Open Access

Original Article

Various Clinicopathological Presentaions of Cholestasis in Infants Presenting to Tertiary Care Hospital

Javaid Iqbal, Shabbir Hussain*, Sana Khan, Hafiz Abdul Quddus***, Hafiz Muhammad Murtaza****, Muhammad Nadeem Chohan*****

Department of Pediatric, Combined Military Hospital Skardu/National University of Medical Sciences (NUMS) Pakistan, *Department of Pediatric, Pakistan Navy Station Shifa Hospital, Karachi Pakistan, **Department of Psychiatry, Combined Military Hospital Skardu/National University of Medical Sciences (NUMS) Pakistan, ***Department of Pediatric, Combined Military Hospital Hyderabad/National University of Medical Sciences (NUMS) Pakistan, ****Department of Pediatric, Combined Military Hospital Tarbela/National University of Medical Sciences (NUMS) Pakistan, *****Department of Pediatric, Bilawal Medical College for Boys LUMHS Jamshoro, Karachi Pakistan

ABSTRACT

Objective: To determine various Clinico-pathological presentations of cholestasis in infants presenting to Tertiary Care Hospital.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Pediatric Medicine, Pakistan Navy Station Shifa Hospital, Karachi Pakistan, from Jan 2022 to Jun 2022.

Methodology: A total of 95 infants with persistent jaundice aged 2 weeks to 12 months of either gender were included. Jaundice case secondary to hemolysis and serious illness were excluded. After taking informed written consent from all children's parents, clinical presentations i.e. Jaundice, clay-coloured stools, pale stools, hepatomegaly and splenomegaly of cholestasis were noted. Essential labs and radiological investigations were also done at the clinico-pathological Laboratory of our institute.

Results: Mean age of the infants was 4.85±2.48 months. Out of the 95 infants, 61(64.21%) were male and 34(35.79%) were females with a male to female ratio of 1.8:1. Jaundice was present in 95(100%), hepatomegaly 78(82.11%), Acholic stools 74(77.89%), and splenomegaly in 66(69.47%) patients. The common causes of cholestasis were idiopathic neonatal hepatitis in 54(56.84%), biliary atresia in 25(26.32%) and Progressive Familial Intrahepatic Cholestasis in 26(27.37%) patients.

Conclusion: This study has shown that the common clinical feature of cholestasis in infants is jaundice followed by hepatomegaly, acholic stools and splenomegaly. The common cause was idiopathic neonatal hepatitis followed by biliary atresia and progressive familial intrahepatic cholestasis.

Keywords: Idiopathic neonatal hepatitis, Jaundice, neonatal cholestasis.

How to Cite This Article: *Iqbal J, Hussain S, Khan S, Quddus HA, Murtaza HM, Chohan MN. Various Clinicopathological Presentaions of Cholestasis in Infants Presenting to Tertiary Care Hospital. Pak Armed Forces Med J 2025; 75(Suppl-1): S118-S122.*

DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-1.4776

INTRODUCTION

A yellow coloring of the skin, sclera, and mucous membranes is called jaundice, and it results from a high serum bilirubin content. When the serum bilirubin level is more than 5 mg/dL (>85.5 micro mol/L) in babies and greater than 2 to 3 mg/dL (34 to 51 micro mol/L) in children, it is noticeable.[1] An incidence of 2.4 percent to 15 percent of babies develop jaundice, which typically manifests in the first two weeks of life. Neonatal cholestasis affects 1 to 5 percent of live births.[2]

Within the first week of life, up to 60% of all healthy babies develop jaundice. A pathological condition, such as immune hemolysis or a lack of RBC enzyme, can cause jaundice in newborns. However, it is more frequently caused by the infant's physiological inability to handle bilirubin effectively due to the interaction between elevated RBC turnover and a temporary deficit in bilirubin conjugation in the liver. [3]

The term "physiologic jaundice of the infant" refers to this kind of non-pathological jaundice.[4] The majority of newborns with physiologic jaundice do not develop elevated bilirubin levels that necessitate therapy. However, bilirubin levels in the blood can rise to extremely high levels in some children with exaggerated physiologic jaundice and in many infants with pathologic jaundice, putting the infant at risk for both acute and chronic bilirubin encephalopathy (kernicterus). In these situations, bilirubin concentration-lowering therapy (e.g., phototherapy, Exchange transfusion etc.) becomes necessary to prevent kernicterus.

Correspondence: Dr Hafiz Muhammad Murtaza, Department of Pediatric, Combined Military Hospital Tarbela, Pakistan

Received: 28 Sep 2022; revision received: 25 Feb 2023; accepted: 27 Feb 2023

Idiopathic neonatal hepatitis (INH) was observed in 26.0% of cases in research involving 1692 newborns, whereas extra-hepatic biliary atresia (EHBA) was present in 25.89% of cases.[5] Out of 1248 individuals with a carrier rate of 6% for PFIC, another investigation on the prevalence of hereditary metabolic diseases in patients with infantile liver disease indicated 9% of cases have progressive familial intrahepatic cholestasis.[6] A research on 60 babies from Sri Lanka found that jaundice (100%), hepatomegaly (83.3%), pale stools (76.6%), and splenomegaly (76.6%) were the most prevalent clinical characteristics (56.6%). Idiopathic neonatal hepatitis (26.6%) and biliary atresia were the most frequent causes (26.6 %).[7]

Different etiologies of cholestasis manifest with an average onset delay of three to five months. If biliary atresia, as one of the most frequent curable causes, is not identified timely and treated promptly, liver transplantation becomes the only remaining alternative to save life of a child or to reduce morbidity. This is not economically viable for poorer nations.[8] The purpose of this study was to classify the causes and clinical characteristics of cholestasis that manifests in infancy in order to determine the disease burden and to identify reasons that can be treated surgically.

METHODOLOGY

This cross-Sectional study was conducted at the Department of Pediatric Medicine, PNS Shifa Karachi Pakistan, from January 2022 to June 2022. Non-probability, consecutive sampling technique was used. The sample size was 95, calculated using WHO Sample size calculator with a 10% margin of error, 95% confidence level and Population of Prevalence 40%.[8]

Inclusion Criteria: Infants of either gender with age ranging from 2 weeks to 12 months, presenting in Outpatient Department with persistent jaundice (S, conjugated bilirubin >2 mg or more than 20% of total bilirubin), were included in the study.

Exclusion Criteria: Jaundiced infants secondary to established hemolysis and serious illness were excluded.

After permission from the hospital ethical review committee (IERB number: ERC/2022/PAEDS/26), the total number of 95 infants were included. After taking informed written consent from all children's parents, clinical presentations i.e. Jaundice, Acholic stools, and pale stools, hepatomegaly and splenomegaly of cholestasis were documented in each patient. Essential labs and radiological investigations were also done at the clinico-pathological Laboratory of our institute. Investigations and Radiology imaging were verified by consultant pathologist and radiologist. All this data was recorded on a specially designed proforma.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0. Results were presented as mean and standard deviation for quantitative variables i.e. age, duration of disease, and weight (BMI). Frequency and percentage were calculated for qualitative variables i.e. Jaundice, stool color, hepatomegaly, splenomegaly, Biliary atresia, Progressive Familial Intrahepatic Cholestasis, Idiopathic Neonatal Hepatitis.

Effect modifiers like age, gender, duration of disease and BMI were controlled through stratifications and post-stratification, and chi-square was applied to see their effect on the outcome. *p*-value ≤0.05 was taken as significant.

RESULTS

This study was conducted to determine various clinico-pathological presentations of cholestasis in infancy. The age range in this study was from 2 weeks to 12 months with a mean age of 4.85±2.48 months. The mean duration of the disease was 8.06±2.87 days. The mean BMI was 28.36±2.92 kg/m^2.

