Pediatr Pol 2023; 98 (4): 300-306
DOI: https://doi.org/10.5114/polp.2023.133533
Submitted: 11.06.2023, Accepted: 26.08.2023, Published: 11.12.2023

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

ORIGINAL PAPER

Neonatal cholestasis in Jordanian children: a single-center experience

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ABSTRACT

Introduction: Neonatal cholestasis refers to conjugated hyperbilirubinemia that either presents at birth or develops within the first three months of life. The causes of neonatal cholestasis are extensive and can be classified based on the anatomical location of the pathology into extrahepatic and intrahepatic causes This study aimed to assess the frequency and underlying etiologies of neonatal cholestasis in a tertiary care center in Jordan.
Material and methods: We retrospectively reviewed the medical records of infants diagnosed with neonatal cholestasis during the study period. Demographic data, clinical presentations, laboratory results, imaging studies, and liver biopsies were collected and analyzed. Data were presented as percentages and averages.
Results: Of the 47 patients diagnosed with neonatal cholestasis, 55.3% were male, and the average age at presentation was 16.7 days. Jaundice was the most common clinical feature (100%), followed by clay-colored stools and dark urine (29.7%). Notably, 12.8% of patients had skeletal abnormalities. At presentation, the average total and direct bilirubin levels were 14.3 mg/dl (± SD 7.3 mg/dl) and 10.1 mg/dl (± SD 6.5 mg/dl), respectively. Abnormal liver ultrasound findings were observed in 8 patients (17%). In our cohort, metabolic and genetic disorders were the most common underlying causes of neonatal cholestasis, followed by extrahepatic anatomical biliary disorders.
Conclusions: Causes of neonatal cholestasis vary depending on the population. Metabolic and genetic disorders were the leading causes of death in our cohort. Hence, genetic testing may help reduce costs and fruitless investigations in affected infants.

KEY WORDS:
cholestasis, neonates, metabolic disorders, genetic disorders.

INTRODUCTION

Cholestasis is characterized by the accumulation of substances that are normally excreted in bile into the blood and extrahepatic tissues. Although cholestasis is not always accompanied by conjugated hyperbilirubinemia (the abnormal retention of bilirubin), serum conjugated bilirubin is the most clinically useful marker of cholestasis due to its low cost and wide availability for testing [1, 2].

Neonatal cholestasis refers to conjugated hyperbilirubinemia that either presents at birth or develops within the first three months of life. Conjugated hyperbilirubinemia is defined as conjugated bilirubin greater than 20% of the total serum bilirubin with a minimum level of 1 mg/dl [3, 4].

The causes of neonatal cholestasis are extensive and can be classified based on the anatomical location of the pathology into extrahepatic and intrahepatic causes [5]. Extrahepatic causes include biliary atresia and cho-

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ledochal cysts, while common intrahepatic causes include idiopathic neonatal hepatitis [6, 7], genetic/metabolic disorders, infections, parenteral nutrition (PN)-associated liver disease, and a range of generally rare disorders [4]. In the Middle East, the incidence of neonatal cholestasis is approximately 1 in 2500 live births, with biliary atresia and idiopathic neonatal hepatitis being the most common causes, along with rare cases of alpha-1 antitrypsin deficiency [8–12].

In Europe, biliary atresia is the most common cause of jaundice in term neonates, accounting for approximately one-third of all cases. Alpha-1 antitrypsin deficiency accounts for 5–15% of cases, while inborn errors of metabolism and congenital infections account for 20% and 5% of cases, respectively. Other inherited forms of cholestasis occur in 10–20% of cases [13]. In Sweden, progressive familial intrahepatic cholestasis may be a more common cause of neonatal cholestasis than previously reported [14].

The epidemiology, causes, and outcomes of neonatal cholestasis in Asian populations in Japan and Taiwan are not well understood. In a prospective observational study of 146 Malaysian infants with cholestasis, biliary atresia, and idiopathic neonatal hepatitis were the two most common causes of neonatal cholestasis [15].

Compared to infants in North American centers, the three most common causes of cholestatic liver disease in infants in Japan are biliary atresia , idiopathic neonatal hepatitis, and alpha-1 antitrypsin deficiency, which account for > 80% of cases [16].

