

## Biopsy-driven diagnosis in infants with cholestatic jaundice in Iran

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### Abstract

**AIM:** To determine the frequencies of diagnoses confirmed by liver biopsy in infants with cholestasis in an Iranian pediatric hospital.

**METHODS:** This was a retrospective study conducted in a tertiary referral children's hospital in Iran. We retrieved all pathology reports of liver biopsies from children less than two years of age who had presented for evaluation of cholestatic jaundice from March 2001 to March 2011. Additional specimen samples obtained from archived pathology blocks were reviewed by a pathologist blinded to the final diagnosis. These results were compared with the pathology reports from chart records to ensure consensus and eliminate any inconsistencies in final diagnoses. A structured checklist was used to gather information on multiple variables including age, sex, gestational age at birth, birth weight, age

at which hyperbilirubinemia manifested, presence and identification of associated anomalies, clinical manifestations, and histological findings from liver biopsies. The baseline data are reported using descriptive statistics, and differences between groups were assessed by Fisher's exact test and Student's *t* test when indicated.

**RESULTS:** Fifty-five cases (28 females; 27 males) of infantile cholestasis (IC) were included in this study. The mean serum total bilirubin and direct bilirubin at presentation were  $13.6 \pm 5.9$  and  $7.3 \pm 3.4$ , respectively. Forty cases (72.7%) were the product of term pregnancies. Common associated clinical findings were acholic stool in 33 cases (60.0%), hepatomegaly in 30 cases (54.5%), and dark-colored urine in 21 cases (38.2%). Biliary atresia (BA) was the most frequent diagnosis, found in 32 cases (58.2%), followed by intrahepatic bile duct paucity found in 6 cases (10.9%), metabolic disease in 6 cases (10.9%), idiopathic neonatal hepatitis in 5 cases (9.1%), choledochal cyst in 2 cases (3.6%), liver cirrhosis in 2 cases (3.6%), and progressive familial intrahepatic cholestasis and portal fibrosis each in 1 case (1.8%). The mean times for jaundice onset and liver biopsy were 43.8 and 102.0 d, respectively. In BA, the mean age at jaundice presentation was 21 d and for liver biopsy was 87.5 d, representing a mean delay of 66.5 d.

**CONCLUSION:** A significant delay was found between IC presentation and liver biopsy, which is detrimental in conditions that can cause irreversible liver damage, such as BA.

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**Key words:** Cholestasis; Neonate; Hepatitis; Biliary atresia; Neonatal hepatitis; Infant; Conjugated hyperbilirubinemia; Liver biopsy

**Core tip:** Infantile cholestasis is a heterogeneous disorder

der characterized by abnormal direct hyperbilirubinemia after the second week of life. While biliary atresia (BA), progressive familial intrahepatic cholestasis, and idiopathic neonatal hepatitis are among the most prevalent causes, BA specifically needs early surgical intervention to avoid cirrhosis. This makes liver biopsy a crucial procedure for timely surgical consideration. We found that there was a significant delay from the time that jaundice was noted to the time of liver biopsy in those eventually diagnosed with BA. These results demonstrate that an early diagnostic approach is prudent to avoid irreversible hepatic complications.

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## INTRODUCTION

Jaundice, also known as icterus, is a common heterogeneous condition in neonates that usually resolves by the end of the second week after birth<sup>[1]</sup>. Icterus lasting beyond 2 wk of life, and especially if it is of the conjugated type, is perceived as clinically significant<sup>[2,3]</sup>. Conjugated serum bilirubin is considered abnormal if measured more than 1 mg/dL when total bilirubin is less than 5 mg/dL, or more than 20% of the total bilirubin in cases of more severe hyperbilirubinemia<sup>[3-5]</sup>.

Cholestasis caused by diminished canalicular bile flow is clinically characterized by persistent conjugated hyperbilirubinemia<sup>[5]</sup>. Anatomical approaches to diagnosing cholestatic jaundice, which categorize the causes as either intrahepatic or extrahepatic, can be useful in the clinical setting, however not all conditions, including biliary atresia (BA), fit into a single category. Therefore, a more plausible classification separates the causes into functional and structural types. Using this strategy, functional derangements include metabolic, infectious, toxic, hemodynamic and idiopathic insults and structural abnormalities encompass biliary atresia, choledochal cysts and bile duct strictures<sup>[6]</sup>.

BA usually presents in the first few weeks of life<sup>[7]</sup>. Progressive familial intrahepatic cholestasis (PFIC) begins in infancy with a mean age for jaundice onset of about 3 mo, although some patients do not develop jaundice until much later, even into adolescence<sup>[6]</sup>. The common causes of infantile cholestasis vary with age of onset, with the relative frequency of any individual diagnosis shifting when moving from a neonatal to a late infancy period<sup>[5,6]</sup>.

When evaluating infants with conjugated hyperbilirubinemia, liver biopsy is the most reliable and definitive procedure<sup>[4,5]</sup>. Liver histopathology provides important clues to the correct diagnosis with a diagnostic yield as high as 95%<sup>[5,6,8]</sup>. Specimens displaying a proliferation of bile ducts, biliary plugs, portal tract edema and fibrosis

suggest BA, while derangement in lobular architecture and ballooning of hepatocytes in association with focal hepatic necrosis along with the presence of multinucleated giant cells is highly indicative of neonatal hepatitis<sup>[6,9,10]</sup>. In practice, the main purpose for liver biopsies in infants with cholestasis is to define whether biliary obstruction is present or not. Furthermore, a liver biopsy can help with the determination of the severity of hepatocellular injury and assessment of the prognosis<sup>[6,8]</sup>.

The literature suggests that since 1970, there has been a shift from identifying idiopathic neonate hepatitis (INH) as the most common cause of cholestasis to more clearly defined disorders such as PFIC and bile acid synthetic defects<sup>[6]</sup>. Unfortunately, there is a paucity of data on the prevalence of diverse etiologies of cholestasis in non-western countries, especially in the middle east area<sup>[11-13]</sup>. This study was conducted to determine the frequency of different diagnoses confirmed by liver biopsy in infants with cholestasis admitted to a pediatric hospital in Iran.

## MATERIALS AND METHODS

In this retrospective study, we retrieved all pathology reports on liver specimens from children of less than two years age who were admitted to the Ali-Asghar Children's Hospital between March 2001 and March 2011. The corresponding hospital files were reviewed and those with cholestatic jaundice identified. A structured checklist was used to gather information on: age, sex, gestational age at birth, birth weight, age at which hyperbilirubinemia manifested, presence of associated anomalies, clinical manifestations, and histological findings from liver biopsies. The final diagnoses were obtained from hospital files. Original pathology reports were compared with the study pathologist's interpretation and both were correlated with a final diagnosis to avoid inconsistencies. SPSS version 18 statistical software was used to analyze the data. Descriptive statistics were employed to report frequencies and means  $\pm$  SD. To show differences between groups we used a Fisher's exact test and Student's *t* test as indicated; *P* < 0.05 was considered significant.

## RESULTS

In total, 55 infants with cholestatic jaundice and available biopsy reports were entered into the study. Twenty-eight (51%) were female and 27 (49%) were male. Although the mean time for the onset of jaundice was 43.8 d, the mean time for taking liver biopsy was 102 d after birth, representing a notable delay in attempting to perform diagnostic liver biopsy. The baseline clinical and laboratory characteristics can be found in Table 1.

Liver biopsies from 32 infants had firm histopathological evidence of BA, making it the most common cause of cholestasis, with no significant sex difference (*P* = 0.45). Twenty-four (75%) of these BA cases were in infants from term pregnancies with normal birth weights. The next most frequent diagnoses were paucity of bile ducts, metabolic disorders, and INH (Table 2). The pau-

**Table 1 Clinical and laboratory characteristics of the 55 infants with cholestasis included for analysis of biopsy diagnosis**

Variable	Mean $\pm$ SD	Range
Gestational age (wk)	38.4 $\pm$ 2.7	31-41
Birth weight (g)	2785 $\pm$ 658	1300-3980
Age when jaundice came to clinical attention (d)	43.8 $\pm$ 93	1-630
Age at liver biopsy (d)	102 $\pm$ 110	8-690
Total bilirubin (mg/dL)	13.6 $\pm$ 5.9	3.9-36
Direct bilirubin (mg/dL)	7.3 $\pm$ 3.4	2.4-19
Alkaline phosphatase (IU/L)	1244 $\pm$ 800	9.5-3379
AST (IU/L)	280 $\pm$ 223	36-1009
ALT (IU/L)	238 $\pm$ 486	16-3510
GGT (IU/L)	412 $\pm$ 508	35-1981
PT (s)	14.6 $\pm$ 4.5	11-38
PTT (s)	39.2 $\pm$ 10	26-82
Albumin (g/dL)	3.5 $\pm$ 0.9	1.3-5.4
Hgb (g/dL)	10 $\pm$ 1.9	6.9-16.4
Platelet $\times 10^3/\mu\text{L}$	381 $\pm$ 164	76-700

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; Hgb: Hemoglobin; PT: Prothrombin time; PTT: Partial thromboplastin time.

city of bile ducts was an isolated finding in five of the six observed cases, however one male had Alagille's syndrome, characterized by a ventricular septal defect, hypertelorism, a prominent forehead and cholestatic jaundice. Six cases were affected by metabolic disease, comprised of five cases with glycogen storage disease and one case with galactosemia. Another frequent cause of conjugated hyperbilirubinemia in our series was INH, affecting 5 infants (9%). Three of these were premature with a birth weight of less than 2500 g.

Frequencies for a set of selected variables for individual diagnoses (including sex, birth weight, perinatal findings, clinical findings and jaundice course) are shown in Table 3. Jaundice was invariably present and acholic stool, hepatomegaly and dark-colored urine were all common. Reported in Table 4 are the frequencies of some laboratory findings including hemoglobin, platelet and liver function tests for different disease entities. The highest levels of hyperbilirubinemia were detected in PFIC with a mean value of 28 mg/dL followed by BA with a mean of 14.4. Alkaline phosphatase levels were elevated in all diagnostic categories without statistically significant differences between the subgroups. Levels of gamma-glutamyl transpeptidase, however, were significantly higher in cases with BA (Fisher's exact test,  $P < 0.05$ ). Coagulopathy was seen in several subgroups, but the lone abnormal coagulation test with a significant prediction for a specific group was the partial thromboplastin time (PTT), which was abnormal in those proved to have cirrhosis by liver biopsy (Fisher's exact test,  $P < 0.05$ ).

## DISCUSSION

The results of this study show that BA was the most common cause of cholestasis, identified in 58% of the liver biopsies examined. BA is the most common cause

of prolonged cholestatic jaundice in neonates and accounts for 40%-50% of all pediatric liver transplants<sup>[4,6,7]</sup>. The majority of infants diagnosed with BA in our study had normal birth weights from term pregnancies, in agreement with results from Mowat *et al.*<sup>[14]</sup>, showing that only one infant out of 32 had been born prematurely. A tendency for female preponderance was noted a tendency for female preponderance was noted (Table 3). All cases displayed jaundice, with common occurrences of acholic stool, hepatomegaly and dark colored urine, consistent with previous reports in the literature<sup>[4,13-15]</sup>. While congenital malformations have been reported in one-third of BA cases<sup>[16,17]</sup>, only 13% of the infants included in this study had congenital anomalies.

INH is a differential diagnosis for BA, as both conditions are characterized by conjugated hyperbilirubinemia presented early after birth and are associated with hepatomegaly. In this study, five cases of INH were identified, all of which displayed hepatomegaly, which is often a presenting feature of liver disease. Three of the infants diagnosed with INH were premature and of low birth weight, two features that are frequently reported in INH<sup>[4,14]</sup>. Interestingly, two infants had acholic stools. Although acholic stool is a cardinal feature of biliary obstruction, it may also occur as a result of severe bile secretory failure at the level of the hepatocyte<sup>[14]</sup>. Thus, liver biopsy is required for accurate diagnosis in most cases<sup>[4,7,8,18-20]</sup>.

While BA and INH cannot be distinguished based on clinical features, such as hepatomegaly, splenomegaly, coagulopathy or acholic stool<sup>[7,14,19]</sup>, they can differ with regard to their course, prognosis and management<sup>[4,18]</sup>. While INH has a variable and sometimes a self-limiting course<sup>[17,18]</sup>, BA is a relentlessly progressive disease requiring surgical intervention and/or liver transplantation<sup>[4,16,21]</sup>. In our case series, all of the five INH cases had progressive jaundice before liver biopsy. However, our selected population was confined to those who underwent liver biopsy, therefore we assume a selection bias which could have caused overrepresentation of a subgroup of INH cases whose cholestasis progressed such that a biopsy procedure was attempted. Noteworthy, there was a mean time lapse of 66.5 d in BA and 55 d in INH from the time jaundice first came to clinical attention to the time that diagnostic liver biopsy was performed, in comparison to a previous study reporting a mean delay of 120.8 d in BA and 65.9 d in INH<sup>[22]</sup>.

Since unmanaged biliary atresia may result in cirrhosis within a few weeks, a prompt and accurate diagnosis is of outmost importance<sup>[23]</sup>. Therefore, neonatal cholestasis beyond the second week of life should be considered as a serious condition that needs urgent investigation and possible liver biopsy<sup>[5,24,25]</sup>. Causes for delayed intervention, as identified in a study by Mieli-Vergani *et al.*<sup>[26]</sup>, include a lack for follow-up of neonatal jaundice, inadequate investigation of hemorrhagic disease, misdiagnosis of breast milk jaundice, pigmented stools and decreased serum bilirubin. For many cases, delayed recognition and referral for specialty care remain major barriers to timely

**Table 2** Diagnoses from liver biopsies and their frequencies in cases of infantile cholestasis *n* (%)

Biopsy findings	Frequency	Mean gestational age in weeks	Mean birth weight in grams	Mean age when jaundice came to clinical attention (range)	Mean age at liver biopsy in days
BA	32 (58)	38.4	2850	21 (1-120)	87.5
Paucity of bile ducts	6 (11)	39.0	2600	20.5 (1-60)	59
Metabolic disease	6 (11)	39.4	3380	221 (44-630)	266
INH	5 (9)	36.4	2230	38 (3-90)	93
Choledochal cyst	2 (3.6)	40.0	2750	20 (15-26)	82
Liver cirrhosis	2 (3.6)	38.5	1950	10 (9-13)	34
PFIC	1 (1.8)	40.0	3300	135	165
Portal fibrosis	1 (1.8)	34.0	1400	30	45

BA: Biliary atresia; INH: Idiopathic neonatal hepatitis; PFIC: Progressive familial intrahepatic cholestasis.

**Table 3** Frequencies of selected variables for each diagnosed cause of infantile cholestasis *n* (%)

Variable	Frequency	BA	INH	Paucity of bile ducts	Choledochal cyst	Metabolic disease	Cirrhosis	PFIC and portal fibrosis
Sex	Female	28 (50.9)	20	3	1	2	0	1
	Male	27 (49.1)	12	2	5	4	2	1
Maturity	Preterm	15 (27.3)	8	3	1	0	1	1
	Term	40 (72.7)	24	2	5	5	1	1
Birth weight	Low	15 (27.3)	7	3	1	0	2	1
	Normal	40 (72.7)	25	2	5	6	0	1
Perinatal findings	Bacterial infection	5 (9.0)	3	0	0	1	0	1
	Congenital anomalies	10 (18.0)	4	1	1	0	2	0
	Parenteral nutrition	1 (2.0)	0	0	0	0	1	0
	Seizure	3 (5.5)	3	0	0	0	0	0
	Meconium stained amniotic fluid	4 (7.2)	2	0	2	0	0	0
	Fetomaternal hemorrhage	1 (2.0)	1	0	0	0	0	0
	Apnea	1 (2.0)	1	0	0	0	0	0
	Others	13 (23.0)	7	1	2	0	2	0
	Nil	31 (56.0)	18	4	3	5	0	1
Clinical findings	Dark urine	21 (38.0)	13	3	4	0	0	0
	Acholic stool	33 (60.0)	22	2	4	2	3	0
	Hepatomegaly	30 (54.5)	19	5	1	0	4	0
	Splenomegaly	17 (31.0)	12	2	0	0	2	0
	Clubbing	1 (2.0)	0	0	0	0	1	0
	Failure to thrive	14 (25.5)	9	1	1	0	2	1
	Ascites	8 (14.5)	4	1	1	0	1	0
	Jaundice	55 (100)	32	5	6	2	6	2
	Pruritus	3 (5.5)	1	0	0	0	1	0
Jaundice temporal course	Progressive	33 (60.0)	17	5	2	2	4	1
	Intermittent	4 (7.2)	3	0	1	0	0	0
	Continuous	6 (10.9)	3	0	1	0	1	0

BA: Biliary atresia; INH: Idiopathic neonatal hepatitis; PFIC: Progressive familial intrahepatic cholestasis.

surgical intervention<sup>[7,22]</sup>, adversely affecting nutritional support, control of complications such as ascites, and cost. Accordingly, it has been recommended that infants presenting with acholic stools should be referred to a pediatric gastroenterologist for urgent evaluation to rule out BA<sup>[2,27,28]</sup>. Attempts to restore biliary flow, such as with the Kasai procedure, should be performed in BA cases before two months of age<sup>[7,29,30]</sup> in experienced centers to increase the chance for a successful surgery<sup>[8,31,32]</sup>.

Coagulopathy, measured by prothrombin time (PT) and PTT, is a serious complication that may be present in infantile cholestasis<sup>[4,6,33]</sup>. Obstructed biliary flow may cause fat malabsorption, resulting in a deficiency in vitamin K, a fat soluble vitamin. If the symptomatic prolongation of the PT and PTT remains uncorrected after

vitamin K administration, this may indicate a hepatocellular injury that is secondary to biliary obstruction, as occurs in patients with prolonged jaundice<sup>[25]</sup>, rather than a vitamin K deficiency. In the current study, we found abnormal PTT was significantly more common in those diagnosed with cirrhosis after a liver biopsy.

There are a number of limitations in extrapolating the results of this study. Our case series is composed of a highly selective group of infants with progressive cholestasis who underwent liver biopsies at the Ali-Asghar Children's Hospital. As a result, an undefined number of cases with a self-limiting course or diagnosed by other investigations have not been included in this study, thereby underrepresented the frequency of benign cases. The results of this study are most relevant for cases of progres-



**Table 4 Mean laboratory findings from each diagnosed cause of infantile cholestasis**

Cause	Total bilirubin in mg/dL	Direct bilirubin in mg/dL	ALP in IU/L	AST in IU/L	ALT in IU/L	GGT in IU/L	PT in sec	PTT in sec	Hgb in g/dL	Platelet × 10 <sup>3</sup> /μL
BA	14.4	8.0	1230	313	310	597 <sup>a</sup>	14.0	38	9.7	390
INH	10.5	6.0	1343	287	113	-	16.0	44	10.0	406
Paucity of bile ducts	11.5	6.5	1475	223	250	310	18.0	37	11.0	410
PFIC	28.0	13.0	1455	65	57	44	12.0	39	9.5	700
Choledochal cyst	11.5	5.2	1667	212	170	-	13.0	33	8.5	300
Metabolic disease	13.8	6.7	843	205	114	66	13.0	34	9.5	355
Cirrhosis	11.6	5.3	1710	226	45	-	16.0	76 <sup>a</sup>	12.0	200
Portal fibrosis	8.0	5.1	453	380	120	-	13.5	39	10.0	187

<sup>a</sup>P < 0.05. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; Hgb: Hemoglobin; PT: Prothrombin time; PTT: Partial thromboplastin time.

sive conjugated hyperbilirubinemia that are candidates for liver biopsy. Two counterpart studies that mainly recruited cases from clinical diagnosis rather than liver biopsies, found INH, not BA, to be the most common cause of infantile cholestasis<sup>[12,13]</sup>. While some familial INH cases may represent unrecognized underlying inborn errors, specifically defects in synthesis or transport of bile acids, the sporadic INH is usually transient and has a rather favorable outcome<sup>[14,34-36]</sup>, which is in stark contrast to the serious complications caused by BA.

In summary, we found that BA was the most common cause of infantile cholestasis as determined by liver biopsies. Additionally, there was a significant delay from the recognition of jaundice to the time of liver biopsy, averaging approximately two months. Considering the rapid progression of BA to cirrhosis along with the potentially curative role of early surgical intervention, an emphasis should be placed on obtaining prompt diagnostic testing in all infants presenting with conjugated hyperbilirubinemia that lasts beyond the first two weeks of life.

## COMMENTS

### Background

The prevalence of individual causes of infantile cholestasis (IC) has changed in recent decades, shifting from idiopathic neonate hepatitis as the most common cause, to more clearly defined disorders such as progressive familial intrahepatic cholestasis and bile acid synthetic defects. However, biliary atresia (BA) remains an important contributor to IC.

### Research frontiers

There is very little data on the causes of prolonged cholestatic jaundice during infancy in developing countries. The data that are available are mainly derived from clinical findings that are not necessarily pathologically based. A known cause of IC is BA, a condition requiring surgical intervention to avoid permanent liver damage. Therefore, it is crucial to identify when a liver biopsy is needed for a timely diagnosis to occur.

### Innovations and breakthroughs

This study examined the diagnoses of a selected population of IC patients who underwent liver biopsies. The frequencies of final diagnoses, as based on histopathology, and their time courses were evaluated. The results reveal that BA is in fact the most frequent diagnosis made from biopsied cases, with an unfavorable delay of 87.5 d after birth, on average.

### Applications

The frequency data reported in this study provide a framework for physicians to reference regarding the timely diagnosis for infants with progressive conjugated hyperbilirubinemia. This study also highlights the need to consider early liver biopsies in cases of IC to avoid irreversible hepatic damage from causative

conditions that are frequently diagnosed.

### Terminology

Infantile cholestasis is a liver condition in neonatal infants describing direct hyperbilirubinemia that persists or appears after 14 d of life. Direct hyperbilirubinemia refers to conjugated serum bilirubin of more than 1 mg/dL when the total bilirubin is less than 5 mg/dL or if conjugated bilirubin accounts for greater than 20% of total serum bilirubin in cases of more severe hyperbilirubinemia. Biliary atresia is a potentially life-threatening blockage of bile ducts that occurs in infants.

### Peer review

The authors examined the frequencies of diagnoses made from liver biopsies of infantile cases of cholestasis. The analysis shows that a very serious and potentially life-threatening condition is the most common cause of pediatric liver disease in the population examined. This identification suggests that liver biopsies should be more routinely considered in cases of IC, as early intervention is crucial for successful recovery. The authors document a significant delay between the appearance of conjugated jaundice in pediatric patients and the liver biopsy, which is required for an accurate diagnosis. Therefore, it is recommended that neonatologists and pediatricians conduct prompt diagnostic work-ups in all infants presenting with conjugated jaundice beyond the second week of life.

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