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Clinico-Laboratory Assessment of Infantile Cholestasis in Fayoum University Hospital

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Abstract:

Introduction: Cholestasis occurs during the first three months of life, is characterized by a direct bilirubin level greater than 1 mg/dl when total bilirubin is less than 5 mg/dl or greater than 20% when total bilirubin is greater than 5 mg/dl.

Aim of the study: to determine the various cholestasis causes, conduct investigations, and treat newborns who arrive at Fayoum University Children's Hospital.

Subjects and Methods: A retrospective, detailed review of all relevant information from the medical records of cholestatic infants presenting to the Hepatology Clinic in Fayoum University Hospital during the period from 2016 to June 2023. Data were gathered at Fayoum University Hospital through chart review utilizing the Best-Care system.

Results: At presentation, the average age was 97.9±164.5 days (range 1-146). At the time of presentation 78% of our infants were in the age group 0-3 months old. Jaundice was the first clinical symptom in 85% of infants that presented with cholestasis, with a mean age of onset of 20.2±25.6 days.

Conclusions: Jaundice was the most common presenting symptom in our cholestatic infants (95%), with a mean age of onset of 20.2±25.6 days. BA, sepsis, and TORCH are the most common etiologies. Twenty-two of our cases improved with treatment, and twenty-seven cases were lost to follow-up.

Keywords: Neonatal Cholestasis; Biliary Atresia.

1. Introduction

During the first three months of life, cholestasis is defined as a direct bilirubin level of greater than 1 mg/dl when total bilirubin is less than 5 mg/dl or greater than 20% when total bilirubin is greater than 5 mg/dl [1].

Neonatal infections, genetic and inborn metabolic errors, endocrine disorders, exposure to toxins and drugs,

hypoxia/ischemia, idiopathic neonatal hepatitis, anatomic obstruction of the biliary system (BA, choledochal cyst, cholelithiasis), and other miscellaneous causes are among the extrahepatic and intrahepatic etiologic categories [2].

The two most typical signs of cholestasis are jaundice and itching skin. Although it can happen anywhere on the body, cholestasis itching is typically more noticeable on the palms and soles of the feet. In the evenings, it can get worse [3].

When an infant has chronic jaundice, personal and family medical information should be gathered [2]. The differential diagnosis should take congenital infection or genetic-metabolic factors into account [4]. Detailed information about the onset of jaundice, changes in stool pigmentation, and urine color must be obtained [5].

The best indicator of a biliary obstructive disorder is acholic stools that are completely decolored and have a clay-like appearance [5]. In order to detect intermittent or chronic pale stool, stool color charts (SCC) are very helpful when reviewing medical history and performing bedside examinations [6]. Complete blood count, serum assays for liver function and damage, and fractionated serum bilirubin analysis [7].

Since abdominal Ultrasonography is non-invasive, it can rule out various extra-hepatic problems as cholelithiasis and pancreatitis. It can identify biliary atresia by looking for the (TC) triangular cord sign; it is typically done first [8].

When evaluating a cholestatic infant for the first time, the study of liver biopsy is a useful diagnostic technique with good accuracy [9].

For all cholestatic newborns, optimizing nutrition is a crucial part of treatment in order to maintain growth and development and avoid the consequences of malnutrition [10].

The general principles of medical treatment include: fat-soluble vitamins (vitamins A, D, E, and K), choleretic therapy (e.g., ursodeoxycholic acid [5].

Liver transplantation: Biliary atresia (BA) is one of the most frequent reasons for pediatric liver transplantation [11].

2. Subjects and Methods

2.1.Subjects

All infants who attended the Hepatology Clinic with cholestasis are included in this study at Fayoum University Children's Hospital during the period from 2016 to June 2023. Patients were given serial numbers in order. All patient files were enumerated, and every patient presenting with cholestasis fulfilling the inclusion and exclusion criteria was enrolled in the study.

Inclusion criteria

- The age of the first presentation is less than 3 months.
- Direct bilirubin level more than 2.0 mg/dl.

Exclusion criteria

- Age of first presentation > 3 months.
- Patients with indirect bilirubinemia, such as Crigler-Najjar syndrome and hemolytic diseases.

2.2.Methods

A retrospective, detailed review of all relevant information from the medical records of all cholestatic infants presenting to the Hepatology Clinic during this period.

Detailed history taking, thorough clinical examination, investigations including laboratory and radiology, treatment received, complications, and outcome of patients were analyzed.

