

Original Research Article

ETIOLOGICAL PROFILE OF NEONATAL CHOLESTASIS: A PROSPECTIVE OBSERVATIONAL STUDY FROM A TERTIARY CARE CENTRE IN KASHMIR, INDIA

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ABSTRACT

Background: Neonatal cholestasis (NC) is defined as conjugated hyperbilirubinemia in the newborn and represents an important cause of chronic liver disease in infancy. Early identification of etiology is critical, as certain causes—particularly biliary atresia (BA)—require urgent surgical intervention. Data on the etiological spectrum of NC from the Kashmiri population in northern India remain limited. The objective is to study the etiological profile of neonatal/infantile cholestasis at a tertiary referral paediatric centre in Kashmir, India.

Materials and Methods: A prospective observational study was conducted over 18 months at GB Pant Children's Hospital, GMC Srinagar. