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Diagnostic Problems in Infantile Cholestatic Jaundice

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Abstract **Previously proposed screening criteria for selection of infants with cholestatic jaundice for a diagnostic laparotomy was retrospectively assessed for reliability in 173 infants , between 1-4 months of age, who were treated at the Children's Hospital during 1990-1995. Cases of cholestatic jaundice associated with sepsis or concomitant administration of parenteral nutrition were not included in the study. Data from this study supported the reliability of the criteria. If these criteria were strictly followed, none of the infants with biliary atresia (BA) in this study would be missed. However, about 25 per cent of infants with neonatal hepatitis (NH) would have to be subject to a diagnostic laparotomy.**

It is concluded that any infant with cholestatic jaundice and acholic stool should undergo a diagnostic laparotomy at the age of 2 months if total serum bilirubin is 6-25 mg/dl, unless there is a steady decrease of serum bilirubin and the cause of jaundice is documented by other laboratory investigations and clinical evidences. Those who have a positive serology test for syphilis should be treated accordingly and closely followed. If the infants' jaundice and stool colour are not improved in an expected timing and treatment, they should also undergo a diagnostic laparotomy. Radionuclide hepatobiliary scan needs further assessment for its sensitivity. If this test can be proved to have a 100 per cent sensitivity, it could be included in the screening criteria. Ultrasonographic study should be done in every case in order to detect choledochal cyst, but not to differentiate NH from BA.

Causes of cholestatic jaundice in newborn infants are numerous. It may be due to metabolic, genetic, infectious or toxic causes or anatomical abnormalities[1-3]. In some cases, specific causes may be readily recognized by clinical observation and laboratory investigations. However, the majority of cases have either neonatal hepatitis (NH) or biliary atresia (BA)[1-9]. The differentiation between these two conditions has been a serious diagnostic problems for clinicians. Several diagnostic investigations have been evaluated, but none has been found to be totally reliable to differentiate BA from NH[1-6,8-14]. Those who are not familiar with these

diagnostic problems may erroneously make an incorrect diagnosis on the basis of some investigative results. Most infants with NH usually have improvement of jaundice during observation period without definitive treatment. However, early differentiation between BA and NH is utmost important, because BA requires an early surgical intervention, preferably before 2 months of age, prior to the development of cirrhosis. If jaundice fails to improve by 2 months of age, the majority of these infants eventually require a diagnostic laparotomy to differentiate between these two conditions. Several diagnostic algo-rithms have been proposed, aiming at minimizing the number of infants who undergo unnecessary diagnostic laparotomy[2,3,7,15].

Based on our experience in infants who were treated at the Children's Hospital, Bangkok, during the period of 6 years (1984-1989), criteria for selection of patients for a diagnostic laparotomy have been proposed in our previous communication[9]. These included a total bilirubin level between 6 to 25 mg/dl at about 2 months of age in infants with acholic stool, regardless of the result of the ultrasonography and radionuclide hepatobiliary scan. Positive serology for syphilis was not considered to be an exclusive evidence against BA. If the stool colour failed to return to normal and total bilirubin failed to decrease significantly within an expected timing and after the adequate treatment for syphilis, the patient should be subject to a diagnostic laparotomy and intraoperative cholangio-graphy (IOC).

The present study has been undertaken to test the reliability of the proposed criteria in infants who were treated after 1989.

Materials and Methods

Medical records of all infants between 1-4 months of age who were treated for cholestatic jaundice at the Children's Hospital during the years 1990-1995 were studied. Those who were operated upon at the age older than 4 months were excluded from the study. Data concerning the stool colour, total bilirubin at the age nearest to 2 months, serology for syphilis, ultrasonography, radionuclide hepatobiliary scan, intra-operative cholangiography, operative findings and clinical follow-up data were collected. Excluded from the study were infants with cholestatic jaundice associated with sepsis and those who developed cholestatic jaundice during the administration of parenteral nutrition.

A total of 173 cases were available for the review. For practial purpose, all intrahepatic cholestasis were included in NH.

Results

Etiologies of Jaundice

The etiologies of cholestatic jaundice are shown in Table 1. Of the 63 infants with BA, 36 were female and 27 were male. All the causes were proved at surgery.

Of the 98 cases of NH, 71 were male and 27 were female. Twenty-five cases were proved at surgery by IOC. The diagnosis of NH in the remaining 73 cases was supported by clinical course and follow-up data.

Of the 5 cases of choledochal cyst (CDC), 4 were female and 1 was male.

The cause of cholestatic jaundice was not known in 7 cases because of the lack of clinical evidence and appropriate follow-up data.

Stool Colour

All of the 63 infants with BA had acholic stool. All previously had normal colour of meconium after birth. The onset of acholic stool varied widely among the patients, ranging from one or two weeks to two months or later. The paleness of the stool colour on admission to the hospital varied from case to case.

