

Comparison of different diagnostic methods in infants with Cholestasis

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Received: 2006-05-19 Accepted: 2006-08-15

Dehghani SM, Haghghat M, Imanieh MH, Geramizadeh B. Comparison of different diagnostic methods in infants with Cholestasis. *World J Gastroenterol* 2006; 12(36): 5893-5896

<http://www.wjgnet.com/1007-9327/12/5893.asp>

Abstract

AIM: To evaluate different methods in differentiating idiopathic neonatal hepatitis from biliary atresia.

METHODS: Sixty-five infants with cholestatic jaundice and final diagnosis of idiopathic neonatal hepatitis and biliary atresia were studied prospectively from September 2003 to March 2006. A thorough history and physical examination were undertaken and the liver enzymes were examined. All cases underwent abdominal ultrasonography, hepatobiliary scintigraphy, and percutaneous liver biopsy. The accuracy, sensitivity, specificity and predictive values of these various methods were compared.

RESULTS: There were 34 girls and 31 boys, among them 46 subjects had idiopathic neonatal hepatitis (age, 61 ± 17 d) and 19 had biliary atresia (age, 64 ± 18 d). The mean age at onset of jaundice was significantly lower in cases of biliary atresia when compared to idiopathic neonatal hepatitis cases (9 ± 13 d vs 20 ± 21 d; $P = 0.032$). The diagnostic accuracy of different methods was as follows: liver biopsy, 96.9%; clinical evaluation, 70.8%; ultrasonography, 69.2%; hepatobiliary scintigraphy, 58.5%; and liver enzymes, 50.8%.

CONCLUSION: Our results indicate that clinical evaluation by an experienced pediatric hepatologist and a biopsy of the liver are considered as the most reliable methods to differentiate idiopathic neonatal hepatitis and biliary atresia.

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Key words: Idiopathic neonatal hepatitis; Biliary atresia; Clinical evaluation; Liver biopsy

INTRODUCTION

Cholestatic jaundice in early infancy is an important clinical condition that results from diminished bile flow and/or excretion, and can be caused by a number of disorders. Idiopathic neonatal hepatitis (INH) and biliary atresia (BA) are two main causes^[1,2].

It is important to distinguish INH from BA in an infant presented with jaundice, as the former purely needs a medical management and the later requires surgical intervention as soon as possible. Therefore, rapid and accurate differentiation is crucial for early surgery in patients with BA^[3]. In this study, we evaluated and compared the different diagnostic methods for this differentiation.

MATERIALS AND METHODS

In a prospective study from September 2003 to March 2006, the differential diagnosis and etiologic work-up of cholestasis in infancy were carried out. A written consent was provided from all parents after informing them about this study which was also approved by the Ethic Committee of the University. Sixty-five consecutive cholestatic infants (34 girls, 31 boys) with a final diagnosis of INH or BA were entered in our study. These patients were all referred to the Department of Pediatric Gastroenterology in Nemazee Hospital affiliated with Shiraz University of Medical Sciences, which is the major referral center in Southern Iran.

A thorough history and physical examinations were provided, including age at onset of jaundice, birth weight, stool color, and any signs of systemic diseases. Ophthalmologic, cardiac and rectal examination, presence of any organomegaly, and assessment of growth state were performed.

For all patients, a complete blood count, urinalysis, urine reducing substances, thyroid function tests, bacterial culture of both urine and blood, serum alpha-1-antitrypsin and screening for cystic fibrosis (sweat chloride test) were performed. Acid-base status was determined as

Table 1 Comparison of various diagnostic methods for INH and BA

Method	Patients (n)	Results	Final diagnosis				P ¹
			BA (n = 19)		INH (n = 46)		
			n	%	n	%	
Clinical evaluation	65	BA	16	84.2	16	34.8	< 0.001
		INH	3	15.8	30	65.2	
Liver enzymes	65	BA	13	68.4	26	56.5	0.373
		INH	6	31.6	20	43.5	
Ultrasonography	65	BA	10	52.6	11	23.9	< 0.05
		INH	9	47.4	35	76.1	
Hepatobiliary scintigraphy	65	BA	16	84.2	24	52.2	< 0.05
		INH	3	15.8	22	47.8	
Liver biopsy	65	BA	19	100	2	4.3	< 0.001
		INH	0	0	44	95.7	

¹BA vs INH, κ^2 analysis.