Table-I showed that most of the patients 69(72.63%) were between 2 weeks to 6 months of age. Out of the 95 patients, 61(64.21%) were male and 34(35.79%) female. The common causes were idiopathic neonatal hepatitis in 54(56.84%), biliary atresia in 25(26.32%) and Progressive Familial Intrahepatic Cholestasis in 26(27.37%) patients. Only 40% presented within one week of symptoms. Jaundice was most common finding (100%) while splenomegaly was least common (69.47%).

Table-II showed age comparison. Half of patients in both groups (below 6 months and above 6 months) had Idiopathic Neonatal Hepatitis. Biliary Atresia and PFIC slightly more prevalent in age group more than 6 months. Hepatomegaly was seen more in older group likewise splenomegaly commoner in younger age group.

Table-III showed Biliary Atresia was more common in male and PFIC commoner in female. Findings of jaundice, acholic stools and splenomegaly were approximately equally seen in male and female

patients. However, hepatomegaly was more prevalent in female patients of the study group.

Table-I: Demographic Variables and Clinical Features of the Study Participants (N=95)

Variable	n (number) %
Age (in months)	
2 weeks-6 months	69(72.63%)
6-12 months	26(27.37%)
Gender	
Male	61(64.21%)
Female	34(35.79%)
Duration of disease (in days)	
1-7	38(40.00%)
>7	57(60.00%)
BMI (in kg/m²)	
≤27	38(40.00%)
>27	57(60.00%)
Clinico-Pathological Features	
Idiopathic Neonatal Hepatitis	54(56.84%)
Biliary Atresia	25(26.32%)
Progressive Familial Intrahepatic Cholestasis	26(27.37%)
Jaundice	95(100.0%)
Acholic stools	74(77.89%)
Hepatomegaly	78(82.11%)
Splenomegaly	66(69.47%)

Table-II: Clinico-Pathological Presentations of Cholestasis with Respect to Age (N=95)

Age Groups		2 weeks to 6 Months (n=69)	6-12 Months (n=26)	*p*-value
Idiopathic Neonatal Hepatitis	Yes	41(59.42%)	13(50.0%)	0.409
	No	28(40.58%)	13(50.0%)	
Biliary Atresia	Yes	17(24.64%)	08(30.77%)	0.545
	No	52(75.36%)	18(69.23%)	
Progressive Familial Intrahepatic Cholestasis	Yes	11(15.94%)	05(19.23%)	0.703
	No	58(84.06%)	21(80.77%)	
Jaundice	Yes	69(100.0%)	26(100.0%)	----
	No	00(0.0%)	00(0.0%)	
Acholic stools	Yes	54(78.26%)	20(76.92%)	0.889
	No	15(21.74%)	06 (23.08%)	
Hepatomegaly	Yes	54(78.26%)	24 (82.31%)	0.111
	No	15(21.74%)	02 (7.69%)	
Splenomegaly	Yes	50(72.46%)	16 (61.54%)	0.303
	No	19(27.54%)	10(38.46%)	

In our study group two third of patients presented within 7 days with most of patients having Idiopathic Neonatal Hepatitis as shown in Table IV. Patients with Biliary Atresia and PFIC presented after first week of disease. Clinical findings of jaundice, acholic stools, splenomegaly and hepatomegaly remained largely unaffected by age at presentation of disease.

Table III: Clinico-Pathological Presentations of Cholestasis with Respect to Gender. (n 95)

Gender		Male (n=61)	Female (n=34)	*p*-value
Idiopathic Neonatal Hepatitis	Yes	35(57.38%)	19(55.88%)	0.888
	No	26(42.62%)	15(44.12%)	
Biliary Atresia	Yes	18(29.51%)	07(20.59%)	0.344
	No	43(70.49%)	27(79.41%)	
Progressive Familial Intrahepatic Cholestasis	Yes	08(13.11%)	08(23.53%)	0.194
	No	53(86.89%)	26(76.47%)	
Jaundice	Yes	61(100.0%)	34(100.0%)	----
	No	00(0.0%)	00(0.0%)	
Acholic stools	Yes	48(78.69%)	26(76.47%)	0.803
	No	13(21.31%)	08(23.53%)	
Hepatomegaly	Yes	47(77.05%)	31(91.18%)	0.085
	No	14(22.95%)	03(8.82%)	
Splenomegaly	Yes	43(70.49%)	23(67.65%)	0.773
	No	18(29.51%)	11(32.35%)	

