Original Article

Pathological Variables and Laboratory Values in Infants with Neonatal Cholestasis Showing Nonexcretion on Tc-99m Mebrofenin Hepatobiliary Scans: A Descriptive Study

Abstract

Introduction: Cholescintigraphy using Tc-99m Mebrofenin is routinely performed as an initial diagnostic test in infants with neonatal cholestasis suspected of having biliary atresia. Demonstration of drainage of bile into the small intestine indicates patency of the biliary tract and thus rules out biliary atresia. Non-excretion of tracer into the small intestine, however, can be caused by obstructive as well as non-obstructive conditions, and it is known that false-positive findings are found with the use of Tc-99m Mebrofenin scintigraphy. **Aim:** In the present study, we retrospectively calculated the proportion of infants eventually diagnosed to have biliary atresia that were initially ruled to have a non-excreting cholescintigraphy pattern in our institution. We have also attempted a systematic description of the cardinal histological characteristics, haematological and hepatic biochemical variables in infants with non-excreting patterns. **Materials and Methods:** This retrospective, descriptive study was conducted in Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry. We reviewed data from infants who underwent cholescintigraphy with Tc-99m Mebrofenin between January 2016 through June 2022. We included infants in whom the scan was ruled "non-excreting" i.e. those infants in whom biliary atresia could not be ruled out based on the results of the scan. The difference in mean for haematological parameters and ALP were compared between the two groups i.e., biliary atresia versus other than biliary atresia by using Independent student's t-test; the remaining liver biochemical parameters were compared by using Mann-Whitney U Test and a p value < 0.05 was considered to be statistically significant. **Results:** A non-excretory pattern on cholescintigraphy was found to be due to biliary atresia in 49% of cases (as confirmed by exploratory surgery) and an additional 19.6 % of cases by trucut biopsy (total 68.6%). The difference in the mean serum GGT levels was found to be statistically significant (<0.001). **Conclusion:** A non-draining pattern on cholescintigraphy is caused by biliary atresia in the greater percentage of cases presenting with cholestasis. The difference in mean GGT levels was found to be statistically significant between biliary atresia and other causes of non-draining patterns on cholescintigraphy.

Keywords: *Biliary atresia, neonatal cholestasis, Tc-99m mebrofenin*

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Introduction

Neonatal cholestasis is a condition that results from an obstruction to bile flow in newborns, leading to the accumulation of bile components within the liver and bloodstream. It is often characterized by jaundice, pale stools, dark urine, and hepatomegaly. Various etiologies contribute to neonatal cholestasis, including biliary atresia, neonatal hepatitis, choledochal cysts, and metabolic disorders such as alpha-1 antitrypsin deficiency and cystic fibrosis. Prompt investigation is essential for accurate diagnosis, typically involving a battery of laboratory tests such as liver function tests and imaging studies such as ultrasonography. In addition, a liver biopsy may be performed to assess the extent of liver damage and aid in identifying the underlying cause.

Biliary atresia stands out as a severe form of neonatal cholestasis, necessitating specific diagnostic and therapeutic approaches. The primary treatment for biliary atresia is the Kasai procedure, a surgical intervention aimed at restoring bile flow by excising damaged bile ducts and connecting a segment of the small intestine directly to the liver. Despite the intervention, the long-term prognosis remains variable, with some patients necessitating liver transplantation due to disease progression. Timely diagnosis and intervention are critical, as untreated biliary atresia can lead to liver failure and poor outcomes in

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infancy. However, with early surgical management and appropriate follow-up care, outcomes can be significantly improved, offering affected infants a chance at better long-term quality of life.

Cholescintigraphy using Tc-99m mebrofenin is routinely performed as an initial diagnostic test in infants with neonatal cholestasis suspected of having biliary atresia. The utility of these scans lies in the demonstration of drainage or excretion of bile into the small intestine, thereby confirming patency of the biliary tract. In an infant with persistent jaundice beyond the age of 2 weeks, this can be used to rule out biliary atresia with a high degree of accuracy.[1,2] This is a priority early in the course of investigation, as it is well established that a favorable long-term prognosis of biliary atresia depends on prompt surgical intervention.[3,4]

Nonexcretion of the radiotracer into the small intestine can be caused by obstructive as well as nonobstructive conditions.[5] Biliary atresia is eventually confirmed by surgical exploration with or without an intraoperative cholangiogram (IOC), which is considered the gold standard.[6] Nonexcretory Tc-99m mebrofenin scans, along with other clinical, serological, and imaging parameters are taken together while deciding on which infants should be taken up for surgery. Still, there remains a risk of negative laparotomy, which carries with it a significant risk of morbidity and incurs a high cost of therapy to the patient. Therefore, some authors recommend performing a prelaparotomy percutaneous liver biopsy to decrease the frequency of nondiagnostic laparotomy and improve the cost–benefit ratio, especially in developing countries.[7]

False-positive findings are well known with the use of Tc-99m mebrofenin scintigraphy[5] and can occur due to factors such as incomplete fasting before the scan, medications such as opioids causing sphincter of Oddi spasm, liver dysfunction impacting tracer uptake, or technical errors during the procedure. Neonatal cholestasis can be caused by several conditions in infancy presenting with overlapping clinicopathological and biochemical features which may contribute to this. The information gained from a nonexcreting scan can be augmented by performing further studies such as single-photon emission computed tomography (SPECT) imaging and duodenal fluid sampling.[8,9] Another approach is the use of a diagnostic algorithm wherein the serum gamma-glutamyl transferase (GGT) levels are used in combination with nonexcreting scans to reduce the false positivity of individual tests.[1,10] The refinement of such diagnostic processes is guided by the knowledge of factors that influence the scan findings in cholescintigraphy such as hepatic extraction of the radiotracer used, priming with biliary secretagogues such as phenobarbital, low birth weight, parenteral nutrition, conjugated hyperbilirubinemia, and hepatocellular function.[4,11]

The present literature on cholescintigraphy, while extensive, does exhibit some gaps or lacunae that warrant further investigation. One area of concern is the variability in interpretation criteria and protocols across different medical institutions, which can lead to inconsistencies in results and diagnostic accuracy. The impact of technical factors, such as the choice of premedication and imaging protocols, on the diagnostic accuracy of cholescintigraphy, requires further investigation to optimize its utility in clinical practice. Addressing these lacunae in the literature would enhance our understanding of cholescintigraphy's role in the diagnosis and management of hepatobiliary disorders.

Earlier studies have shown that Tc-99m mebrofenin hepatobiliary scintigraphy exhibits nearly 100% sensitivity in detecting biliary atresia with a specificity that has been documented to vary between 88.6% and 92% in different studies.[12] In the present study, we retrospectively calculated the proportion of infants eventually diagnosed to have biliary atresia that were initially ruled to have a nonexcreting cholescintigraphy pattern in our institution. In addition, we have attempted a systematic description of the cardinal histological characteristics, hematological, and hepatic biochemical variables in all the infants with nonexcreting patterns. The histological scoring system devised by Lee and Looi is widely used in our institution and was compared between the two groups along with the presence or absence of seven cardinal histological features that can distinguish between biliary atresia and neonatal hepatitis.[13-15]

This study aimed to explore the causes of nonexcreting patterns on Tc-99m mebrofenin cholescintigraphy in infants with neonatal cholestasis and assess their corresponding histological, hematological, and hepatic biochemical characteristics. The primary objective was to determine the proportion of infants who had initially been diagnosed with a nonexcreting cholescintigraphy pattern in our institution and were subsequently diagnosed with biliary atresia. The secondary objective involved describing the cardinal histological characteristics, hematological parameters, and hepatic biochemical variables among all infants displaying nonexcreting patterns.

Materials and Methods

Patient population

This retrospective, descriptive study was conducted in a Tertiary Referral Hospital and Teaching Centre in South India. We retrospectively reviewed data from infants who underwent cholescintigraphy with Tc-99m mebrofenin between January 2016 and June 2022 using the online health information system. Infants had been diagnosed with neonatal cholestasis and referred to us from the Department of Pediatrics or the Department of Pediatric Surgery. We included infants in whom the scan

was ruled "nonexcreting" defined as nonvisualization of the small bowel till 20 h of the study. We then collected laboratory values within a week of the date of the scan and recorded the diagnostic procedure and biopsy results. We excluded those infants in whom the biopsy reports were either equivocal, unavailable, or uninterpretable (due to inadequacy of specimen or presence of artifacts) and infants in whom bilioenteric continuity was demonstrated on a repeat scan. In addition, infants in whom the histological diagnosis was documented, but the score was not recorded at the time of reporting were excluded from further analysis.

Imaging protocol

All the infants had undergone cholescintigraphy with Tc-99m mebrofenin IDA (2,4,6-trimethyl-5-bromo iminodiacetic acid). In infants suspected of having biliary atresia, priming involves the administration of medications before the radiotracer injection to induce liver enzyme induction, which can improve the excretion of the radiotracer into the biliary system. This priming step helps enhance the sensitivity of the cholescintigraphy in infants with impaired bile flow from the liver. Before the scan, all infants had been primed with either phenobarbital 5 mg/kg body weight/day in two equally divided doses, for 5–7 days or, ursodeoxycholic acid administered at 20 mg/kg/day in 2–3 divided doses for 2–3 days depending on the treating physician's discretion. The administered activity was ~0.05 mCi/kg, with a minimum administered activity of 0.5 mCi. The radiopharmaceutical had been injected intravenously followed by the acquisition of static images of the abdomen in anterior and posterior views at 5, 10, 15, 20, and 30 min, and delayed images had been taken at 1, 2, 4, and 24 h on a 128 × 128 image matrix. The images had been acquired on a Symbia-T6 dual-headed SPECT-computed tomography system and processed on the Symbia. Net workstation. Radiopharmaceutical purity of Tc-99m mebrofenin was recorded as more than 95% in all cases. The presence of tracer in the small intestines at any time was taken as a sign of biliary tract patency. All protocols adhered to the standard guidelines outlined in the SNM practice guideline for hepatobiliary scintigraphy 4.0.[16]

Assessment of histological characteristics and laboratory parameters

Infants, who had nonexcreting scans and in whom the clinical features did not strongly suggest a specific diagnosis other than biliary atresia, were subjected to either an exploratory laparotomy (with or without an IOC followed by Kasai Portoenterostomy and on-table wedge biopsy of the liver) or a Trucut biopsy of the liver. The biopsy reports were reviewed and seven histological criteria were recorded as well as the Lee and Looi score assigned by the reporting pathologist. Seven major histological features were chosen based on high discriminatory values reported by authors in previous studies.[13-15] These included three features considered highly specific for biliary atresia (bile duct proliferation, bile plugin portal ductules, and portoportal bridging) and four features indicative of neonatal hepatitis (lymphocyte infiltration in portal region, multinucleated hepatocytes, neutrophils in the infiltrate, and hepatocyte swelling). Following this, laboratory parameters from within a week of performing the scan were collected.

To accomplish the main goal of the study, we initially calculated the proportion of patients diagnosed with biliary atresia using either IOC, Trucut biopsy, or both methods. Subsequently, we conducted a comprehensive analysis of histological, hematological, and hepatic biochemical parameters for all infants for whom the requisite data were accessible.

