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Original Article (Pages: 16281-16290)

The Diagnostic Value of Different Sonography Findings and Color Doppler Sonography in Detecting Biliary Atresia in Infants and Neonates

Mohammad Ali Kiani[1], Seyed Ali Jafari[2], * Homa Jajarmi Khayyat[1], Seyed Ali Alamdaran[3], Masood Mahdavi Rashed[3], Maryam Khalesi[1], Elham Bakhtiari[4]

1 Department of Pediatric, Mashhad University of Medical Sciences, Mashhad, Iran.

2 Department of Pediatric Gastroenterology, Mashhad University of medical sciences, Mashhad, Iran.

3 Department of Radiology, Mashhad University of Medical Sciences, Mashhad, Iran.

4 Research Center for Patient Safety, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Background: Biliary atresia (BA) is one of the most common etiologies of cholestasis in infants and toddlers. The most important factor in case of patients' prognosis is its early diagnosis. There are many diagnostic tools in this field, sonography seems to be the most appropriate and fastest tool in early detecting and differentiating BA from other causes of neonatal cholestasis. The aim of this study was to evaluate the diagnostic value of new ultrasound and Doppler ultrasound methods in BA in infants and toddlers.

Methods: This cross-sectional study was performed during a one-year period on 35 infants and toddlers admitted to the gastrointestinal department of Akbar Children's Hospital with suspicion of cholestasis. These children underwent sonography by a radiologist to diagnose BA. All required information was extracted from the hospital records of these children and analyzed after entering the checklist. Data were analyzed using SPSS software version 26.

Results: Totally, 35 patients including 18 boys (51.4%) and 17 girls (6.48%) with a mean age of 4/29±4/17 months were enrolled. According to the findings of the analysis, 21 patients (60%) had bile duct atresia and 14 patients (40%) had other diseases. Ultrasound sensitivity in the diagnosis of bile duct atresia was 90%, with an accuracy of 74%, specificity of 50% and positive and negative predictive value of 73% and 77%, respectively. The highest diagnostic value was related to the former hepatic capsular flow.

Conclusion: Biliary atresia can be accurately diagnosed by ultrasonography. The high sensitivity and accuracy of ultrasound indicate the appropriateness of this method in diagnosing this disease.

Key Words: Biliary atresia, Children, Conjugated hyperbilirubinemia, Doppler ultrasound, Ultrasound.

* Please cite this article as: Kiani MA1, Jafari SA, Khayyat HJ, Alamdaran SA, Rashed MM, Khalesi M, Bakhtiari E. The Diagnostic Value of Different Sonography Findings and Color Doppler Sonography in Detecting Biliary Atresia in Infants and Neonates. Int J Pediatr 2022; 10 (7):16281-16290. DOI: **10.22038/ijp.2022.59436.4635**

Corresponding Author:

Homa Jajarmi Khayyat, Department of Pediatric, Mashhad University of Medical Sciences, Mashhad, Iran. Email: h.jajarmi88@gmail.com

Received date: jul.27,2020; Accepted date:Sep.21,2020

1- INTRODUCTION

Biliary atresia (BA) is a rare condition characterized by obliteration of the extrahepatic biliary tract and the absence of normally branching intrahepatic ducts (1). The condition presents with different epidemiologies in east and west. The western incidence of the disease ranges between 0.52-0.71 per 10,000 live births in the west (2-4), while it is estimated to be 1.06 per 10,000 live births in the east. Among these, the highest incidence is in China with 2 in every 10,000 live births (5). With this regard, it seems that ethnicity may play a role and several candidate genes have been reported for this disease (6-8).

BA is categorized into four different major classes including isolated, syndromic, cystic, and Cytomegalovirus (CMV) associated. The majority of the cases are still in the isolated form, comprising 80 to 90 percent of the patients. Also, the most known syndrome that is associated with BA is Biliary Atresia Splenic Malformation (BASM) (9, 10). However, there are some other disorders related to BA such as gastrointestinal luminal atresia, polycystic kidney and cleft palate. The other types of BA including cystic and CMV related ones are extremely rare (11).

Early diagnosis is a challenge in all types of BA. It is reported that early diagnosis helps prompt management of the patients and brings better prognosis. The timely detection of jaundice is still hard, as the examination of sclera is not easy in toddlers and the skin changes happen too late (7). Moreover, physiologic jaundice is expectable and can be misdiagnosed. There are many ways that are implicated in BA diagnosis such as abdominal ultrasonography (12), Hepatobiliary Imino Diacetic Acid (HIDA) scan (13), immunochemistry (ALP, AST, ALT, GGT, MMP-7), and liver biopsy (14). However, some of these approaches like liver biopsy, despite being the gold standard, are invasive. Some are expensive and not easily accessible, like HIDA scan. With this regard, the proposal of an accessible and non-invasive method is really helpful (15). Abdominal ultrasonography is a modality of choice, with these considerations (12). It is reported that absence of gallbladder detection in ultrasonography has a specificity of 99% (16). However, there are many different sonography findings in case of detecting BA. Moreover, sonography is operator dependent and its diagnostic value has been under question in different studies (17, 18). Here, we aimed to assess the diagnostic value of different sonography findings in patients with BA.

2- MATERIAL AND METHODS

2-1. Study design, population, and sampling

This cross-sectional study was conducted during a one-year period between 2019 and 2020 on 35 toddlers and infants, who referred with icterus and raised direct bilirubin with the suspicion of cholestasis according to the pediatric gastrointestinal specialist, in Akbar children hospital in Mashhad, Iran. The age range of the patients was between 1 month to 24 months and all should have sonography with suspicion of cholestasis. Those who had insufficient data were excluded.

The sample size was calculated according to the reported sensitivity and specificity of sub-capsular blood flow in sonography in diagnosing biliary atresia in the study by Lee et al. (19), which was 100% and 80%, respectively. Using the following formula and considering a 5% alpha and a power of 80%, the sample size was calculated as 35 cases for the two study groups:

$$N= p1q1+ p2q2^* (z1\alpha/2+z1-\beta)/(p1-p2)^2$$

2-2. Atresia diagnosis

An experienced radiologist in case of pediatric radiology conducted the sonographies. The patients were to be NPO for 4 hours before sonography. The sonography studies were conducted using a WS80 Samsung device with 5-8 MHz Curvilinear probe and a 5-12 MHz linear probe. The size and morphology of gallbladder (with normal cut-off of 5.1 cm), hepatic artery diameter, portal vein diameter, anterior triangular cord sign, superior triangular cord sign, central periportal echogenicity, diffuse periportal echogenicity, biliary dilatation, fibrotic change (heterogeneity), cirrhotic change (nodularity), echogenicity, liver size, and presence of ascites were assessed.

The linear probe was used to assess the subcapsular blood flow anterior to the ligamentum falciforme according to the following criteria: 1. Color box (with 1 cm length and 3 to 4 cm height), pulse repetition frequency (1200 to 1500 Hz), power gain percentage (82 to 92 percent), and medium flow velocity (medium wall filtration). In color Doppler sonography, the subcapsular blood flow is considered whenever the vessel structures continue to the capsular level (19). Besides these, the definite diagnosis was made according to the liver biopsy, surgery, or complementary laboratory examinations.

2-3. Data Collection

Data extraction was conducted using predesigned forms. Data including demographics (age and gender), the way of definite diagnosis (biopsy, surgery, and complementary laboratory exams), final diagnosis (cholestasis or non-cholestasis), type of non-cholestasis disease, and sonography findings were extracted and recorded.

2-4. Data analysis

All analyses were conducted using SPSS version 26. The frequency and percent of qualitative data, central tendency, and dispersion were calculated. The comparison of qualitative data between the two study groups were done by chi-square and fisher's exact tests. Moreover, quantitative data were compared by t-test. Finally, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated and ROC curve was designed. P values under 0.05 were considered significant.

3- RESULTS

Totally, 35 toddlers and infants were enrolled in the study, who were suspected of biliary atresia. The mean age of the patients was 4.17±4.29 months and in case of gender, 18 (51.4%) were males and 17 (48.6%) were females. Moreover, the definite diagnosis of the BA was confirmed by surgery in 16 cases (45.7%), biopsy in 12 cases (34.3%), and complementary laboratory exams in 4 cases (11.4%). **Table 1** shows the details of the demographic findings.

Table 1 also illustrates sonography findings of all participants. The most common found sign was anterior triangular cord sign in 24 cases, followed by central periportal echogenicity in 23 cases (65.7%), hepatic subcapsular flow in 14 cases (45.7%), and superior triangular cord sign in 14 cases (40.0%).

Table 2 compares demographic and sonographic findings between the two study groups. Hepatic subcapsular flow ($p<0.001$), anterior triangular cord sign ($p=0.011$), and ultrasound diagnosis ($p=0.012$) showed significant differences between the two study groups.

Fig. 1 also shows the ROC curve of different sonography findings including liver artery diameter, portal vein diameter, and liver size. The area under the curve (AUC) for liver artery diameter, portal vein diameter, and liver size were 0.679 cm, 0.510 cm, and 0.585 cm, respectively.

Table 3 shows sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for different sonography findings. The highest sensitivity was for anterior triangular cord sign with 85.71% and the highest specificity was for hepatic subcapsular flow with 92.85%. Moreover, the highest PPV and NPV was for hepatic subcapsular flow and anterior triangular cord sign with 93.75% and 72.72%, respectively.

Table-1: Demographic and sonographic findings of all cases

Variable			Statistic
Demographics	Age (months; mean±SD)		4.17±4.29
	Gender N (%)	Male	18 (51.4)
		Female	17 (48.6)
	Definite diagnosis method N (%)	Surgery	16 (45.7)
		Biopsy	12 (34.3)
		Complementary lab	4 (11.4)
	Definite diagnosis N (%)	Biliary atresia	21 (60.0)
		Tyrosinemia	2 (5.7)
		Fibro vascular disease	1 (2.9)
		Progressive intrahepatic cholestasis	1 (2.9)
		Hemangioma	1 (2.9)
		Hypothyroidism	1 (2.9)
		Due to the intestine surgery	1 (2.9)
		Unknown	1 (2.9)
		Other non-biliary disease	1 (2.9)
Sonography findings	Atretic gallbladder N (%)		22 (62.9)
	Presence of fibrotic changes N (%)		11 (31.4)
	Presence of cirrhotic changes N (%)		4 (11.4)
	Hepatic subcapsular flow N (%)		16 (45.7)
	Anterior triangular cord sign N (%)		24 (68.6)
	Superior triangular cord sign N (%)		14 (40.0)
	Central periportal echogenicity N (%)		23 (65.7)
	Diffuse periportal echogenicity N (%)		4 (11.4)
	Biliary dilatation N (%)		8 (22.9)
	Ascites N (%)		5 (11.3)
	Hepatic artery diameter (cm; mean±SD)		1.92±0.44
	Hepatic vein diameter (cm; mean±SD)		3.86±0.6
	The liver span size below the edge of the ribs (cm; mean±SD)		3.38±1.63

N: Number; SD: Standard Deviation

Table-2: Comparison of the demographic and sonographic findings between the two study groups

