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Predictive value of hepatic ultrasound, liver biopsy, and duodenal tube test in the diagnosis of extrahepatic biliary atresia in Serbian infants

BILIARY TREE

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Original Article

ABSTRACT

Background/Aims: Extrahepatic biliary atresia (EHBA) is the most important cause of neonatal cholestasis. The validity of different diagnostic methods in the diagnosis of EHBA in developed countries has been presented elsewhere, but data from developing countries with low national incomes are scarce. The aim of this study was to investigate the relative accuracy and roles of abdominal ultrasonography, duodenal tube test (DTT), and liver biopsy in the diagnosis of EHBA in Serbia.

Materials and Methods: The study included 156 infants with cholestasis admitted at the Mother and Child Health Care Institute. Data were collected according to the medical records observation technique.

Results: Extrahepatic biliary atresia was diagnosed in 72 of 156 infants with cholestasis. The frequency was insignificantly higher in females than in males (1.25:1). Most patients were diagnosed prior to 60 days of life (median 58, range 30-67). In a group of 156 infants with cholestasis, 109 had ultrasound, liver biopsy, duodenal tube test, and intraoperative cholangiography done. Liver biopsy confirmed surgical disease in 71/109 patients and denied it in 38/109 patients (sensitivity- Sn 98%, specificity- Sp 100%, diagnostic efficiency of test- DgEf 99.08%). Duodenal tube test had Sn 97%, Sp 72%, and DgEf 88.99%, and the ultrasound findings showed Sn 78%, Sp 81%, and DgEf 77.92%. Five-year survival rate after Kasai operation was 76%.

Conclusion: A well-coordinated multidisciplinary approach is required in the assessment of suspected cases of biliary atresia. Histology examination of biopsy specimens is an integral part of the diagnostic algorithm and, therefore, plays a pivotal role in the diagnostic evaluation of this disease.

Keywords: Extrahepatic biliary atresia, liver biopsy, duodenal tube test, Kasai operation

INTRODUCTION

Extrahepatic biliary atresia is the most important cause of neonatal cholestasis and is characterized by necroinflammatory obliterating cholangiopathy of extrahepatic bile ducts of unknown etiopathogenesis. It typically occurs in the first month of life as icterus and acholia with or without hepatomegaly in previously healthy neonates of average body weight for gestational age. The optimal treatment is to establish satisfactory bile flow from the liver to the gastrointestinal tract by Kasai portoenterostomy during the first 8 weeks of life (1,2). If this fails and/or the disease progresses towards biliary cirrhosis and life-threatening complications, then liver transplantation is indicated, for which biliary atresia (BA) represents the most frequent pediatric indication. Of importance, the earlier the Kasai is performed, the later a liver transplantation is usually needed. Extrahepatic biliary atresia remains one of the major hepatic causes of death in early childhood. Though a number of hypotheses have been developed to account for this disease, its etiopathogenesis is poorly understood. The aim was to investigate the relative accuracy and roles of abdominal ultrasonography, duodenal tube test (DTT), and liver biopsy in the diagnosis of biliary atresia (BA) in Serbia.

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MATERIALS AND METHODS

The study included patients with cholestasis, admitted to the Mother and Child Health Care Institute, Serbia in a 10- year period (2002-2011). Diagnostic procedures included clinical presentation, laboratory studies, imaging studies, liver biopsy, histopathology features in biopsy specimens, duodenal tube test (DTT), and intraoperative cholangiography.

Abdominal ultrasonography was performed after 8 to 12 hours of fasting, with BA being suspected if the gallbladder was absent or shrunken despite the absence of feeding, if the liver hilum was hyperechogenic ("triangular cord sign"), or if there was a cyst at the liver hilum without bile duct dilatation (3).

Percutaneous blind liver biopsy was performed by Menghini 1-second liver biopsy technique with local anesthesia, on the intercostal medioaxillary line, using a large-diameter needle (Hepafix 1.6 mm, Luer Lock; Braun, Melsungen, Germany) (4).

In the biopsy specimen, the main features that suggested BA were biliary tracts containing inflammatory and fibrous cells surrounding miniscule ducts, likely remnants of the original ductal system, with fibrotic liver parenchyma exhibiting signs of cholestasis, and proliferation of biliary neoductal structures (5).

For the duodenal tube test, a nasoduodenal tube was placed at the distal duodenum, and fluid was collected for 24 hours. DTT was considered bile-positive when yellow biliary fluid was observed; the test was concluded at this time. When no yellow biliary duodenal fluid was observed, the collection was continued for 24 hours and, if negative, was reported as bile-negative (6).

All 156 children with cholestasis were clinically evaluated; only 47 of them did not have all the diagnostic procedures done, so they have been excluded from the statistical calculations of the diagnostic procedure validity.

