normal; **cbd**=common bile; **chd**=common hepatic duct

Table 3
Hepatobiliary Scintigraphy and Histopathologic Findings

	Histopathological Diagnosis		
	(+) biliary atresia	(-) biliary atresia	Total
(+) scintigraphy	15	5	20
(-) scintigraphy	3	10	13
Total	18	15	33

$p < 0.005$
Sensitivity = 83.3 %
Specificity = 66.7 %
Positive Predictive Value = 75.0 %
Negative Predictive Value = 76.9 %

Table 4
Ultrasound and Histopathologic Findings

	Histopathological Diagnosis		
	(+) biliary atresia	(-) biliary atresia	Total
(+) ultrasound	11	2	13
(-) ultrasound	5	9	14
Total	16	11	27

$p < 0.05$
Sensitivity = 68.8 %
Specificity = 81.8%
Positive Predictive Value = 84.6 %
Negative Predictive Value = 64. 3 %

Table 5. Hepatobiliary Scintigraphy and Ultrasound vs. Histopathologic Findings

	(+) HBS (+)US	(-) HBS (-)US	(+) HBS (-) US	(-) HBS (+)US	Total
(+)BA	8	2	3	2	15
(-)BA	0	5	4	2	11
Total	8	7	7	4	26

BA=biliary atresia; **HBS**=hepatobiliary scintigraphy; **US**=ultrasound

$p<0.05$

DISCUSSION

There are different types of biliary atresia. The most common variants include: 1) complete obliteration of the extrahepatic ducts; 2) patency of the distal biliary tree (gallbladder, cystic duct and common bile duct) with proximal obliteration; and 3) proximal hilar bile cyst (formerly considered the "correctable" type).[1]

It is associated with neonatal hepatitis and choledochal cyst in a disease spectrum which Landing in 1974 called "infantile obstructive cholangiopathy".[10] Some hypotheses as to the etiology includes 1) viral infection with reovirus type 3, 2) blood supply catastrophe, 3) abnormal bile acid metabolism, 4) genetic influences and 5) developmental anomaly.[2] Reovirus type 3 in particular, persists in the murine liver and shows BA-like effects in offspring of infected pregnant mice.[11]

Two patients with neonatal hepatitis studied by Park et al had marked dilatation of the endoplasmic reticulum and mild mitochondrial alterations without the cytoplasmic biliary necrosis of bile canalicular injury.[2] These two patients later proved to be cases of BA reinforcing the idea that early pathological changes of BA are similar to neonatal hepatitis.

Without surgery BA is a progressive disease which results in cirrhosis. Liver cirrhosis may be a pre-cancerous lesion although no causal relationship has been elaborated satisfactorily. However, the association between chronic hepatic disease and hepatoma is even stronger in children than in adults.[12]

Biliary atresia is diagnosed histopathologically when there is intrahepatic bile duct degeneration and lymphocytic infiltration of portal areas and biliary epithelial cells.[13] In addition, the porta hepatis is encased in fibrous tissue. In the development of the fetus, there is failure of the remodeling process at the hepatic hilum, with persistence of fetal bile ducts poorly supported by mesenchyme. An intense inflammatory reaction results as bile flow increases perinatally which culminates in biliary tree obliteration.[14]

With an incidence of as high as 1 in 15,000 and a possible role for reovirus type 3, BA may, in fact, be even more prevalent in developing and population-dense countries. It is difficult to generate incidence data for BA in the Philippines, for example, because of poor patient follow-up, low autopsy rate, and the relative unpopularity of the

surgical intervention indicated for the condition (Kasai portoenterostomy and liver transplantation).

The work-up of jaundiced infants varies little from the diagnostic work-up of jaundiced adults. Blood exams and US are standard owing to their accessibility and inexpensiveness. In infants, jaundice beyond two weeks warrants, aside from serum and urine bilirubin measurements, imaging to immediately rule out a potentially surgically-correctable cause. Some authors recommend that HBS should be the first imaging modality given its high sensitivity and specificity (90 - 95 % for both).[15] In the neonate, delay in the definitive management causes a marked decline in survival rates. In a study by Oh et al in 1995, 35 out of 42 (83.3 %) BA patients who had surgery before two months of age were still alive during the study. Contrast this with 6 out of 17 (35.3 %) living biliary atresia patients who had surgery after the "golden period" of two months. Delay in surgery also results in more complications like portal hypertension and growth retardation.[9]

Hepatobiliary imaging is not without its variations. It started originally with the use of iodine-131 Rose Bengal. Later, it was replaced by the technetium-based radiopharmaceuticals exemplified by the iminodiacetic acids IDA.[16] Advances in the field have yielded agents with higher hepatic extraction and lower renal excretion. Diisopropyl-IDA (DISIDA) exhibits faster hepatic transit and higher gallbladder-to-liver ratio. The problem with highly jaundiced patients (as high as bilirubin levels of 30 mg/dl) is surmounted.[7] To increase the sensitivity of the test, neonates are "primed" with phenobarbital a few days prior to the procedure. Morphine is used in adults in order to lessen the investigation period to a few hours without sacrificing sensitivity.[17]

The sample of patients in the study were highly selected patients. The patients had intractable jaundice since birth and many had acholic stools. There were more male infants affected. Laboratory examinations such as liver function tests, were elevated. The sensitivity of hepatobiliary scintigraphy (HBS) for diagnosing biliary atresia in persistently jaundiced infants was 83.3%, which is higher compared to US (68.8%). On the other hand, the specificity of US was 81.8% while HBS has 66.7% specificity. US has 84.6% positive predictive value which was better than HBS (75.0%). The data on table 5 shows that if HBS was positive and US was negative for biliary atresia, the chances of the patient to have BA was <50% while if the HBS was negative and US was positive, the chances of the patient to have BA was 50%. When both HBS and US were positive, 100% positive predictive value was noted. However, it was observed that when both HBS and US were negative, 28% of these patients may still have a false negative result.

CONCLUSION

Persistently jaundiced infants pose problems to clinicians in differentiating between a medical and surgical case despite good clinical evaluation and laboratory examinations. This study shows that ultrasonography is a useful initial imaging modality in the diagnosis of biliary atresia in persistently jaundiced infants compared to HBS given the better positive predictive value of ultrasound.

The study also shows that if HBS and US have both positive findings for biliary atresia, the positive predictive value of the procedures increase.

The other role of US is in the identification of other causes of biliary obstruction such as choledochal cyst, determination of hepatic size, and to provide information about the liver parenchyma.

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