Variable			Definite diagnosis		p value
			Biliary atresia	Non-biliary atresia	
Demographics	Age (months; mean±SD)		5.12±5.11	2.75±2.11	0.152
	Gender N (%)	male	10 (47.6)	8 (57.1)	0.418
		Female	11 (52.4)	6 (42.9)	
Sonography findings	Gall bladder N (%)	Atretic	15 (71.4)	7 (50.0)	0.177
		Normal	6 (28.6)	7 (50.0)	
	Echogenicity (fibrotic changes) N (%)	Normal	16 (76.2)	10 (71.4)	0.526
		Heterogeneous	5 (23.8)	4 (28.6)	
	Nodularity (cirrhotic changes) N (%)	Yes	2 (9.5)	2 (14.3)	>0.999
		No	19 (90.5)	12 (85.7)	
	Hepatic subcapsular flow N (%)	Yes	15 (71.4)	1 (7.1)	<0.001
		No	6 (28.6)	13 (92.9)	
	Anterior triangular cord sign N (%)	Yes	18 (85.7)	6 (42.9)	0.011
		No	3 (14.3)	8 (57.1)	
	Superior triangular cord sign N (%)	Yes	8 (38.1)	6 (42.9)	>0.999
		No	13 (61.9)	8 (57.1)	
	Central periportal echogenicity N (%)	Yes	15 (71.4)	8 (57.1)	0.477
		No	6 (28.6)	6 (42.9)	
	Diffuse periportal echogenicity N (%)	Yes	2 (9.5)	2 (14.3)	>0.999
		No	19 (90.5)	12 (85.7)	
	Biliary dilatation N (%)	Yes	6 (28.6)	2 (14.3)	0.431
		No	15 (71.4)	12 (85.7)	
	Ascites N (%)	Yes	2 (9.5)	3 (21.4)	0.627
		No	19 (90.5)	11 (78.6)	
	Ultrasound diagnosis N (%)	Atresia	19 (90.5)	7 (50.0)	0.012
		Normal	2 (9.5)	7 (50.0)	
	Hepatic artery diameter (cm; mean±SD)		2.02±0.48	1.77±0.33	0.322
	Hepatic vein diameter (cm; mean±SD)		3.87±0.60	3.85±0.63	0.431
	The liver span size below the edge of the ribs (cm; mean±SD)		3.57±1.66	3.1±1.61	0.849

