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An Insight Into Neonatal Cholestasis; A Tertiary Care Hospital Experience in Rawalpindi, Pakistan

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ABSTRACT

Objective: To determine the frequencies of various etiologies of neonatal cholestasis diagnosed by clinical findings and laboratory investigations at the Pak Emirates Military Hospital, Rawalpindi, Pakistan.

Study Design: Cross-sectional study.

Place and Duration of Study: Pediatric Department of Pak Emirates Military Hospital, Rawalpindi Pakistan, from Jan 2021 to Apr 2022.

Methodology: Infants of either gender aged 14 days to six months admitted to Inpatient facility who had jaundice with direct bilirubin and more than 20% of total bilirubin were included in the study. The proforma was formulated to record the clinical features, laboratory investigations, weight, level of activity and consanguinity among the parents.

Results: A total of 146 infants were included in the study. Jaundice was seen in 100% of infants, hepatomegaly in 66.4%, splenomegaly in 38.4%, followed by ascites in 25%. The most common aetiology of neonatal cholestasis was Biliary Atresia 26.7% in the extrahepatic Group, Idiopathic Neonatal Hepatitis 25.3% in the intrahepatic Group. Consanguinity was present in parents of 65% of infants.

Conclusion: The most common aetiology of extrahepatic Neonatal Cholestasis was Biliary Atresia, while Idiopathic Neonatal Hepatitis and Progressive Familial Intrahepatic Cholestasis were the most common causes of intrahepatic cholestasis.

Keywords: Biliary atresia, Consanguinity, Idiopathic neonatal cholestasis, Neonatal cholestasis, Pakistan.

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INTRODUCTION

Physiological jaundice of newborns is a relatively common presentation, a nonfatal condition seen in 60% of infants that rarely extends after two weeks of life.[1] However, the persistence of this seemingly benign condition often delays the diagnosis of a pathological condition known as Neonatal Cholestasis (NC) that can be life-threatening.[2] In case jaundice is noted in a full term infant beyond 14 days or in a preterm infant after 21 days, the serum bilirubin level should be split into unconjugated (indirect) and conjugated (direct) bilirubin.[3]

It is crucial to have a timely and definite diagnosis of neonatal cholestasis as the number of disorders associated with it involve multiple organs/ systems of the body.[4] Early intervention remarkably affects the outcome with certain treatment modalities, supportive management, improved survival, and guidance to mothers/caregivers for future pregnancies. It also influences anticipation of extrahepatic problems associated with neonatal cholestasis and its eventualities.[5]

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Inadequate information is available about neonatal cholestasis's epidemiology, aetiology and outcomes in Asian populations, except for countries like Taiwan and Japan.[6] Likewise, there needs to be more data about neonatal cholestasis in Pakistan, which includes clinical features of infants with neonatal cholestasis, laboratory findings, imaging studies, liver biopsies, management and short/long-term outcomes.[7] While several advancements have been made in developed countries associated with etiologies, management and revolutionizing the diagnosis of neonatal cholestasis, Pakistan faces many limitations with a huge volume of infants suffering from neonatal cholestasis.[8,9]

Considering the dearth of knowledge about aetiologies of Neonatal Cholestasis in Pakistan, this research has been undertaken to determine the frequencies of various aetiologies of neonatal cholestasis diagnosed by clinical findings and laboratory investigations at the Pak Emirates Military Hospital, Rawalpindi Pakistan.

METHODOLOGY

The cross-sectional study was conducted at Paediatric Department, Pak Emirates Military

Hospital, Rawalpindi Pakistan, from January 2021 to April 2022, after approval of the Ethical Committee of PEMH, Rawalpindi (Ref: A/28/135/EC/449). The sample size was calculated using OpenEpi, calculator with prevalence of neonatal cholestasis as 30%.[10]

Inclusion Criteria: Infants of either gender aged 14 days to six months admitted to Inpatient Facility who had jaundice with direct bilirubin and more than 20% of total bilirubin were included in the study.

Exclusion Criteria: Infants with direct bilirubin was less than the mentioned criteria (less than 20% of total bilirubin) and whose clinical parameters or biochemical results were unavailable were excluded from the study.