2.3. Statistical Methods

The statistical program for social science (SPSS) was used to gather, tabulate, and statistically analyze all the data

3. Results

The mean age at the onset of jaundice in our patients was 20.2 ± 25.6 days (range: 1–105), and the mean age at their first presentation to the clinic was 97.9 ± 164.5 days (range: 1–146). At the time of presentation, 78% of the infants were between 0 and 3 months old (**Table 1**).

Table 1: Basic demographic characteristics of the studied group (N=100):

Category		**Mean ±SD**	**Median (Range)**
Age of onset of jaundice (days)		20.2±25.6	7 (1-105)
Age of first presentation to the clinic (days)		97.9±164.5	60 (1-146)
Category		**No**	**%**
Age of presentation (months)	0-3 m	78	78
	3-6 m	10	10
	6-9 m	4	4
	9-12 m	8	8
Sex	Male	58	58
	Female	42	42
Residence	Rural	73	73
	Urban	27	27
Parent consanguinity	Positive	64	64
	Negative	36	36
Similar condition	Absent	91	91
	Present	9	9

Jaundice was the first clinical symptom in 85% of infants presenting with cholestasis. It was present in 95% of all patients. Clay-colored stools were observed in 41% of patients. Other common findings included abdominal distention (50%), fever (22%), bleeding tendency (17%), and a history of repeated diarrhea (15%). A history of convulsions and DCL was found in 7% and 6% of patients, respectively (**Table 2**).

Table 2: Symptoms at presentation (N=100).

Category		**No.**	**%**
1st presenting symptom	Jaundice	85	85
	Clay stool	1	1
	Pruritus	1	1
	Abdominal distention	5	5
	Bleeding	5	5
	Vomiting	3	3
	Convulsion	0	0
Jaundice	Present	95	95
Stool color	Clay	41	41
	Yellow	59	59
Urine color	Normal	23	23
	Deep yellow	77	77
Pruritus	Present	16	16
Bleeding tendency	No	83	83
	Present	17	17

Abdominal distention	Present	50	50
Repeated diarrhea	Present	15	15
Repeated chest infection	Present	7	7
Fever	Present	22	22
Convulsion	Present	7	7
DCL*	Present	6	6

DCL(disturbed conscious level)*

The provisional diagnoses were as follows:

- Biliary atresia (BA) was the most common diagnosis (17%); 14% of the total cohort underwent surgical confirmation.
- Sepsis was found in 14% of cases.

Rare diagnoses included one case each of Caroli syndrome, reduced serum alpha-1-antitrypsin level, and galactosemia. Among the 100 infants, 17 (17%) were diagnosed with biliary atresia (BA), while the remaining 83 (83%) had cholestasis due to other causes (non-BA) (**Table 3**).

Table 3: Provisional diagnosis of the cholestatic infant (N=100):

Provisional diagnosis	**No.**	**%**
BA	17	17
Sepsis	14	14
TORCH	9	9
Cholestasis with normal GGT	8	8
Cholestasis with high GGT	3	3
Alagille syndrome	9	9
Tyrosinemia	7	7
Neimann Pick disease	5	5
Transient NH	5	5
Post-hemolytic cholestasis	4	4
Direct hyperbilirubinemia syndrome	4	4
Choledochal cyst	2	2
Alpha 1 antitrypsin deficiency	1	1
Caroli syndrome	1	1
Galactosemia	1	1
Cases undiagnosed	10	10

The majority of non-BA patients were male (60.2%), but there was no significant difference in sex distribution between the two groups (p = 0.577). Although the mean age of jaundice onset was higher in non-BA patients than in BA patients (21.4 ± 25.9 days vs. 14.4 ± 23.8 days), the difference was not statistically significant (p = 0.198). Clay-colored stool was present in 100% of BA patients and 89.2% of non-BA patients, but this difference was also not significant.

Table 4: Comparison between BA and Non-BA Groups.

Variables		**BA (n=17)**		**Non-BA (n=83)**		***P*-value**
		N	%	N	%	
Sex	**Male**	9	53	50	60	0.577
	Female	8	47	33	40	
Age of onset of jaundice (days)	**Mean ±SD** **Median (range)**	14.4±23.8 4 (1-90)		21.4±25.9 8 (1-105)		0.198
Age of presentation (days)	**Mean ±SD** **Median (range)**	63±44.1 54 (30-210)		105.1±178.8 60 (1-1460)		0.651
stool color		N	%	N	%	0.534
	Clay	17	100	74	89.2	
	Yellow	0	0	9	10.8	

The presence of clay-colored stool was 100% sensitive and specific for predicting BA (*P* < 0.001). A high GGT level with a cutoff value of 188 had a sensitivity of 88.2% and a specificity of 72% (*P* < 0.001). An abnormal gallbladder on ultrasound had 100% sensitivity and 62.7% specificity, with a 100% negative predictive value (NPV).