Table-V: Clinico-Pathological Presentations of Cholestasis with Respect To Bmi (N= 95)

BMI		≤27 (n=38)	≥27 (n=57)	*p*-value
Idiopathic Neonatal Hepatitis	Yes	22(57.89%)	32(56.14%)	0.866
	No	16(42.11%)	25(43.86%)	
Biliary Atresia	Yes	08(21.05%)	17(29.82%)	0.342
	No	30(78.95%)	40(70.18%)	
Progressive Familial Intrahepatic Cholestasis	Yes	08(21.05%)	08(14.04%)	0.371
	No	30(78.95%)	49(85.96%)	
Jaundice	Yes	38 (100.0%)	57(100.0%)	----
	No	00(0.0%)	00(0.0%)	
Acholic stools	Yes	30(78.95%)	44(77.19%)	0.840
	No	08(21.05%)	13(22.81%)	
Hepatomegaly	Yes	30(78.95%)	48(84.21%)	0.512
	No	08(21.05%)	09(15.79%)	
Splenomegaly	Yes	29(76.32%)	37(64.91%)	0.237
	No	09(23.68%)	20(35.09%)	

BMI correlation shows that those diagnosed with Idiopathic Neonatal Hepatitis falling equally in both groups (BMI ≤27 and BMI ≥27) as shown in Table V. Those diagnosed with Biliary Atresia mostly had BMI ≥27. PFIC cases commonly had BMI ≤27. However, splenomegaly was commoner in patients with BMI

≤27 and hepatomegaly prevalent in BMI ≥27 patients in this study.

DISCUSSION

Conjugated hyperbilirubinemia that develops during the newborn period or soon after is often referred to as neonatal cholestasis. Reduced bile synthesis and/or excretion, which can be brought on by a variety of diseases, is the common cause of cholestasis. Instead of only referring to the neonatal era, the term "neonatal cholestasis" is frequently used to describe a cholestatic liver disease that is present at birth and/or develops within the first few months of life (the first 28 days of life). The golden time for diagnosing newborns with biliary atresia, the most frequent cause of cholestasis in this age group, is the first two months of life. In clinical practice, these illnesses typically manifest during this time. Similar diagnostic criteria, however, are still relevant for newborns whose cholestasis is discovered beyond two months of age. Cholestatic newborns require a step-by-step, thorough evaluation due to the frequent lack of unique clinical signs allowing for separation between hepatocellular and obstructive illnesses. The clinical, biochemical, radiographic, and histological aspects should all be included in the diagnostic paradigm. However, a serologic test or imaging study may be used at any stage of the diagnostic process to determine the most likely etiology of cholestasis.

According to a comparable Iranian study, jaundice, which occurs in 100% of cases, is followed by hepatomegaly (78%), splenomegaly (52%), acholic stool (35%) and dark urine (37%).[9] An international study found that PNALD, or Parenteral Nutrition-Associated Liver Disease, was the most frequent cause of cholestatic jaundice in babies (29.5%) and occurred more frequently in preterm infants (75.5%). Septicemia (13.1%) and idiopathic newborn hepatitis (17.2%) were prevalent in 14(11.5%) of the 16 neonates with biliary atresia (BA) and choledochal cysts (2% each) exhibited abnormalities of the biliary tract.[10]