Detailed data of each infants' age, gender, weight, onset and duration of jaundice, stool colour, hepatosplenomegaly, and ultrasound liver were recorded. It also included blood chemistry like complete blood picture, liver function tests, urine for reducing substances other than glucose, thyroid function tests, Hepatitis B surface antigen and TORCH screening/ PCR. Other tests included percutaneous liver biopsy (where possible) and HIDA (Hepatobiliary Iminodiacetic Acid) scintigraphy.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages.

RESULTS

A total of 146 infants were included in the study. Jaundice was noted in all (100%) patients. The average weight at the time of admission was 3.55±1.1kg (Table-I). Ultrasound of the liver showed coarse echotexture in 27(18%) patients and helped diagnose obstructive neonatal cholestasis in 30(20%) patients. Consanguinity among the parents was found to be 63%. Based on the final diagnosis, extrahepatic cholestasis was found in 42(28%) infants, while intrahepatic cholestasis was identified in 104(71%) infants (Table-II). HIDA scan was done in 30 infants (Figure-1). The distribution of TORCH syndrome is shown in Figure-2.

Average levels of Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), Albumin, Total Bilirubin/direct bilirubin, Prohrobin time (PT), Gamma- Glutamyl Transferase (gamma GT) and Hemoglobin were compared in both Groups, (Table-III).

Table-I: Clinical Parameters of Infants with Neonatal Cholestasis (n=146)

Clinical Parameters	n(%)
Jaundice	
Present	146(100%)
Appearance	
Sick Looking	56(38.4%)
Stool Colour	
Acholic	47(32.2%)
Mixed Pattern	28(19.2%)
Pigmented	71(48.6%)
Hepatomegaly	
Not Present	49(33.6%)
Present	97(66.4%)
Splenomegaly	
Not Present	90(61.6%)
Present	56(38.4%)
Ascites	
Absent	104(71.2%)
Present	42(28.8%)
Pruritis	
Present	19(13.0%)
Consanguinity in Parents	
Absent	54(37.0%)
Present	92(63.0%)

Table-II: Etiology of Neonatal Cholestasis (n=146)

Etiology of Neonatal Cholestasis	n(%)
Extrahepatic	
Extrahepatic BA	39(26.7%)
Choledochal Cyst	3(2.1%)
Intrahepatic	
INH	37(25.3%)
PFIC-II	25(17.1%)
Metabolic	
Tyrosinemia	10(6.8%)
Galactosemia	4(2.7%)
Torch Hepatitis	12(8.2%)
Sepsis	8(5.5%)
Gald	4(2.7%)
Hypothyrodism	1(0.7%)
Caroli's Disease	2(1.4%)
Down's syndrome	1(0.7%)

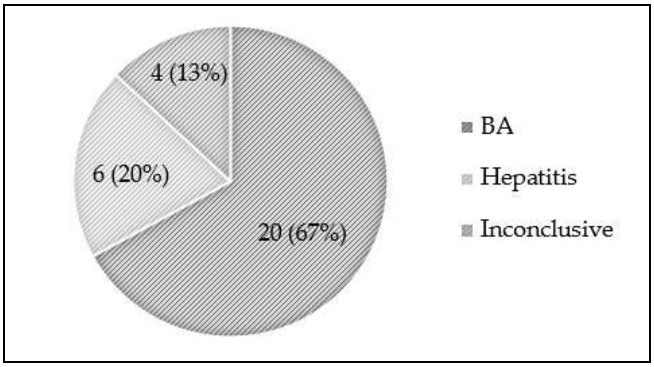

Figure-1: Hepatobiliary Imino Diacetic Acid (HIDA) Scan Results

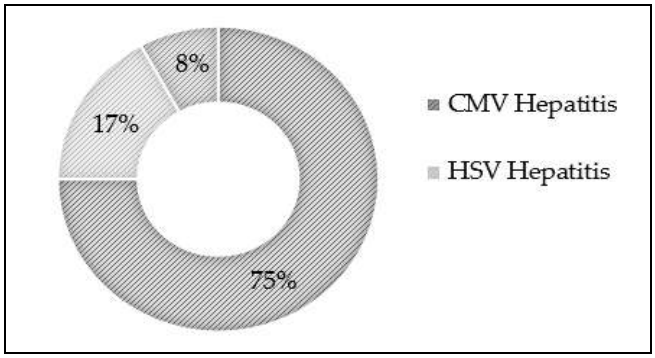

Figure-2: Neonatal Cholestasis caused by Toxoplasma gondii, Other agents, Rubella, Cytomegalovirus, Herpes simplex virus (TORCH) syndrome

Table-III: Average Laboratory Findings of Extrahepatic and Intrahepatic Groups (n=146)

Biochemical Parameters	Groups	Mean±SD
Total Bilirubin (µmol/L)	Extrahepatic	251.62±99.1
	Intrahepatic	227.96±103.1
Direct Bilirubin (µmol/L)	Extrahepatic	162.79±63.8
	Intrahepatic	141.30±68.88
Alanine Transaminase (U/L)	Extrahepatic	213.88±87.5
	Intrahepatic	253.38±133.8
Alk Phos	Extrahepatic	808.36±286.5
	Intrahepatic	702.32±442.7
Albumin (g/dL)	Extrahepatic	35.17±5.0
	Intrahepatic	34.13±6.6
Gamma- Glutamyl Transferase (Gamma GT)	Extrahepatic	598.21±269.4
	Intrahepatic	205.75±205.2
Prohrobin Time (PT)	Extrahepatic	17.36±4.8
	Intrahepatic	18.96±8.19
Haemoglobin (mg/dl)	Extrahepatic	9.73±1.1
	Intrahepatic	9.57±1.5

DISCUSSION

Neonatal Cholestasis has wide spectrum of etiologies, broadly classified as obstructive, infectious, genetic, metabolic and endocrine, along with parenteral nutrition and drugs. In the past, etiologies of neonatal cholestasis had fewer categories, with Idiopathic Neonatal Hepatitis (INH) being the main umbrella and the most common diagnosis, followed by Biliary Atresia (BA).[11 12]

Nevertheless, another study had results with infection (35%) as the main cause of neonatal cholestasis, with Biliary Atresia (25%) and INH (24%) almost equal prevalence.[13] Over the last 20 years, newer etiologies such as PFICs identified with the latest diagnostic gears have been introduced into the clinical routine. However, BA still represents the major cause of neonatal cholestasis.[14]

Over 100 neonatal cholestasis hepatobiliary and metabolic causes have been identified with advancements in genetic research panels and bioinformatics.[15] Our study indicated Biliary Atresia being the most common cause of neonatal cholestasis, followed by INH, which is comparable with other studies. The Third leading cause of neonatal cholestasis in our study was PFIC, which matches the latest studies. Even though the literature review of earlier studies showed the infectious and metabolic as the third important cause of neonatal cholestasis. In a recent study, Biliary Atresia is followed by PFIC as the most common cause of neonatal cholestasis, which indicates the paradigm shift.[16]

Clinical features of jaundice, hepatosplenomegaly, pruritis and laboratory investigation comprising of low gamma GT, raised to normal serum bile acid levels, high alkaline phosphate levels, prolonged coagulopathy and liver biopsy (where possible) helped us to reach the diagnosis of PFIC. Among the metabolic etiologies, Tyrosinemia was the leading cause. The mean age of infants covered by this study for obstructive NC was 76 days (ranging from 18-120 days), which falls into the category of delayed referral and is considered one of the main problems in dealing with such patients, especially in developing countries. Delayed age of presentation, referral and diagnosis is found to have a significant impact on the outcomes. Less than 20% of the patients who undergo hepatic PE at older than 90 days of age achieve inadequate bile drainage. In two reports, mean referral age of Indian infants with neonatal cholestasis was 3-3.9 months. Mean age of referral in a study carried out in the capital of Iran was four months,[16] and 58 days (1.9 months) in another study.[17] Mean age of hospital referral was 92.7 days in a study at a tertiary care hospital.[18] Referral age was delayed by 50% even in countries with high levels of professional education over the last two decades, resulting in the development of chronic liver disease and early requirement for liver transplant.

The emergence of next-generation sequencing has considerably reduced the time for diagnosis from several weeks to days, making a speedy diagnosis on a molecular basis for different causes which cannot be determined from blood tests or liver biopsy.

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LIMITATION OF THE STUDY

The major limitation in this research has been the non-availability of genetic test facilities to determine the aetiology of NC in the hospital where the study was conducted. Further, the lack of facility to check the level of various enzymes, e.g. galactose-1-phosphate uridylyltransferase (GALT) enzymes in RBCs and alpha one antitrypsin, has also limited the scope of this study. The provision of these facilities will enable clarity on the spectrum of neonatal cholestasis in future studies.