Of the 98 infants with NH, 39 never had acholic stool at any time while 59 had acholic stool during admission for investigation. Twenty-five of the latter group eventually required a diagnostic laparotomy and IOC to prove the patency of the biliary tree, while the remaining 34 infants did not require surgery. Improvement of the stool colour during hospitaliza-

Table 1 Causes of cholestatic jaundice.

Causes	Number of patients
1. Biliary atresia	63
2. Neonatal hepatitis	98
3. Choledochal cyst	5
4. Unknown cause	7
Total	**173**

Table 2 Total serum bilirubin at 2 months of age in infants with BA and NH.

Bilirubin (mg/dl)	Diagnosis	
	BA	NH
Less than 6	0	10
6 - 7	1	8
7 - 25	62	77
Over 25	0	3
Total	**63**	**98**

Table 3 Ultrasonography finding in infants with BA and NH.

Ultrasonographic Finding	Final Diagnosis		Total
	BA	NH	
Positive (for BA)	44	45	89
Negative (for BA)	15	42	57
Total	**59**	**87**	**146**

Sensitivity	*= 74.6%*
Specificity	*= 48.3%*
Positive predictive value	*= 49.4%*
Negative predictive value	*= 73.7%*
Accuracy	*= 58.9%*

tion or during investigations was the main reason for selection of non-operative management in most cases in the latter group. Presence of radio-isotope in the intestine in radionuclide hepatobiliary scan was demonstrated in 13 infants of this group.

Bilirubin Level

Total serum bilirubin at the age nearest to 2 months was studied in the 161 cases of BA and NH (Table 2). None of the infants with BA had total serum bilirubin below 6 mg/dl or above 25 mg/dl, while 13 of infants with NH did so.

Serology for Syphilis

Seventeen infants had positive serology for syphilis. All were adequately treated with penicillin. Fourteen of these patients had improvement of jaundice and stool colour after such treatment. Two patients continued to have acholic stool and the jaundice was not improved after the treatment. Both were subject to a diagnostic laparotomy and were found to have BA. One infant, who was a premature baby and was treated with penicillin on the first week of life, was operated at the age of 60 days and the other at the age of 87 days.

The remaining one patient, who still had pale stool colour at time of discharge from the hospital, never returned for a follow-up. It was not possible to exclude BA in this patient. She was one of the 7 cases with unproved etiology (Table 1).

Ultrasonography

Ultrasonography of the hepatobiliary system was done in 146 cases of NH and BA (Table 3). Interpretation was based mainly on the size of the gall bladder (GB). If the GB was not visualized or appeared to be small, it was interpreted as consistent with BA. If the GB was normal in size or distended, BA was considered unlikely.

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were all too low to be meaningful in differentiating BA from NH.

Preoperative ultrasonographic diagnosis was correct in all of the 5 cases of CDC.

Radionuclide Hepatobiliary Scan

Seventy-three cases had radionuclide hepatobiliary scan done. DISIDA scan was done in most cases. BROMIDA (trimethyl bromoimino diacetic acid) scan was done in recent cases. Of these, the cause of jaundice was proved by either diagnostic laparotomy, postmortem examination or clinical course in 69 cases. In the remaining 4 cases, the cause of jaundice was not proved by any of the mentioned criteria. In one case, whose hepatobiliary scan showed no excretion of tracer into the intestine, his parents refused surgery. In the remaining 3 cases, the diagnosis of NH was unfortunately made on the basis of the presence of tracer in the intestine in the scan. One of these 3 cases also had positive serology test for syphilis. None of these 3 cases returned for a follow-up. According to our experience[9], as well as others[4,5,10,12,15,16], the presence of tracer in the intestine in the hepatobiliary scan did not exclude BA completely. If these 3 cases were excluded from the calculation, computation of statistic evaluation of this test may not be statistically accurate.

Of the 69 infants whose diagnosis could be proven,

39 showed no tracer in the intestine while 30 had tracer in the intestine in the scan.

Of the 39 infants without tracer in the intestine in the scan, 26 had BA and 13 had NH. All of the 30 infants who showed tracer in the intestine in the scan had NH.

Computation from the data of the 69 cases, with the exclusion of the 4 cases with unproven etiology, showed the sensitivity of 100 per cent, specificity 69.8 per cent, positive predictive value 66.7 per cent, negative predictive value 100 per cent and accuracy 81.2 per cent.