In one study with a total of 90 children in all, 65.6% of them were boys, there were 118.01 days in the average age. The most prevalent symptoms in children were jaundice, dark urine, and hepatomegaly, while ophthalmologic abnormality, congenital heart disease, and itching were the least prevalent.[11] A regional survey found that biliary atresia was the most common etiology, followed by idiopathic neonatal hepatitis/INH (21.9%). Among the other etiologies identified were progressive familial intrahepatic cholestasis/PFIC (4.4%), galactosemia (4.4%), and choledochal cyst (3.5%). Rubella, cytomegalovirus (CMV), and herpes/TORCH infection (8.61%) as well as galactosemia (4.4%) were also found.[12] Quelhas *et al.,* reported an incidence of 1:2500 live births of neonatal cholestasis with jaundice, hypocholic stools, and choluria common symptoms. Rarely, it present with steatorrhea or profuse bleeding. Choluria in infants is yellow-colored urine that stains diapers.[13] Vij *et al.,* described similar presentation of biliary atresia that if not treated leads to progressing fibrosis, portal hypertension and end-stage liver disease and death within the first 2 years of life. Prompt diagnosis and surgical intervention that is Kasai portoenterostomy (KPE) is linked with short-term jaundice clearance in 50–60% of infants in western population.[14] Emphasis on histopathological evaluation of liver biopsy is important in definite diagnosis as well-timed management is lifesaving.[15] Childhood Liver Disease diagnosis is challenging due to the liver's limited response to injury, rarity and lack of experience. Liver transplantation is an emerging treatment but mandates long-term use of immune suppressants.[16] Mehta *et al.,* reported 8 months median delay in diagnosis of progressive familial intrahepatic cholestasis (PFIC), a heterogeneous group of rare autosomal recessive liver disorders that may present as progressive neonatal cholestasis probably owing to lack of awareness among general pediatricians. PFIC may cause end stage liver disease in early childhood and adolescents that may otherwise be treated by available medical and surgical intervention if timely diagnosed.[17] A study done at Pakistan by Ali *et al.,* reported PFIC more prevalent in Asia as compared to Western literature with incidence between 1 in 50,000 and 1 in 100,000 births. Early diagnosis is a challenge and management can be assisted by clinico-pathologic correlation and genetic testing. Common presentation in early childhood of this intrahepatic cholestasis is pruritus, dark urine, pale stool, lack of appetite, and fatigue.[18]

ACKNOWLEDGMENT

We are grateful to the paramedical and nursing staff of pediatric medicine department, PNS SHIFA Karachi, Pakistan for their sincere contribution and co-operation in the study

CONCLUSION

This study has shown that the common clinical feature of cholestasis in infants is jaundice, followed by hepatomegaly, acholic stools and splenomegaly. The common cause was idiopathic neonatal hepatitis followed by

biliary atresia and progressive familial intrahepatic cholestasis. Awareness at national and international level to encourage early consultation, diagnosis and management may improve outcome and reduce morbidity.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

JI & SH: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

SK & HAQ: Data acquisition, data analysis, approval of the final version to be published.