Table 2 Accuracy of various diagnostic methods for BA and INH

Diagnostic method	n ¹	BA (%)	n	INH (%)	n	INH vs BA (%)
Liver biopsy	19/19	100	44/46	95.2	63/65	96.9
Clinical evaluation	16/19	84.2	30/46	65.2	46/65	70.8
Ultrasonography	10/19	52.6	35/46	76.1	45/65	69.2
Hepatobiliary scintigraphy	16/19	84.2	22/46	47.8	38/65	58.5
Liver enzymes	13/19	68.4	20/46	43.5	33/65	50.8

¹Accurately diagnosed cases/performed cases.

an initial step to evaluate the metabolic disorders.

For all patients, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were checked and all underwent ultrasonography of the abdomen, hepatobiliary scintigraphy and percutaneous liver biopsy.

Cases with etiologies other than INH and BA were excluded from the study. Cases suspicious for BA underwent laparotomy and intraoperative cholangiography.

Later onset of jaundice, lower birth weight, poor growth, deep yellow or greenish stools, presence of signs of systemic diseases and consanguinity were considered as clinical criteria for diagnosis of INH. ALT and AST 10 times more than normal mean and ALP 5 times less than normal mean are considered as criteria for INH. ALT and AST 5 times less than normal mean and ALP 5 times more than normal mean are considered as criteria for BA. Ultrasonographic evidences of dilatation or absence of the main bile duct near the hilum, absence of the gall bladder and presence of triangular cord sign were considered as criteria for BA.

Finally, the accuracy of the five diagnostic methods (clinical evaluation, liver enzymes, abdominal ultrasonography, hepatobiliary scintigraphy, and liver biopsy) was evaluated for differential diagnosis of INH and BA. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each method were also calculated.

RESULTS

There were 65 cholestatic infants, including 34 (52.3%) girls and 31 (47.7%) boys with a mean age of 62 ± 17 d (30-91 d). There were 46 (70.8%) cases (22 girls, 24 boys) of INH, and 19 (29.2%) cases (12 girls, 7 boys) of BA. The mean age of INH patients was 61 ± 17 d (33-90 d), and BA patients was 64 ± 18 d (30-91 d) and the difference was not statistically significant.

Mean birth weight of patients with INH was 2893 ± 629 g (1150-3900 g) and with BA was 2951 ± 556 g (1900-4150 g), and the difference was not significant.

Age at onset of jaundice in INH was 20 ± 21 d (1-65 d) and in BA was 9 ± 13 d (1-45 d), and the difference was significant ($P = 0.032$).

Forty-four (67.7%) cases had clay-colored stools, among them, 26 cases had INH and 18 cases had BA; and 21 (32.3%) cases had normal-colored stools, among them, 20 cases had INH and one had BA ($P = 0.003$).

The difference in mean ALT, AST and ALP values between INH and BA patients was not significant.

Table 1 shows comparison of the various methods in diagnosing of 65 infants with cholestasis. Table 2 shows the diagnostic accuracy of each method in the order of accuracy. Liver biopsy had 100% diagnostic accuracy for BA and 95.2% for INH, and clinical evaluation had diagnostic accuracy of 84.2% and 65.2% for BA and INH, respectively. Table 3 shows the sensitivity and specificity and Table 4 demonstrates the positive and negative predictive values of each method in differentiating BA and INH. Liver biopsy had the highest sensitivity and specificity for differentiating BA and INH.

DISCUSSION

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guideline for the evaluation of cholestatic jaundice in infants recommends that any infant noted to be jaundiced at the two-week well child visit should be evaluated for cholestasis^[1]. Evaluation of breast-fed infants may be delayed until three weeks of age if they have a normal

Table 3 Sensitivity and specificity of various diagnostic methods for BA and INH

Diagnostic method	Sensitivity for BA		Specificity for BA	
	%	<i>n</i>	%	<i>n</i>
Clinical evaluation	84.2	16/19	65.2	30/46
Liver enzymes	68.4	13/19	43.5	20/46
Ultrasonography	52.6	10/19	76.1	35/46
Hepatobiliary scintigraphy	84.2	16/19	47.8	22/46
Liver biopsy	100	19/19	95.7	44/46

Sensitivity for BA was equivalent to specificity for INH, and specificity for BA was identical to sensitivity for INH.

physical examination, no history of dark urine or light stools, and can be reliably monitored^[1,4,5]. Neonatal hepatitis and BA, which typically occur in term infants, account for 70%-80% of cases^[6].