To the best of our knowledge, there have been no reports of neonatal cholestasis in our country, Jordan. Therefore, we conducted a retrospective review of all cases of neonatal cholestasis that were referred to a single tertiary center over an eight-year period to identify the clinical and laboratory features, causes, and outcomes of the disease.

MATERIAL AND METHODS

This retrospective observational study aimed to investigate all cases of neonatal cholestasis diagnosed and followed up at the King Abdullah University Hospital (KAUH) between January 2012 and January 2020. The neonatal unit at KAUH is a level three NICU unit in North Jordan, whereas the gastrointestinal service at KAUH is a referral service for North Jordan with access to advanced radiological, histopathological, and hepatobiliary surgical services. Metabolic screening was limited to succinylacetone in urine, reducing substances in urine, and organic and amino acid chromatography. Genetic testing was only available for a few patients.

Cases of neonatal cholestasis admitted to our hospital during the study period were included. Exclusion criteria included infants who developed cholestasis after the age of three months (chronological age), infants with direct bilirubin < 1 mg/dl, infants with insufficient data and infants whose direct hyperbilirubinemia resolved within 2 weeks with no intervention. Electronic medical records were reviewed, and demographic data such as gestational age, sex, birth weight, and maternal characteristics were collected. Additionally, clinical features, including age at presentation, presence of jaundice, urine and stool colors, abdominal distension, organomegaly, cardiac examination, and presence of dysmorphic features, were collected (Tables 1–2). Laboratory results, including liver enzymes, liver synthetic function, metabolic workup, infectious panel, imaging studies, liver imaging and hepatobiliary iminodiacetic acid (HIDA) scans (when available), and any additional testing related to the patient's condition were also collected.

TABLE 1. Patients' demographics

Parameter	Data
Age of presentation [days]	16.5
Sex	
Male, *n* (%)	26 (55.3)
Female, *n* (%)	21 (44.6)
Gestational maturity	
Term, *n* (%)	34 (72.3)
Preterm, *n* (%)	13 (27.6)
Consanguinity	
Yes, *n* (%)	22 (46.8)
Long-term outcome	
Survived, *n* (%)	23 (49)
Lost to follow-up, *n* (%)	11 (23)
Died, *n* (%)	13 (28)
Underwent liver transplantation*, *n* (%)	1 (2.1)

**Done outside Jordan.*

TABLE 2. Clinical characteristics of cholestatic infants

Associated symptoms	*n*	%
Clay colored stool	14	29.7
Dark urine	14	29.7
Abdominal distention	13	27.6
Poor feeding and hypoactivity	9	19.1
Vomiting	7	14.8
Diarrhea	7	14.8
Neurological manifestations (change in LOC, abnormal movement)	5	10.6
Bleeding	2	4.2
Clinical findings		
Hepatosplenomegaly	9	19.1
Neurological findings	6	12.7
Skeletal abnormalities	6	12.7
Dysmorphic features	5	10.6

TABLE 3. Basic laboratory findings

Test	Average	Range
Bilirubin (total) [mg/dl]	14.3	4.9–32.6
Bilirubin (direct)	10.1	1.4–27.2
Maximum ALT [U/l]	276.3	3.2–958
Maximum AST [U/l]	505.2	9–3050
Prolongation of INR (INR > 1.5)*, *n* (%)	14 (29.8)	

**26 patients (55%) were on vitamin K supplements (therapeutic or prophylactic).*
ALT – alanine aminotransferase, AST – aspartate aminotransferase.

TABLE 4. Imaging and histopathology examination

Variable	Number of exams	Number of abnormal exams
Hepatic ultrasound	44	8
Gallbladder ultrasound	44	5
HIDA scan	26	17
Liver biopsy	19	19

HIDA – hepatobiliary iminodiacetic acid.

Liver biopsy results and genetic studies were recorded if performed, and medical and surgical management was reviewed and reported if needed. Final diagnoses and outcomes were documented.

ETHICS

This study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine and the Scientific Committee of Jordan University of Science and Technology (20200053).

STATISTICAL ANALYSIS

Data were collected using a preprepared Excel spreadsheet. Data were analyzed using a complementary descriptive method. Categorical variables are presented as averages and percentages.

RESULTS

During the study period, 47 neonates with cholestasis were identified, of whom 26 (55.3%) were males. Most neonates (72.3%) were delivered at term, and the mean age at presentation was 16.5 days. Jaundice was the most common presentation, affecting all neonates. Associated symptoms, such as clay-colored stool and dark urine, were observed in 14 (29.7%) patients, whereas abdominal distension and hypoactivity were observed in 13 (27.6%) and nine (19.1%) patients, respectively. Clinically significant bleeding was observed in only 2 patients, with pulmonary and intracranial hemorrhages. Skeletal abnormalities were observed in six (12.7%) patients, and five (10.6%) were dysmorphic.

The mean total and direct bilirubin at presentation were 14.3 mg/dl (± SD 7.3 mg/dl) and 10.1 mg/dl (± SD 6.5 mg/dl), respectively. The mean alanine transaminase and aspartate transaminase at presentation were 112 U/l (range 3.2–736 U/l) and 180.7 U/l (12–1133 U/l), respectively. The mean of the maximum readings during the course of follow-up was 276.3 (U/l) for alanine aminotransferase (range: 8–958 U/l) and 505.2 for aspartate aminotransferase (range: 15–3050 U/l) (Table 3).

Eight patients (17%) had abnormal liver ultrasound findings, with five showing only hepatomegaly. Two other patients had dilated common bile ducts, and one was diagnosed with a type II choledochal cyst with associated biliary atresia. Five patients (10.6%) had a non-visualized gallbladder, four of whom were ultimately diagnosed with biliary atresia (Table 4).

In our cohort, 26 (55.3%) patients underwent HIDA scans, and four (15.3%) were suspected of having biliary atresia, which was consistent with liver biopsy findings in three cases. One patient was diagnosed with progressive familial cholestasis (PFIC) type 1. Among the nine patients diagnosed with biliary atresia, a HIDA scan was performed in six patients, with three showing suggestive results, two showing hepatocellular dysfunction, and one having normal scans. The positive predictive value (PPV) for HIDA scanning in the diagnosis of biliary atresia was 75%, whereas the negative predictive value (NPV) for HIDA in the exclusion of biliary atresia was 86.3%. One patient underwent a HIDA scan twice, as the initial scan was reported as normal, but the patient was ultimately diagnosed with biliary atresia (Table 5).

Liver biopsy was performed 19 times (40.4%), and nine cases of biliary atresia were identified. Six children were diagnosed with idiopathic neonatal hepatitis. One infant had both PFIC-1 (ATP8B1 mutation) and congenital defects in bile acid synthesis (AKR1D1 mutation) based on genetic testing. Nonspecific and fibrotic changes were described in three patients who were found to have cerebrotendinous xanthomatosis (CYP27A1 mutation), tyrosinemia (FAH mutation), and a choledochal cyst (confirmed intraoperatively).

The most common causes of neonatal cholestasis in our cohort were genetic and metabolic conditions (28%), followed by extrahepatic anatomical conditions (BA/choledochal cysts) (21%), inspissated bile syndrome (13%), and idiopathic neonatal hepatitis (13%) (Table 6, Figure 1).

In our cohort, 36 patients had an adequate follow-up: 23 (48.9%) cases resolved with expectant management, and only one patient underwent a liver transplant. Thirteen (27.6%) patients died from complications of liver cirrhosis or postoperatively (Figure 2).

Of the nine patients who were diagnosed with biliary atresia by liver biopsy, the Kasai procedure (hepatoportoenterostomy) was attempted in our facility in four patients, performed in three, and canceled in one after finding the liver to be poorly functional and cirrhotic. The median

TABLE 5. Results of HIDA scan in our patients

HIDA scan result	Number of cases	Final diagnosis	Number
Normal	10	No final diagnosis	1
		Transient neonatal cholestasis	1
		Inspissated	2
		Neonatal hepatitis	2
		Galactosemia	2
		Sepsis	1
		Biliary atresia	1
Biliary atresia	4	Biliary atresia	3
		PFIC type 1	1
Hepatocellular dysfunction	11	Neonatal hepatitis/ hemochromatosis	3
		Transient neonatal cholestasis	2
		Not diagnosed	1
		Biliary atresia with choledochal cyst	1
		Biliary atresia with congenital CMV infection	1
		Sepsis	1
		Transient leukemoid reaction	1
		Cerebrotendinous xanthomatosis	1
Not conclusive	1	Tyrosinemia	1

HIDA – hepatobiliary iminodiacetic acid, PFIC – progressive familial cholestasis.

TABLE 6. Metabolic and genetic conditions

Variable	Number
Galactosemia	3
Tyrosinemia	2
PFIC type 1	2
Trisomies	2
Gaucher	1
Caroli	1
ARC	1
Cerebrotendinous xanthomatosis	1

PFIC – progressive familial cholestasis.

age of the patients at the time of the procedure was 38 days. Unfortunately, all three patients died at a median age of 5 months due to complications of liver cirrhosis.

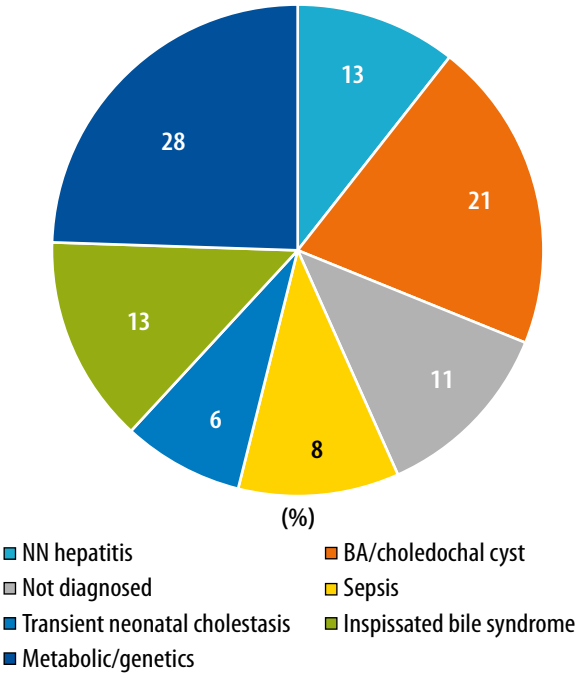

FIGURE 1. Etiology of neonatal cholestasis in our cohort

DISCUSSION

This study described the clinical presentation and causes of neonatal cholestasis in a cohort of Jordanian children. To the best of our knowledge, this is the first study in Jordan to report cases of neonatal cholestasis in Jordanian children [1]. The most common causes of neonatal cholestasis in our cohort were metabolic or genetic disorders (28%), and biliary atresia was the second most common cause.

In our cohort, a negligible male predilection was noted with a male-to-female ratio of 1.2 : 1. Comparable

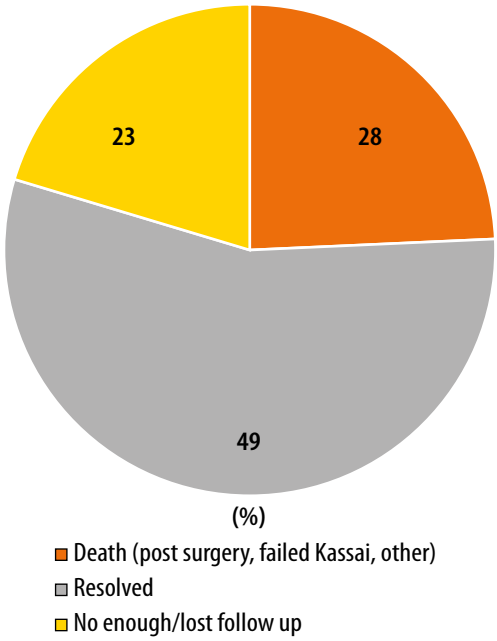

FIGURE 2. Patients' outcomes

results have been observed in other studies, with male-to-female ratios ranging from 1.17 : 1 [17] to 1.65 : 1 [9].

Biliary atresia accounts for approximately 33% of neonatal cholestasis cases worldwide [7] and ranges from 26% to 37% in four different Middle Eastern countries (Iran, Turkey, Saudi Arabia, and Egypt) [18–21]. Nine (19%) patients were diagnosed in the present study. When reviewing studies from the Middle Eastern region, the percentage of patients diagnosed with neonatal hepatitis – which was previously seen as the most common cause of neonatal cholestasis – decreased from 72% down to 45% as more genetic/metabolic and infectious conditions were described [18–21]. Metabolic and genetic conditions accounted for 28% of the cases in our cohort, which is consistent with other studies worldwide [4] and might be attributed to the high consanguinity rate in our country. Around half of our patients were born to consanguineous parents (Table 1), while the overall rate of consanguinity in Jordan is reported as 28% according to the Jordan Population and Family Health Survey 2017–2018.

The final diagnosis was difficult to reach in approximately 20.8% of the cases. These facts emphasize the importance of genetic testing (whole-genome sequencing – WGS/WES) to modify the care of this patient population after the initial conventional evaluation. However, cost and availability are major limiting factors in these investigations [3].

Jaundice is a common symptom in the neonatal period. It is mostly associated with benign, non-cholestatic causes. However, prolonged neonatal jaundice raises the suspicion of neonatal cholestasis, which mandates checking total and direct bilirubin levels in these infants [22].

Jaundice was invariably present in all our patients and was the most common (although nonspecific) symptom of neonatal cholestasis. This finding is consistent with those of previous studies [3, 5, 6]. Acholic stool (clay-colored stool) is a cardinal feature of cholestasis, which implies complete cholestasis and, consequently, a worse prognosis [5]. It is important to remember that the absence of clay-colored stools does not rule out neonatal cholestasis or even anatomical causes such as biliary atresia. Acholic stool was described in 29.7% of our cases, and two of the nine cases of biliary atresia had normal stool color.

The differential diagnoses of neonatal cholestasis are very broad, including a battery of investigations. After a detailed history and examination, laboratory workup assessing liver enzymes and synthetic function is usually performed, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGTP), prothrombin time (PT), international normalized ratio (INR), glucose, and albumin [4].

Gamma-glutamyl transpeptidase is usually elevated in cases of neonatal cholestasis, but normal levels can indicate specific differentials such as PFIC 1 and 2 and bile salt disease [23, 24].

Although meticulous revision of local newborn screening is usually helpful, as many diseases that cause neonatal cholestasis are usually screened, including tyrosinemia, cystic fibrosis (CF), and galactosemia [4], this is not the case in Jordan, where newborn screening is limited to G6PD deficiency, PKU, and thyroid function tests [25]. Among these diseases, only hypothyroidism is considered a known cause of neonatal cholestasis.

Other important initial workups focused on identifying treatable causes, including blood and urine cultures, especially in critically ill patients, and reducing substances in the urine (looking for galactosemia). Three of our patients had positive cultures for Gram-negative organisms, ESBL + urine cultures, KPC urine cultures, and *Stenotrophomonas* blood cultures, in addition to one patient who was diagnosed with sepsis based on the clinical picture and high inflammatory markers. Although no positive cultures were obtained in this case, the patient responded well to antibiotics. Cholestasis is a common manifestation of Gram-negative septicemia in the neonatal period, with a prevalence of up to 42% [26]. In this study, all our documented cases were caused by Gram-negative organisms.

In contrast, reducing substances in the urine was of low yield in our cohort. Only one of three patients who were diagnosed with galactosemia tested positive for reducing substances in their urine. Another 11 patients tested positive at first, but none were diagnosed with galactosemia. Many factors may trigger false-positive results, including conditions that impair blood galactose clearance, such as severe liver disease or antibiotic treatment [27].

More specific tests should be performed by pediatric hepatologists/gastroenterologists based on clinical evaluations, enabling a more targeted evaluation [4].

Liver and biliary tract ultrasound studies are the most common imaging modalities used to study cholestasis. Ultrasound is a very sensitive method for recognizing other surgical causes of neonatal cholestasis, such as a choledochal cyst, or for identifying the structural abnormalities of biliary atresia-splenic malformation syndrome. Ultrasonography is mandatory before performing a liver biopsy in neonatal cholestasis, as the findings may demonstrate the need for surgical exploration, irrespective of biopsy findings. Some centers have reported that the 'triangular cord sign' (an echogenic area in the porta hepatis) is highly specific for biliary atresia [5]. After performing an ultrasound for all patients, 5 had an absent gallbladder on ultrasound and 3 were diagnosed with biliary atresia. The other 8 patients had abnormal liver ultrasound findings, and two of them were diagnosed with biliary atresia.