Statistical analysis

The variables were classified as categorical and continuous. Categorical variables were expressed as frequency and percentage. Continuous variables with a normal distribution were expressed as mean ± standard deviation, whereas continuous variables with a nonnormal distribution were expressed as median with interquartile range. The independent Student's *t*-test was employed to compare the means of two independent groups on a continuous outcome variable. Mean SUV_{max} values were compared using the Mann–Whitney *U*-test, and $P < 0.05$ was considered to be statistically significant. The cutoff value for GGT was determined by receiver operating characteristic (ROC) analysis. Statistical analysis was performed by an experienced biostatistician using SPSS software (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, version 19.0. Armonk, NY, USA: IBM Corp).

Results

Histopathological features in infants with nonexcreting cholescintigraphy patterns

A total of 51 infants with neonatal cholestasis were included in the study. In all infants, Tc-99m mebrofenin cholescintigraphy revealed nonexcretion of bile into the small intestine [Figure 1]. This was followed by either Trucut biopsy or surgical exploration for confirmation of diagnosis based on ancillary investigations and clinical judgment. A total of 25 patients (49%) were confirmed to have biliary atresia on the basis of IOC, whereas an additional 10 patients (19.6%) were reported as biliary atresia on the basis of Trucut biopsy alone. Therefore, the total number of patients who showed an obstructive pattern on the scan and were eventually diagnosed with biliary atresia was 35 (68.6%). A further 16 infants received a diagnosis of neonatal hepatitis (giant cell type, idiopathic, or other causes).

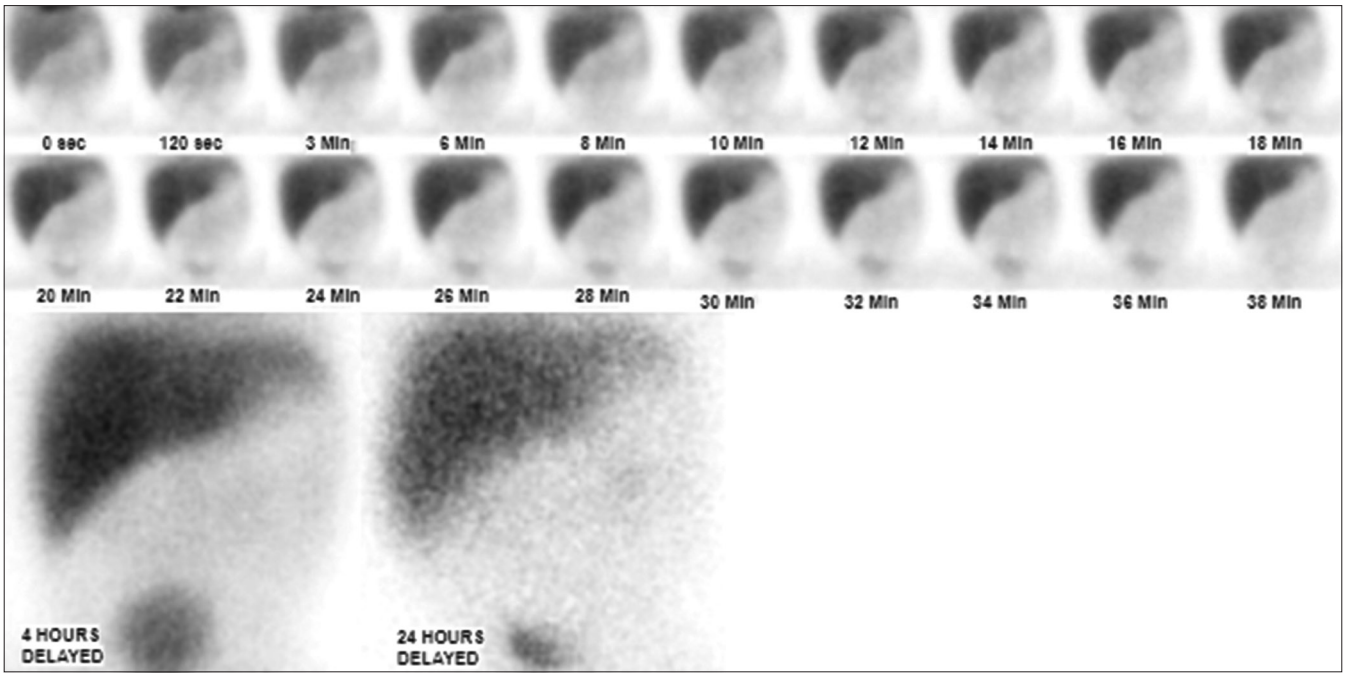

Figure 1: A 2-month-old female child presented with complaints of yellowish discoloration of eyes since birth and passing clay-colored stools. Total bilirubin was 14.5 mg/dL. Direct bilirubin was 2.1 mg/dL. Alkaline phosphatase and gamma-glutamyl transferase levels were 2525 U/L and 709 IU/L, respectively. Ultrasonography revealed the presence of dilated intrahepatic bile ducts. Dynamic images of the abdomen mildly impaired tracer uptake in the liver – suggestive of mildly impaired hepatic tracer extraction (upper and middle rows). Intrahepatic bile ducts, gallbladder, and common bile ducts are not visualized in the dynamic images. Serial static images of the abdomen and pelvis acquired up to 24 h (lowermost row) show persistent retention of tracer in the liver – suggestive of impaired hepatic excretion. Gallbladder and small intestines were not visualized up to 24 h. A final diagnosis of biliary atresia was made on the basis of liver biopsy and intraoperative cholangiography

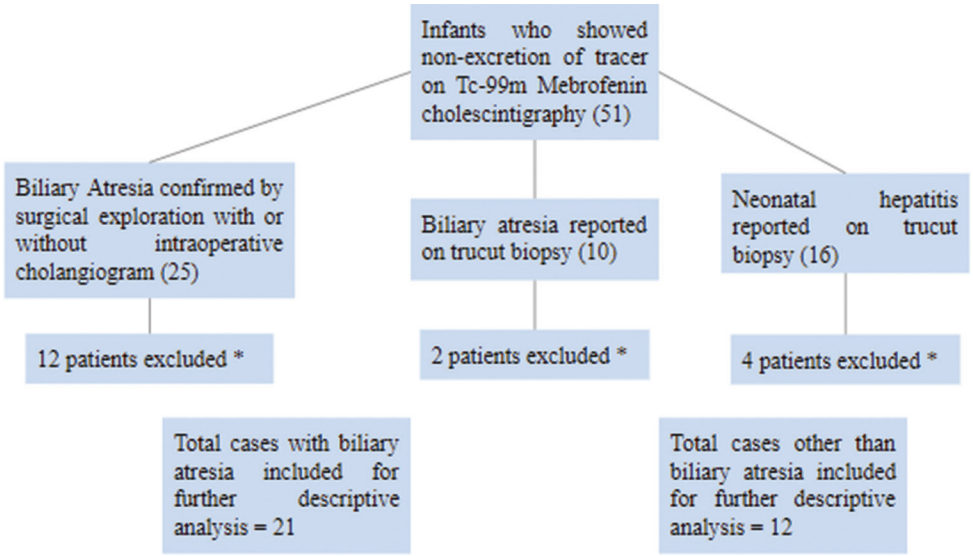

Figure 2: Flowchart of sequential steps in the selection of the study sample. *Due to the nonavailability of laboratory values within a week of performing cholescintigraphy

Of the 51 infants in whom the scan revealed an unequivocally nonexcreting pattern, 33 were included for further descriptive analysis based on the availability of laboratory values within a week of performing the scan. Of these 33 patients, 13 were confirmed as cases of biliary atresia on the basis of IOC and 8 on the basis of Trucut biopsy. The remaining 12 infants were reported as neonatal hepatitis on biopsy [Figure 2]. Each of the seven major histological features was recorded as present or absent in each of the biopsy specimens and the findings were described in frequency and percentage [Table 1]. The most prevalent histopathological characteristics observed in the group with biliary atresia included portal duct proliferation, bile plug formation in portal ductules, and portoportal bridging. In the remaining infants, the most commonly encountered histopathological

characteristics were hepatocellular swelling and multinucleated hepatocytes. Lee and Looi score, as reported by the pathologist, was included separately as a continuous variable, and descriptive statistics were given [Table 2].