Discussion

BA and NH probably represent different extremes of a single spectrum of the same pathologic process[17]. It probably is an inflammatory process of unproven etiology that starts in perinatal period and is dynamic during neonatal period. Both diseases appear very similar in early neonatal period. The clinical and pathologic pictures of both diseases depend on the age at which a child is examined. The stool colour appears normal at birth. The onset of acholic stool varies from case to case. The degree of paleness of the stool also varies considerably. Pale colour of the stool in infants with BA is obviously due to the obliteration of the bile duct, which may be complete at any time after birth. The stool colour in some infants with BA may not be completely white or clay colour. This is probably due to small amount of water-soluble bilirubin in the secretion of the mucosa of gastro-intestinal tract. The stool colour in infants with NH may be normally yellow or acholic in various degrees. In severe cases of NH, the bile excretion is severely retarded as a result of intrahepatic disease. For this reason, it is understandable that if the stool colour is pale, the infant may have either NH or BA. But if the stool colour is normally yellow, the diagnosis is most likely to be NH. Close observation in infants with normal colour of the stool is mandatory for a few months, as complete obliteration of the biliary ductal system may occur late in some cases. Some of our infants with BA had normally yellow stool at 2 months of age but the stool colour became pale a few weeks later. Improvement of the stool colour during hospitalization was observed in several patients. This usually resulted in cancellation of the planned surgical intervention.

Most studies indicated that serum bilirubin did not have any significance in differentiating NH from BA. Comparison of arithmatic means of bilirubin in both groups of patients showed no statistical difference. However, our previous study using different approach found that no infant with BA had total serum bilirubin at about 2 months of age below 6 mg/dl. or above 25 mg/dl[9]. Our present study also shows the same finding.

As in our previous study[9], positive serology test for syphilis did not completely exclude the possibility of BA. Patients with positive serology for syphilis should be treated properly with penicillin and carefully followed. If jaundice does not disappear accordingly, a diagnostic laparotomy may still be indicated. Srinivasan et al[18] also reported similar association of congenital syphilis and BA.

Ultrasonographic study of the biliary tree should be done in every case of infantile cholestatic jaundice. This is not to differentiate BA from NH but to detect a CDC[19]. Ultrasonographers usually focus on the shape and size of the GB. The assumption of a small GB or non-visualization of the GB is associated with BA has low accuracy[4,5,9,15]. Choi et al[20] recently described an ultrasonographic sign of "triangular cord" above the portal vein bifurcation as an indication of BA. They reported diagnostic accuracy of 95 per cent with 85 per cent sensitivity and 100 per cent specificity[15].

In a radionuclide hepatobiliary scan, the presence of tracer in the intestine should exclude the possibility of BA completely. If this assumption could be proved true, this test could at least be used as a screening to exclude infants with patency of bile duct from an unnecessary diagnostic laparotomy. Cases of BA with presence of tracer in intestine in the radionuclide hepato-biliary scan have been reported[4,5,9,10,12,16,17]. The explanation for this paradox is unclear. It may be possible that the lumen of bile ducts was not completely obliterated yet during the scanning procedure but the obliteration was complete by the time of surgery. Another possibility is the incorrect interpretation of the scan with the tracer actually in the kidney or ureter. If the latter assumption is correct, the sensitivity of the scan should be progressively improved with time. Refinement of imaging technique and availability of better imaging agents[21,22] may improve the accuracy of the scan in the future. Once the sensitivity of the test reaches 100%, it can become a good screening tool.

The specificity of the radionuclide hepatobiliary scan has been reported to be from 22 per cent to 90 per cent[4,5,9,13,15]. Pretreatment with pheno-barbital for 3-7 days before the scan has been recommended in order to increase the specificity of the test[13]. Our previous study showed no difference between the group of infants with phenobarbital pretreatment and the group without such treatment[9]. All patients in the present study were pretreated with phenobarbital for at least 5 days prior to the scan. The specificity of the scan in this group was probably about 70 per cent.

Needle biopsy of the liver has not been used in our hospital to differentiate NH from BA. Our limited experience with liver histologic study was disappointing[23]. Histologic interpretation of preoperative needle biopsy of the liver has been reported to have a sensitivity of 44-90 per cent[5,6,11,12,15]. Exceptional was the retrospective study by Ferry et al[2], who reported a sensitivity of 93 per cent and specificity of 96 per cent.

Other diagnostic investigations have been proposed as screening tests, but none has been proved to be totally reliable to differentiate NH from BA. Several algorithms of management of infants with cholestatic jaundice, aiming at minimizing the number of infants to undergo a diagnostic laparotomy, have been proposed[2,3,7,15] . Most of these algorithms suggest the combination of the radionuclide hepatobiliary scan and needle liver biopsy. It is our concern that some infants with BA may not be selected for a diagnostic laparotomy if these algorithms are followed, as none of these 2 investigations has a sensitivity of 100%. A prospective assessment of the accuracy of these algorithms in a large number of infants with cholestatic jaundice is needed before they can be recommended for practical guidelines.

Until a report of such assessment is available, it is our belief that our criteria for selection of infants with cholestatic jaundice for a diagnostic laparotomy appear appropriate, as these are supported by the present study. If these criteria were strictly followed, no infant with BA would be missed out but 25.5 per cent of infants with NH would be subject to a diagnostic laparotomy. It is our optimism that the refinement of hepatobiliary scan technique and availability of better imaging agents may result in 100 per cent sensitivity and improved specificity of the test, so that it can be included in screening criteria for selection of patients for a diagnostic laparotomy. This would hopefully reduce the number of patients to be subject to an unnecessary laparotomy.

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