Other diagnostic modalities, such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP), were shown to be effective and safe in infants with suspected extrahepatic anatomical conditions such as biliary atresia and choledochal cysts. MRCP has sensitivity and specificity of up to 100% and 86.7% for diagnosing choledochal cysts, respectively [28, 29]. ERCP has a 100% negative predictive value in the diagnosis of biliary atresia [30]. Such testing is unavailable at our hospital; ERCP requires specific equipment and advanced training to manage neonatal patients.

The HIDA scan is still used as a diagnostic modality for evaluating infants with biliary atresia. Although it showed relatively convincing sensitivity (up to 94%) in diagnosing biliary atresia, it has limited specificity (58%) [31] and its role is limited and inconclusive in premature babies [32]. In our cohort, the HIDA scan was performed for 26 patients, giving a PPV of 75% for the diagnosis of biliary atresia (compared to only 56% for a study from the USA) and a negative predictive value of approximately 86% for the diagnosis of biliary atresia (compared to 100% from the same study in the USA) [33]. Interestingly, the HIDA scan was performed twice in one of our patients and was reported as normal on both occasions; however, the patient was diagnosed with biliary atresia by liver biopsy. The role of the HIDA scan was more limited in diagnosing conditions other than biliary atresia, with normal results or evidence of hepatobiliary dysfunction, resulting in a very wide range of different diagnoses (Table 5).

The consideration of HIDA scans for the diagnosis of biliary atresia is questionable and should be further investigated in well-structured studies.

Liver biopsy plays a central role in the diagnosis of neonatal cholestasis, especially biliary atresia, with a high sensitivity and specificity, given the specific histopathological findings of bile duct proliferation, plugs, and fibrosis [4]. Nevertheless, it is important to remember that liver biopsies performed early in the course of the disease might give false-negative results, and thus infants with unexplained conjugated hyperbilirubinemia might benefit from repeated liver biopsies [34]. Conversely, intrahepatic processes support the value of liver biopsy in excluding biliary atresia but also agree with other studies questioning the ability of liver biopsies to accurately identify intrahepatic processes.

Early diagnosis of patients with biliary atresia is important, as it improves the outcome and effectiveness of the Kasai procedure [9]. The highest rate of bile flow restoration can be achieved in patients operated on before 60 days of life [35]. Nevertheless, in some early referred cases, the final diagnosis might not be apparent, and the possibility of biliary atresia must be reassessed before the age of 60 days [5]. The average age at presentation in our data was 33.5 days, while the average age of onset of symptoms was 16 days, which provides room for proper evaluation and surgical intervention with the Kasai procedure while waiting for a liver transplant.

The Kasai procedure, which was introduced in 1959, should be seen as a bridge to liver transplantation. Given that long-term survival is between 20% and 25%, even those survivors will sustain long-term complications related to hepatic failure [36]. Although it seems that the procedure extended the life expectancy of these patients by several months, all three patients ultimately died because of the inability to undergo liver transplantation in our country.

Since liver transplantation is not available in our country, patients are referred to neighboring countries for transplantation. One patient received a liver transplant and is currently doing well.

The lack of genetic testing, which is becoming a major diagnostic test for such disorders, limits our conclusion for undiagnosed cases.

CONCLUSIONS

In limited resource countries such as Jordan, cholestasis represents one of the medical issues that put significant pressure on both the patients and their families and the health care system. Reaching a diagnosis in a timely manner, when many of the investigative facilities are not available or need to be sent outside the country, is a major problem. The second issue is the supportive treatment for diagnosed cases. Supportive measures such as MCT oil, fat soluble vitamins (ADEK preparations) and specific treatment (cholic acid) are not available. Establishing a center in Jordan dealing with such patients would improve the care delivered and reduce the cost and hurdles faced.

DISCLOSURE

The authors declare no conflict of interest.

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