N: Number; SD: Standard Deviation

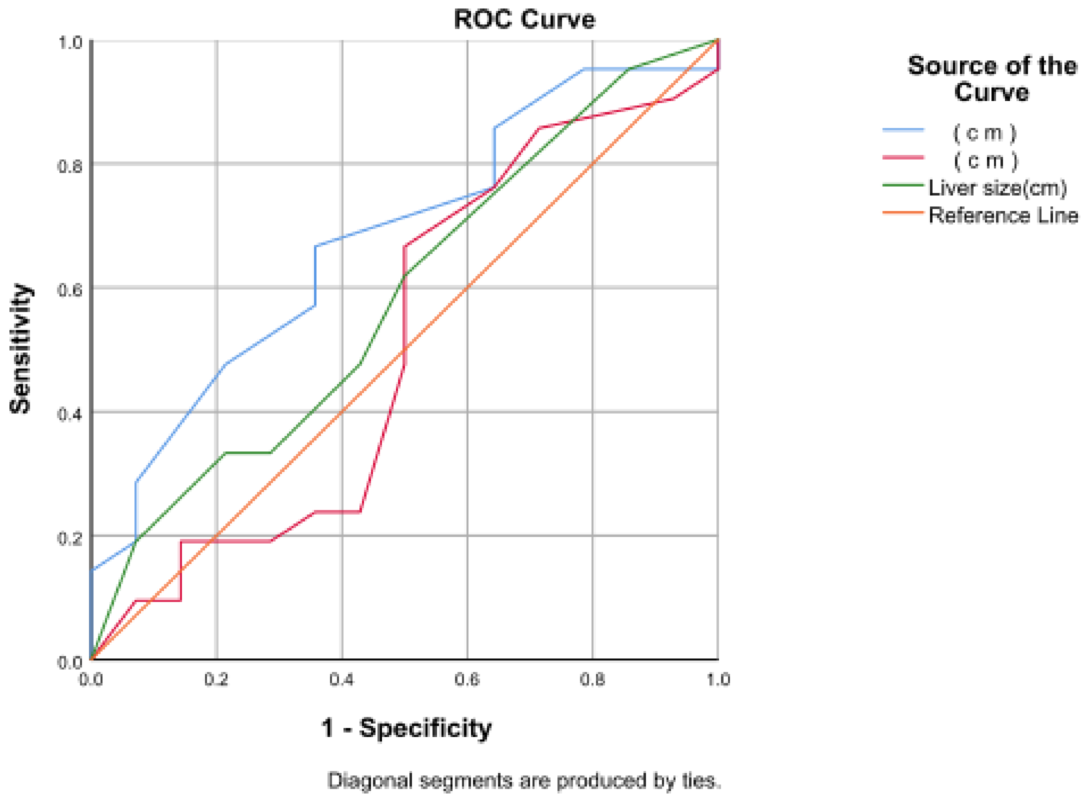

Fig. 1: ROC curve of different sonography findings including livery artery diameter, portal vein diameter, and liver size

Table-3: Sensitivity, specificity, positive predictive value, and negative predictive value for different sonography findings

Sonography features	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Hepatic subcapsular flow	71.42	92.85	93.75	68.42	80.0
Gall bladder presence or absence	71.42	50.0	68.18	53.84	62.85
Anterior triangular cord sign	85.71	57.14	75.0	72.72	74.28
Superior triangular cord sign	38.09	57.14	57.14	38.09	45.71
Central periportal echogenicity	71.42	42.85	65.21	50.0	40.0
Diffuse periportal echogenicity	9.52	85.71	50.0	38.70	40.0
Biliary dilatation	28.57	85.71	75.0	44.44	51.42
Fibrotic changes	28.57	64.28	54.54	37.50	42.85
Cirrhotic changes	23.80	71.42	55.55	38.46	42.85
Ascites	9.52	78.75	40.0	36.66	37.14
Total ultrasound diagnosis	90.47	50.0	73.07	77.77	74.28

PPV: Positive Predictive Value; NPV: Negative Predictive Value

4- DISCUSSION

BA diagnosis and screening, still remained a challenge, worldwide. Some of the proposed modalities are expensive, invasive, or not accessible. Even some of these methods are weird like defining some people to screen the fecal color of neonates to find acholic stool that presents with white color (20, 21). This protocol is used in some Asian countries (22, 23). Among these methods, sonography can fill most of the pre-requisites for a good diagnostic and screening method (24). The reported sensitivity, specificity, PPV, and NPV of sonography in our study were 90.47%, 50.0%, 73.07%, and 77.77%, respectively. Totally, the accuracy of sonography was 74.28%. The optimal sonography finding was hepatic subcapsular flow with a sensitivity of 71.42%, specificity of 92.85%, PPV of 93.75%, and NPV of 68.42%. The accuracy of this finding was 80.0%.

Lee et al. (25) assessed different sonography findings in 100 infants, too. They reported a sensitivity of 100%, specificity of 94.4%, PPV of 93.9%, and NPV of 100% in detecting BA cases in neonates. Their study population was younger than ours and the results were far better. It should be considered that sonography is an operator dependent modality and the difference in results is imaginable. Jancelewicz et al. (26) also assessed sonography in detecting BA. They reported that a combination of different sonography findings has a low sensitivity of 31%, specificity of 99%, and PPV and NPV of 100%. However, due to the absence of enough evidence they did not assess hepatic subcapsular flow and the difference in their results with ours may be due to this.

The most valuable marker in our study seems to be hepatic subcapsular flow. El-Guindi et al. (27) reported that hepatic subcapsular flow had both sensitivity and specificity of 96.3%. Moreover, another similar study reported a sensitivity of 100% and specificity of 86%. Also, the PPV and NPV were 85% and 100%, respectively (19). The results of both studies were far better than our findings; however, the ethnicity and age differences should be considered, too.