Laboratory parameters in infants with nonexcreting cholescintigraphy patterns

The laboratory values analyzed include four hematological variables (hemoglobin, white cell count, percentage of neutrophils, and percentage of lymphocytes) and liver biochemical profile including seven variables [Table 3]. The difference in mean for hematological parameters and alkaline phosphatase (ALP) were compared between the two groups, i.e., biliary atresia versus other than biliary atresia using independent Student's *t*-test; the remaining liver biochemical parameters were compared using the Mann–Whitney *U*-test.

The difference in the mean serum GGT levels between the two groups was found to be statistically significant. ROC analysis identified a GGT level >145 IU/L as the optimal cutoff, exhibiting a sensitivity of 88.7% and a specificity of 77.2% for distinguishing between biliary atresia and neonatal cholestasis of other etiologies [Figure 3]. A substantially elevated cutoff threshold for GGT at 505 IU/L resulted in a specificity of 96.3%, albeit with a concomitant reduction in sensitivity to 49%.

Table 1: Frequency table of histopathological features recorded from infants with nonexcreting cholescintigraphy patterns (total number=33)

Histological feature	Frequency (%)	
	Biliary atresia (*n*=21)	Others (*n*=12)
Portal duct proliferation	21 (100)	4 (33.3)
Bile plug-in portal ductules	16 (76.1)	1 (8.3)
Portoportal bridging	20 (95.2)	7 (58.3)
Lymphocytic infiltrate in the portal region	11 (52.3)	7 (58.3)
Multinucleated hepatocytes	3 (14.2)	9 (75)
Neutrophils in the infiltrate	10 (47.6)	3 (25)
Hepatocellular swelling	10 (47.6)	12 (100)

Table 2: Lee and Looi scores between infants diagnosed with biliary atresia and other than biliary atresia

	Patient group	Mean±SD
Lee and Looi score	Biliary atresia (*n*=21)	9.05±1.85
	Other than biliary atresia (*n*=12)	2.92±1.44

SD: Standard deviation

Discussion

In our study, a nonexcretory pattern on cholescintigraphy was found to be due to biliary atresia in 49% of cases (as confirmed by exploratory surgery) and an additional 19.6% of cases by Trucut biopsy (total 68.6%). This is

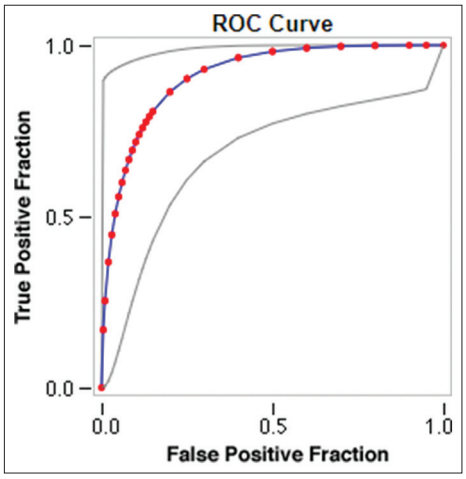

Figure 3: Receiver operating characteristic curve of gamma-glutamyl transferase values as a discriminator for biliary atresia. The area under fitted curve = 0.9116. ROC: Receiver operating characteristic

Table 3: Comparison of laboratory parameters between infants diagnosed with biliary atresia and other than biliary atresia