Data were collected according to the medical records observation technique, reviewing the case histories of children hospitalized during this period. Statistical calculations of the diagnostic procedure validities were performed according to established formulas for sensitivity (SN), specificity (SP), positive predictive value of the test (PPV), negative predictive value of the test (NPV), pretest probability (P), likelihood ratio of positive test (LR+), negative likelihood ratio test result (LR-), probability after diagnosis test (VPT), and diagnostic efficiency of the test (DgEf). The chi-square test was applied as well. Data were analyzed using SPSS 15.0 for Windows (Goldbar Ventures Ltd, West Midlands, UK). The study was observational and retrospective.

RESULTS

In a 10-year period, 156 children with cholestasis (82 with intra- and 74 with extrahepatic) had been admitted to our hospital.

Table 1. Age distribution of infants with BA

At the time of diagnosis			
Days of life	**Frequency**	**Percent**	**Cumulative percent**
30	1	1.4	1.4
34	4	5.6	6.9
35	1	1.4	8.3
38	4	5.6	13.9
44	1	1.4	15.3
46	6	8.3	23.6
55	24	33.3	56.9
58	28	38.9	95.8
67	3	4.2	100
Total	72	100	

BA: biliary atresia

The most common cause of intrahepatic cholestasis was found to be idiopathic neonatal hepatitis in 50/82 patients (60.97%), followed by infectious hepatitis in 10/82 (12.2%), metabolic liver diseases in 9/82 (10.97%), intrahepatic biliary atresia in 8/82 (9.75%), and Alagille syndrome in 5/82 (6.09%). Extrahepatic biliary atresia in 72/74 (97.3%) was the most common cause of extrahepatic cholestasis. Two patients had choledochal cyst (2.7%).

Biliary atresia was diagnosed in 72/156 children (46.15%); 40/72 were female and 32/72 were male. The frequency was insignificantly higher in females than in males (1.25:1).

Median age at diagnosis was 58 days (range 30-67), with 96% diagnosed by 60 days and 4% by 67 days (Table 1).

Ultrasound, duodenal tube test, liver biopsy, and intraoperative cholangiography had been done in 109 patients.

Ultrasound findings confirmed surgical disease in 55/109 patients and denied it in 30/109 patients (Sn 78%, Sp 81%, PPV 88%, NPV 63%, and DgEf 77.92%) (Table 2).

Duodenal tube test confirmed surgical disease in 70/109 patients and denied it in 2/109 patients (Sn 97%, Sp 72%, PPV 87%, NPV 93%, and DgEf 88.99%) (Table 2).

Liver biopsy confirmed surgical disease in 71/109 patients and denied it in 38/109 subjects. Intraoperative cholangiography confirmed the diagnosis in 72/109 patients and excluded it in 37/109 subjects (Sn 98%, Sp 100%, PPV100%, NPV 97%, and DgEf 99.08% (Table 2).

All of them underwent Kasai operation. Ascending cholangitis during the first weeks after the operation occurred in 28% of

Table 2. Validity of diagnostic methods

Diagnostic methods	P	Sn	Sp	PPV	NPV	LR-	LR+	DgEf
Liver biopsy	66	98	100	100	97	0.98	0.14	99
Ultrasound findings	66	78	81	88	63	0.4	0.02	78
Duodenal tube test	66	97	72	88	93	0.3	0.02	89

P: prevalence; Sn: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio of negative result test; LR+: likelihood ratio of positive result test; DgEf: diagnostic efficiency of test

cases. Portal hypertension during the first 5 years after operation developed in 15% of patients. Five patients developed hepatopulmonary syndrome. Five-year survival rate after Kasai was 76%. Seven (9.72%) patients with EHBA underwent liver transplantation (LT) abroad; 3 of them had lethal outcomes in the first few months post-LT.

DISCUSSION

The current management of EHBA patients is sequential and involves two steps: (1) Kasai hepato-porto-enterostomy in the neonatal period, in order to restore bile flow towards the intestine and preserve liver function as long as possible; and (2) liver transplantation (LT), if no clearance of jaundice can be achieved through the Kasai operation or when complications of biliary cirrhosis appear later on.

Short-term results of the Kasai are better when it is done early (1,2,7-10)-that is, at the latest by the end of the third month of life-with clear evidence that the earlier the operation, the better the outcome. In several series, it has been reported that bill flow is reestablished in more than 80% in infants who are referred for surgery within 60 days after birth. The success rate drops dramatically to under 20% in those older than 90 days at the time of operation (1,11). Chardot et al. (1) published that the optimum time for surgery in infants is up to 60 days when the postoperatively reestablished bill flow is 70%-80%. In our series, most patients were diagnosed prior to 60 days of life, at the optimal moment for surgery. Median was 58 days, and range was 30-67 days. Our results are significantly different from our neighbors. In a Croatian study (12), median was 66 days and range was 22-129 days, which makes the success rate drop dramatically.