Table 5: The Marital data of the cases.

Variables	Sensitivity	Specificity	PPV	NPV	AUC	Cutoff	Accuracy	P value
Clay stool	100%	100%	100%	100%	1	----	100%	<0.001*
Direct bilirubin1	52.9%	56.6%	20%	85.5%	0.534	4.35	56%	0.677
Direct bilirubin/ Total bilirubin	76.5	25.3%	17.3%	84%	0.553	46.68	50.9%	0.494
GGT	88.2%	72%	37.8%	95.2%	0.810	188	74%	<0.001*
Absent gallbladder	100%	62.7%	35.4%	100%	0.813	----	81.4%	<0.001*
TC SIGN	29.4%	0%	5.7%	0%	0.853	---	5%	0.99

AUC=Area under curve, PPV=Positive predictive value, NPV=Negative Predictive value.

4. Discussion

The mean age at the onset of jaundice in our patients was 20.2 ± 25.6 days (range: 1–105). This is higher than the mean of 10.23 days (range: 1–17) reported by Mahmud et al. (2021) [12], but lower than the mean of 34 ± 59.11 days (range: 1–300) found by Yahya and Ramadhan (2023) [13]. This variation may be attributable to differences in parental observation.

In our study, the male-to-female ratio was 58% to 42%. This finding is consistent with previous studies, which reported male proportions of 54.3% and 56%, respectively [13, 14]. In contrast, another study reported a higher proportion of females (56.9%) [13].

A high rate of parental consanguinity (64%) was observed in our cohort, which is greater than the 46.8% reported by Altamimi et al. (2025) [15].

Jaundice was the primary presenting symptom in 95% of our infants. Among these, 41% presented with clay-colored stools and 77% with deep yellow urine. These findings are consistent with Yahya and Ramadhan (2023) [13], who reported jaundice in 100% of patients and clay-colored stools in 45.7%. However, Mahmud et al. (2021) [12] reported a higher incidence of clay-colored stools (76.6%) and dark urine (61.6%). These discrepancies may be due to differences in sample size.

In our study, the presence of clay-colored stools was a perfect predictor for biliary atresia (BA), with 100% sensitivity,

specificity, and diagnostic accuracy. This high accuracy may be a consequence of late presentation and referral in our patient population. In contrast, another study reported a diagnostic accuracy of 84.3%, a sensitivity of 96.1%, and a specificity of 74.8% for stool color [16]. The use of stool color cards (SCCs) can be crucial for standardizing this assessment, as demonstrated in a Portuguese pilot study where healthcare professionals achieved high accuracy using photographic references [17].

The gamma-glutamyl transferase (GGT) level in our study had an optimal cutoff of 188 U/L for predicting BA, with a sensitivity of 88.2%, a specificity of 72%, a positive predictive value (PPV) of 37.8%, a negative predictive value (NPV) of 95.2%, and an area under the curve (AUC) of 0.810. This is similar to Gong et al. (2023) [18], who reported a cutoff of 184 U/L.

The triangular cord (TC) sign had low predictive value for BA in our study, with a sensitivity of 29.4%, a specificity of 0%, and an accuracy of 5%. The evaluation of the TC sign can be ambiguous in younger newborns, and its detection rate varies significantly with age [19]. Our low sensitivity aligns with Dong et al. (2018) [16], who reported a sensitivity of 27.5%.

An absent gallbladder on ultrasound had a sensitivity of 100% and a specificity of 62.7% for predicting BA, with an accuracy of 81.4%, a PPV of 35.4%, and an NPV of 100%. This is partially consistent with Gong et al. (2023) [18], who reported a sensitivity of 91.9%. However, another study found a much lower sensitivity (27.5%), albeit with a high specificity (99.5%) [16]. This wide variation suggests that diagnosing BA based solely on gallbladder absence is unreliable.

5. Conclusion

Jaundice was the most common presenting symptom (95%) in our cohort of cholestatic infants, with a mean age of onset at 20.2 ± 25.6 days. The most common etiologies identified were biliary atresia, sepsis, and TORCH infections.