Laboratory parameter (units)	Mean±SD/median (Q_1–Q_3)		*P*
	Biliary atresia (*n*=21)	Other than biliary atresia (*n*=12)	
Hemoglobin (g/ld.)	8.69±2.47	10.05±2.30	0.134
WBC (×10³/mm³)	16.62±6.37	15.44±10.26	0.725
Neutrophils (%)	43.38±19.27	38.14±13.91	0.388
Lymphocytes (%)	47.39±16.98	48.90±12.81	0.780
ALP (IU/L)	1165.71±619.91	1433.42±921.85	0.383
Total bilirubin (mg/ld.)	10.83 (8.10–14.78)	11.51 (7.27–16.05)	0.940
Direct bilirubin (mg/ld.)	3.17 (2.00–4.82)	2.45 (1.84–4.48)	0.549
Serum albumin (g/ld.)	3.40 (3.25–3.62)	3.15 (3.00–3.40)	0.163
AST (IU/L)	213.00 (164.00–374.00)	387.00 (190.75–620.00)	0.125
ALT (IU/L)	111.00 (92.00–193.00)	135.50 (84.75–296.75)	0.736
GGT (IU/L)	505.00 (210.00–884.50)	68.00 (46.75–94.25)	<0.001

WBC: White blood cell, ALP: Alkaline phosphatase, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: Gamma-glutamyl transferase, SD: Standard deviation

similar to findings by Shah *et al*., i.e., 22/29 or 75.8% of patients with nonexcretory scans were found to have biliary atresia.[12] Other studies have confirmed the high sensitivity and low specificity of cholescintigraphy for this indication. Johnson *et al*. found a sensitivity, specificity, and accuracy of 100%, 67%, and 72%, respectively, whereas Jensen *et al*. found a sensitivity, specificity, and area under the curve of 95%, 57%, and 0.60%, respectively.[17,18]

In addition, we undertook an analysis of commonly performed hematological and hepatic biochemical tests. The difference in the mean serum GGT levels between the two groups was found to be statistically significant. In this study, the cutoff value for GGT levels as determined by ROC analysis was 145 IU/L, which closely mirrors the cutoff reported by Arora *et al*. in their study, which is 150 IU/L with a sensitivity of 100%.[10] However, a cutoff value of >145 IU/L did not exclude all cases with neonatal hepatitis as we found two patients diagnosed with neonatal hepatitis who had serum GGT values in excess of 300 IU/L. Mean serum ALP levels were higher in the neonatal hepatitis cases, but this association was not statistically significant. Hematological and other hepatic biochemical variables were comparable in the two groups.

The factors that impede hepatobiliary drainage in neonatal hepatitis are of considerable importance in the interpretation of these scans. Acholic stools and elevated GGT are two such indicators of a high likelihood of biliary atresia.[10] False positives can be further reduced by repeat scanning in patients with high clinical suspicion of neonatal hepatitis.[19]

In our study, we analyzed histological characteristics in patients with nondraining scans and found that while the frequency of most of them varied widely between the two patient groups, i.e., biliary atresia and neonatal hepatitis, the frequencies of portal infiltration by lymphocytes were similar in both (52.3% vs. 58.3%).

Our study was limited by a rather small sample size. Clinical data and detailed information about individual patients' priming with choleretics could not be assessed. The gold standard test, i.e., surgical exploration with or without IOC was not performed in every case diagnosed with biliary atresia. However, liver biopsy is the most accurate method of differentiating between biliary atresia and neonatal hepatitis.[20,21] As an inherent issue with the retrospective nature of our study, all histopathology specimens and scans were interpreted without blinding to clinical information.

Conclusion

A nondraining pattern on cholescintigraphy is caused by biliary atresia in the greater percentage of cases presenting with cholestasis. However, taken alone, it is not sufficient to justify surgical exploration. A drainage pattern observed on cholescintigraphy constitutes a straightforward and noninvasive examination essential for ruling out biliary atresia. This diagnostic modality effectively circumvents the necessity for invasive procedures. Nonetheless, the presence of a nondrainage pattern necessitates further investigation to exclude alternative etiologies, particularly in cases presenting with low levels of GGT. Other factors that lead to false-positive studies must be explored, and further studies are required in this direction.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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