Abdominal ultrasonography is the first choice and gold standard noninvasive imaging investigation when EHBA is suspected. Ultrasonography had high sensitivity and specificity in predicting surgical treatment (13). Farrant et al. (14) determined that an absent gallbladder or one with an irregular wall or abnormal shape had a sensitivity, specificity, and accuracy of 90%, 92.4%, and 91.9%, respectively, in the diagnosis of BA. Hessel et al. (15) reported that sensitivity was 100% with an accuracy of 83%. In our study, sensitivity was slightly lower at 78%, with almost the same accuracy (78%). These results indicate that ultrasound is not a unique approach for prediction of surgical disease. The method is referential, non-invasive, and available.

Magnetic resonance cholangiography in children could visualize the common biliary duct and gallbladder (13,14,16). Numerous scintigraphic methods are popular in developed countries but have little diagnostic value for biliary atresia, because they can not show biliary excretion in 55% of patients with neonatal hepatitis and in 50% of patients with biliary hypoplasia (13,14). In countries with very low national incomes, these methods are understandably much less applied (17).

Faweya et al. (18) indicate that the reliability of the duodenal tube test is very high, because this determines the presence of bile in the duodenal content in 24 hours. The presence of bile in the bile ducts excludes the obstruction. Larrosa et al. (19) reported a sensitivity of 97.3%, specificity of 93.7%, positive predictive value of 92.3%, and negative predictive value of 98.5%. In our study, DTT had similar results (Sn 97%, Sp 72%, PPV 88%, NPV 93%). These results indicate that DTT is extremely sensitive, with very high diagnostic efficacy. The implementation of this test is technically complex and is used in special indications preoperatively and postoperatively for routine assessment of bile drainage.

The other most definitive test for establishing the diagnosis of BA is a liver biopsy, usually performed at the same time as the cholangiography. The main features suggesting BA are biliary tracts containing inflammatory and fibrous cells surrounding miniscule ducts, likely remnants of the original ductal system, with fibrotic liver parenchyma exhibiting signs of cholestasis, and proliferation of biliary neoductal structures (5). In the early stage of life (from about 1-4 weeks), nonspecific features of bilirubin stasis predominate. Form about 4 to 8 weeks, the portal tracks show characteristic changes consisting of rounding of the portal tract, edema, dilation of lymph vessels, and ductal proliferation. This stage is considered diagnostic and explains the recommendation by some to postpone diagnostic liver biopsy until the sixth week of life (20). In our study, 68/72 (94%) patients underwent liver biopsy at 4-8 weeks of life, as recommended. Zerbini et al. (21), in a prospective study of 74 liver biopsies, reported 76% specificity and 100% sensitivity in relation to obstructive and nonobstructive cholestasis. Hessel et al. (15) reported that the sensitivity was 76% for liver biopsy in diagnosing extrahepatic cholestasis, with an accuracy of 86% for biopsy, rising to 96% when both tests (liver biopsy and ultrasound) were considered together. Poddar et al. (22) reported that the liver biopsy was 100% accurate in differentiating BA from neonatal hepatitis.

Yang et al. (23) also indicated that biopsy of the liver is considered the most reliable method to differentiate idiopathic neonatal hepatitis from BA. The diagnostic accuracy of liver biopsy was 97.1%. Our data suggest that liver biopsy is the most sensitive and specific method for predicting surgical disease, with 99% sensitivity, 100% specificity, and 99% accuracy.

The 5-year survival rate after Kasai was 76%, which is among the highest survival rates in Europe. Four-year survival with native liver (SNL) was described to be 48% in France (7), 51% in the 3 supraregional British centers (Birmingham, Leeds, London) (9,24); 5-year SNL was 49% in Madrid (Spain) (25) and 37.4% in a Swiss national series (8). The explanation for our high survival rate might be the optimal timing for operation and low incidence of cholangitis after the operation. It has been reported that the occurrence of cholangitis significantly reduces survival rate in patients with either good or inadequate bile flow (26).

In 2009, Serinet et al. (7) confirmed in a large French national study that the earlier the BA baby is operated on, the later liver transplantation (LT) will be required, with the effect maintained late into adolescence. These authors evaluated the potential benefits of neonatal BA screening; children who were operated on before 6 weeks of life were compared with older kids; a 12.1% improvement in 15-year SNL (34.9% versus 22.8%) was measured following early intervention, clearly confirming that the earlier the diagnosis of BA, the later LT is required (27).

A well-coordinated multidisciplinary approach is required in the assessment of suspected cases of biliary atresia. Pathologic examination of biopsy specimens is an integral part of the diagnostic algorithm and, therefore, plays a pivotal role in the diagnostic evaluation of this disease.

Liver and biliary tree scintigraphy and magnetic resonance cholangiography (MRC) have taken precedence over the duodenal tube test and liver biopsy in the study of cholestatic jaundice due to extrahepatic biliary atresia (EHBA) in developed countries, but in developing countries with low national incomes, these methods are much less applied.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Mother and Child Health Care Institute.

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study.

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