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References

1. Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 11th ed. Elsevier Health Sciences; 2020.
2. Feldman AG, Sokol RJ. Neonatal cholestasis: Emerging molecular diagnostics and potential novel therapeutics. Nat Rev Gastroenterol Hepatol. 2019;16(6):346-360. doi:10.1038/s41575-019-0132-z
3. Langedijk JA, Beuers UH, Oude Elferink RPJ. Cholestasis-Associated Pruritus and Its Pruritogens. Front Med (Lausanne). 2021;8:639674. doi:10.3389/fmed.2021.639674
4. Moreira-Silva H, Maio I, Bandeira A, Gomes-Martins E, Santos-Silva E. Metabolic liver diseases presenting with neonatal cholestasis: at the crossroad between old and new paradigms. Eur J Pediatr. 2019;178(4):515-523. doi:10.1007/s00431-019-03320-z
5. Fawaz R, Baumann U, Ekong U, et al. Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2017;64(1):154-168. doi:10.1097/MPG.0000000000001334
6. Schreiber RA, Masucci L, Kaczorowski J, et al. Home-based screening for biliary atresia using infant stool colour cards: a large-scale prospective cohort study and cost-effectiveness analysis. J Med Screen. 2014;21(3):126-132. doi:10.1177/0969141314535384
7. Yoon HM, Suh CH, Kim JR, et al. Diagnostic Performance of Sonographic Features in Patients With Biliary Atresia: A Systematic Review and Meta-analysis. J Ultrasound Med. 2017;36(10):2027-2038. doi:10.1002/jum.14234
8. Pereira NMD, Shah I. Neonatal cholestasis mimicking biliary atresia: Could it be urinary tract infection? SAGE Open Med Case Rep. 2017;5:2050313X17695998. doi:10.1177/2050313X17695998
9. Cho SJ, Kim GE. A practical approach to the pathology of neonatal cholestatic liver disease. Semin Diagn Pathol. 2019;36(6):375-388. doi:10.1053/j.semdp.2019.07.005
10. Leruez-Ville M, Magny JF, Couderc S, et al. Risk Factors for Congenital Cytomegalovirus Infection Following Primary and Nonprimary Maternal Infection: a Prospective Neonatal Screening Study Using Polymerase Chain Reaction in Saliva. Clin Infect Dis. 2017;65(3):398-404. doi:10.1093/cid/cix337
11. Kwong A, Kim WR, Lake JR, et al. OPTN/SRTR 2018 Annual Data Report: Liver. Am J Transplant. 2020;20 Suppl s1:193-299. doi:10.1111/ajt.15674
12. Mahmud S, Sarma MS, Darma A, Ahmed SS. Neonatal Cholestasis: An Update. Gastroenterol Hepatol Open Access. 2021;12(2):54-66.

13. Yahya NB, Ramadhan AA. The Clinical and Pathological Characteristics of Neonatal Cholestasis. Pharmacophore. 2023;14(5):48-56.
14. Al-Azzawi SI, Al-Badri BA, Mohammad LA. Cholestatic jaundice in a sample of Iraqi Infants (A hospital-based study). J Fac Med Baghdad. 2011;53(1):6-10.
15. Altamimi E, Abuzraiq R, Hamaidi MA, Khasawneh W, Khriesat W. Neonatal cholestasis in Jordanian children: a single-center experience. Pediatr Pol. 2023;98(4):300-306. doi:10.5114/polp.2023.133414
16. Dong C, Zhu HY, Chen YC, Luo XP, Huang ZH. Clinical Assessment of Differential Diagnostic Methods in Infants with Cholestasis due to Biliary Atresia or Non-biliary Atresia. Curr Med Sci. 2018;38(1):137-143. doi:10.1007/s11596-018-1858-5
17. Santos Silva E, Almeida A, Frutuoso S, et al. Neonatal Cholestasis Over Time: Changes in Epidemiology and Outcome in a Cohort of 154 Patients From a Portuguese Tertiary Center. Front Pediatr. 2020;8:351. doi:10.3389/fped.2020.00351
18. Gong Z, Lin L, Lu G, Wan C. Development and validation of a model for early diagnosis of biliary atresia. BMC Pediatr. 2023;23(1):549. doi:10.1186/s12887-023-04375-6
19. Nemati M, Rafeey M, Shakeri AB. Ultrasound findings in biliary atresia: the role of triangular cord sign. Pak J Biol Sci. 2009;12(1):95-97. doi:10.3923/pjbs.2009.95.97