HMM & MNC: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Dantas AV, Farias LJ, de Paula SJ, Moreira RP, da Silva VM, de Oliveira Lopes MV, et al. Nursing diagnosis of neonatal jaundice: study of clinical indicators. Journal of pediatric nursing 2018 Mar 1; 39:e6-10. https://doi.org/10.1016/j.pedn.2017.12.001
2. Saad AA, Altegani Hb, ali ra. Neonatal jaundice; prevalenc and its associated risk factor as seen in omdurman maternity hospital (Doctoral dissertation, Napata College).
3. Rana N, Ranneberg LJ, Målqvist M, Kc A, Andersson O. Delayed cord clamping was not associated with an increased risk of hyperbilirubinaemia on the day of birth or jaundice in the first 4 weeks. Acta Paediatrica 2020; 109(1): 71-77.
4. Goudarzvand L, Dabirian A, Nourian M, Jafarimanesh H, Ranjbaran M. Comparison of conventional phototherapy and phototherapy along with Kangaroo mother care on cutaneous bilirubin of neonates with physiological jaundice. The Journal of Maternal-Fetal & Neonatal Medicine 2019 ; 32(8): 1280-1284. https://doi.org/10.1080/14767058.2017.1404567
5. Misra S, Majumdar K, Sakhuja P, Jain P, Singh L, Kumar P, et al. Differentiating Biliary Atresia From Idiopathic Neonatal Hepatitis: A Novel Keratin 7 Based Mathematical Approach on Liver Biopsies. Pediatric and Developmental Pathology 2021; 24(2): 103-115. https://doi.org/ 10.1177/1093526620983730
6. Mells G, Alexander G. Liver Function in Health and Disease: Clinical Application of Liver Tests. Sherlock's Diseases of the Liver and Biliary System 2018: 20-38.
7. Mahmud S, Gulshan J, Mashud Parvez FT, Ahmed SS. Singapore Journal of Gastroenterology.
8. Hilscher MB, Kamath PS, Eaton JE. Cholestatic liver diseases: a primer for generalists and subspecialists. In Mayo Clinic Proc 2020; 95(10): 2263-2279. https://doi.org/10.1016/j.mayocp.2020.01.015
9. Shahraki T, Miri-Aliabad G, Shahraki M. Frequency of Different Causes of Infant Cholestasis in a Tertiary Referral Center in South-East Iran. Iranian Journal of Pediatrics. 2018 Oct 31; 28(5).
10. Sihaklang B, Piriyanon P, Intarakhao S. Etiology and Clinical presentation of cholestatic jaundice during infancy period in Thammasat University Hospital. TMJ. 2020 Jul 8; 20(2):137-45.
11. Bilal H, Irshad M, Shahzadi N, Hashmi A, Ullah H. Neonatal Cholestasis: The Changing Etiological Spectrum in Pakistani Children. Cureus 2022; 14(6): e25882. https://doi.org/10.7759/cureus.25882
12. Benzamin M, Khadga M, Begum F, Rukunuzzaman M, Mazumder MW, Lamia KN, Islam MS, Rahman AR, Karim AB. Etiologies of neonatal cholestasis at a tertiary hospital in Bangladesh. Paediatrica Indonesiana 2020; 60(2): 67-71.
13. Quelhas P, Jacinto J, Cerski C, Oliveira R, Oliveira J, Carvalho E, et al. Protocols of Investigation of Neonatal Cholestasis—A Critical Appraisal. Healthcare [Internet] 2022; 10(10): 2012. Available from: https://www.mdpi.com/2227-9032/10/10/2012
14. Vij, M., & Rela, M. (2020). Biliary Atresia: pathology, Etiology and Pathogenesis. Future Science OA, 6(5). https://doi.org/10.2144/fsoa-2019-0153
15. Parvez M, Arjuman F, Arshad–Ul–Azim M, Mahmud S, Ahmed SS. Histopathological Evaluation of Childhood Liver Disease: An Experience in a Tertiary Centre of Bangladesh [Internet]. www.bapath.org. Journal of Histopathology and Cytopathology; 2021 [cited 2024 Nov 4]. Available from: https://www.bapath.org/jhc-2021-jan-v5-n1/
16. Akhtar W, Tahir AM, Balooch S, Aslam S, Sohail A, Khan S, et al. Clinical presentations and histopathological types of chronic liver disease in paediatric population. Pak J Pathol 2021; 32(1): 29-32
17. Mehta S, Kumar K, Bhardwaj R, Malhotra S, Goyal N, Sibal A. Progressive Familial Intrahepatic Cholestasis: A Study in Children from a Liver Transplant Center in India. Journal of Clinical and Experimental Hepatology [Internet] 2022; 12(2): 454–60. Available from: https://www.sciencedirect.com/science/article/pii/S0973688321001481
18. Ali M, Cheema HA, Alvi MA, Waheed N,. I, Anjum MN. Phenotypic And Genotypic Characteristics of Progressive Familial Intrahepatic Cholestasis Type 3 In Pediatric Population in Pakistan. Khyber Med Univ J [Internet] 2022 Mar. 31 [cited 2024 Nov. 4]; 14(1): 11-15. Available from: https://www.kmuj.kmu.edu.pk/article/view/21935