Presence or absence of gall bladder had a sensitivity of 71.42% and specificity of 50.0%. Moreover, the PPV and NPV were 93.75% and 68.42%, respectively. The accuracy of this finding was 62.85%. Lee et al. (25) reported the sensitivity, specificity, and accuracy of 84.8%, 94.4%, and 90%, respectively for this marker. However, the mean age of the patients that they assessed was 51 days, which was far lower than that of our patients. The differences in the results of their study and ours may be partly addressed by different ages. They reported that gall bladder abnormalities may be found in other cholestatic conditions other than BA and should be used with caution. Pediatr et al. (28) also assessed gallbladder absence as the marker of BA. The reported sensitivity and specificity were 53% and 94%, respectively. Moreover, the reported PPV was 96% and NPV was 46%. Accuracy of the absent gallbladder was also 66%. Furthermore, it is reported that even 20% of the BA cases may have normal gallbladder (29). Also, amongst the gallbladder abnormalities, lack of contraction after feeding had the highest sensitivity (89%), followed by wall abnormality (83%), absence or length <1.5 cm (79%), and absence of gallbladder (28%) (30).

Although the most valuable marker in our study was hepatic subcapsular flow, anterior triangular cord sign, and Gallbladder presence or absence were precious, too. In fact, it is reported that a combination of triangular cord sign with gallbladder abnormalities has a sensitivity of 95%, which is the greatest among the other findings (30). It is reported that the triangular cord sign is correlated with the absence of gallbladder or a small gallbladder, smaller than 1.5 cm in length, or even abnormal contractility of the gallbladder (16). Jafari et al. (31) assessed the value of triangular cord sign in a population of Iranian BA cases. They reported a specificity of 36%, sensitivity of

95%, and PPV and NPV of 77%. Anterior triangular cord sign also had a sensitivity, specificity, PPV, and NPV of 85.71%, 57.14%, 75.0%, and 72.72%, respectively. Their findings were in line with ours in case of PPV and NPV; however, the sensitivity and specificity differed.

Besides all the above mentioned, our results showed that fibrotic changes, cirrhotic changes, and ascites had a low sensitivity, which were 28.57%, 23.80%, and 9.52%, respectively. However, it is reported that elastography may be helpful in the diagnosis of BA. It is reported that it has a sensitivity of 80.0% and specificity of 97%. Still, this method needs further investigations to find out whether it can detect BA at very early stages or not (32).

Our study assessed different sonography findings in BA patients and this can be considered as a notable strength of our study compared to the others. Moreover, our study was among the few studies conducted on Iranian population (31, 33). However, it is still better to conduct further studies with higher sample sizes. Moreover, it is better to compare sonography with other modalities like HIDA scan and magnetic resonance cholangiopancreatography (MRCP). Yet, previous studies reported that the diagnostic value of sonography is even better than HIDA scan in detecting other differential diagnoses (15). Moreover, the requirement of sedation, preferably general anesthesia, is a significant concern in addition to long image acquisition time for MRCP (34).

5- CONCLUSION

Timely diagnosis of BA helps to reduce the burden of the disease and bring a better prognosis. The condition is rare and application of the screening method is not widely accepted; however, it is used in some Asian countries, in case of monitoring stool color. One easy and valuable method in BA diagnosis seems to be sonography. Different sonography findings have different values. The most valuable markers in our study were hepatic subcapsular flow, anterior triangular cord sign, and Gallbladder presence or absence. However, sonography is an operator-dependent modality and should be investigated in several other studies.

6- ETHICAL CONSIDERATIONS

Written informed consents were obtained from all the parents of the enrolled children. To observe the confidentiality of data, all extracted data were coded anonymously. All the steps of the study were in accordance with Helsinki's declaration. Moreover, the ethics committee of Mashhad University of Medical studies confirmed the study protocol (Code: IR.MUMS.MEDICAL.REC.1399.192).

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