Evaluation should be undertaken in a staged approach^[7]. The initial step is rapid diagnosis and early initiation of therapy of treatable disorders. Conditions, such as sepsis, hypothyroidism, panhypopituitarism, and inborn errors of metabolism (e.g., galactosemia), must be recognized and treated promptly to avoid significant progression of the illness. Extrahepatic biliary atresia must be differentiated from neonatal hepatitis because early surgical intervention (i.e., before two months of age) results in a better outcome.

In our study, clinical evaluation had good accuracy for diagnosing BA (84.2%) and moderate accuracy for INH (65.2%). Prevalences of acholic stools in our study were 94.7% for BA and 56.5% for INH that are comparable to the study by Mowat *et al.*^[2] (i.e., 83% and 52%, respectively). The mean values of ALT, AST and ALP in BA were 161 ± 107, 261 ± 141, and 2150 ± 830, respectively, and in INH were 212 ± 198, 324 ± 258, and 1791 ± 852, respectively, and the difference was not statistically significant. Therefore, considering the level of liver enzymes would not be an accurate method to differentiate BA and INH (diagnostic accuracy of 50.8%).

Abdominal ultrasonography is more helpful in the diagnosis of choledochal cysts but can also suggest the diagnosis of BA. Findings suggestive for the latter are non-visualized gall bladder and the presence of the triangular cord sign^[8-10]. The sensitivity and specificity of a small or absent gall bladder in detecting obstruction range from 73% to 100% and 67% to 100%, respectively, when correlated with pathologic, surgical, and subsequent clinical examinations^[1].

In our study, abdominal ultrasonography had sensitivity and specificity of 52.6% and 76.1% for BA, respectively. Accuracy of ultrasonography for differentiation between BA and INH in our series was 69.2%, that was lower than that reported by Lin *et al.*^[11] (sensitivity, specificity and accuracy were 86.7%, 77.1%, and 79.4%, respectively) and Park *et al.*^[12] (85%, 100%, and 95%, respectively). This lower accuracy may be due to lower experience of our sonographer for detection of triangular cord sign.

Hepatobiliary scintigraphy with technetium-labeled iminodiacetic acid analogs can be helpful for distinguishing

Table 4 Positive and negative predictive values of various diagnostic methods in BA and INH

Diagnostic method	Positive PV for BA and negative PV for INH		Negative PV for BA and positive PV for INH	
	%	<i>n</i>	%	<i>n</i>
Clinical evaluation	50	16/32	90.9	30/33
Liver enzymes	33.3	13/39	76.9	20/26
Ultrasonography	47.6	10/21	79.5	35/44
Hepatobiliary scintigraphy	40	16/40	88	22/25
Liver biopsy	90.5	19/21	100	44/44

PV: Predictive value.

biliary atresia from neonatal hepatitis and other causes of cholestasis. The sensitivity and specificity of scintigraphy in detecting of obstruction range from 83% to 100% and 33% to 100%, respectively^[1]. In the present study, scintigraphy had sensitivity and specificity of 84.2% and 47.8% for detecting BA, respectively. Scintigraphy adds little to the routine evaluation of the cholestatic infant, but may be of value in determining patency of the biliary tract, thereby excluding BA^[1].

Hepatobiliary scintigraphy had an accuracy of 58.5% in this study that is comparable to the data reported by Park *et al.*^[12], and Gupta *et al.*^[3], but lower than that by Lin *et al.*^[11] and Nadal *et al.*^[13].

Percutaneous liver biopsy is generally employed in the evaluation of neonatal cholestasis, particularly when biliary tract obstruction is high on the differential diagnosis^[14]. The NASPGHAN guideline recommends that a percutaneous liver biopsy to be performed in most infants with undiagnosed cholestasis^[1]. The biopsy should be interpreted by a pathologist with expertise in pediatric liver disease. Biopsy is recommended before performing a surgical procedure to diagnose biliary atresia. If the results are equivocal and biopsy was performed when the infant was < 6 wk of age, a repeated biopsy may be necessary.

Liver needle biopsy is the most invasive method among the various tests, but it is also the most accurate one. Our study found that liver needle biopsy was the most reliable method with the highest accuracy rate of 96.9%, which is similar to those in previous reports^[2,12,15].

In conclusion, clinical evaluation by an experienced pediatric hepatologist and liver needle biopsy might be the most reliable methods to differentiate idiopathic neonatal hepatitis and biliary atresia.

ACKNOWLEDGMENTS

We would like to thank Dr. Davood Mehrabani at Gastroenterohepatology Research Center and the Center for Development of Clinical Research at Nemazee Hospital for editorial and statistical assistance.

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S- Editor Liu Y L- Editor Kumar M E- Editor Liu WF