CONCLUSIONS

The most common aetiology of extrahepatic Neonatal Cholestasis was Biliary Atresia, while Idiopathic Neonatal Hepatitis and Progressive Familial Intrahepatic Cholestasis were the most common causes of intrahepatic cholestasis. A significant number of malnourished infants is an important indicator of the overall health status of infants. Further, significant delays occur in primary care health centres in referral for diagnosing NC at tertiary care hospitals, which affects the outcome of the primary disease.

Conflict of Interest: None.

Author's Contribution

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

SA & FI: Conception, study design, drafting the manuscript, approval of the final version to be published.

SZS, JA & RP: Data acquisition, data analysis, data interpretation, critical review, 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. Bansal S, Dhawan A. Neonatal cholestasis syndrome-the saga continues. Indian Pediatr 2000; 37(8): 827-830.
2. Hartley J. The jaundiced baby. Atlas of Pediatric Hepatology. Cham: Springer; 2018.
3. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, 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. https://doi.org/10.1097/mpg.0000000000001334
4. Feldman AG, Sokol RJ. Neonatal Cholestasis. Neoreview 2013; 14(2): 10. https://doi.org/10.1542/neo.14-2-e63
5. Moyer V, Freese DK, Whitington PF, Olson AD, Brewer F, Colletti RB, et al. Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2004; 39(2): 115-128. https://doi.org/10.1097/00005176-200408000-00001
6. Ghazy RM, Khedr MA. Neonatal cholestasis: recent insights. Egyptian Pediatr Assoc 2019; 67(1): 1-4. https://doi.org/10.1186/s43054-019-0009-3
7. Jeyaraj R, Bounford KM, Ruth N, Lloyd C, MacDonald F, Hendriksz CJ, et al. The genetics of inherited cholestatic disorders in neonates and infants: evolving challenges. Genes 202; 12(11): 1837. https://doi.org/10.3390/genes12111837
8. Santos Silva E, Almeida A, Frutuoso S, Martins E, Valente MJ, Santos-Silva A, 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: 351. https://doi.org/10.3389%2Ffped.2020.00351
9. Pandita A, Gupta V, Gupta G. Neonatal cholestasis: a pandora's box. clinical medicine insights: Pediatr 2018: 1-6: https://doi.org/10.1177/1179556518805412.
10. Rafeey M, Golzar A, Javadzadeh A. Cholestatic syndromes of infancy. Pak J Bio Sci 2008; 11(13): 1764-1767. https://doi.org/10.3923/pjbs.2008.1764.1767
11. Benzamin M, Khadga M, Begum F, Rukunuzzaman M, Mazumder MW, Lamia KN. Etiologies of neonatal cholestasis at a tertiary hospital in Bangladesh. Paediatr Indonesia 2020; 60(2): 67-71. https://doi.org/10.14238/ pi60.2.2020.67-71
12. Karim AS, Kamal M. Cholestatic jaundice during infancy: experience at a tertiary-care center in Bangladesh. Indian J Gastroenterol 2005; 24(2): 52-54.
13. Najafi M, Khodadad A, Khatami G, Farahmand F, Falahi G, Motamed F, et al. Prevalence of different etiology in neonatal cholestasis. Iran J Pediatr 2006; 16(3): 289-294.
14. Shahraki T, Miri-Aliabad G, Shahraki M. Frequency of different causes of infant cholestasis in a tertiary referral center in South-East Iran. Iran J Pediatr 2018; 28(5): e65409. https://doi.org/10.5812/ijp.65409
15. Aanpreung P, Laohapansang M, Ruangtrakool R, Kimhan J. Neonatal cholestasis in Thai infants. J Med Assoc Thai 2005: 188(Suppl 8): S9-15.
16. Mahmud S, Gulshan J, Parvez M, Tasneem F, Ahmed SS. Aetiology and outcome of neonatal cholestasis: an experience in a tertiary centre of Bangladesh. Egypt Liver J 2022; 12(1): 11. https://doi.org/10.1186/s43066-021-00168-7
17. Hoerning A, Raub S, Dechêne A, Brosch MN, Kathemann S. Diversity of disorders causing neonatal cholestasis – the experience of a tertiary pediatric center in Germany. Front Pediatr 2014; 2: 65. https://doi.org/10.3389/ fped.2014.00065
18. Lane E, Murray KF. Neonatal cholestasis. Pediatr Clin 2017; 64(3): 621-39. https://doi.org/10.1016/j.pcl.2017.01.006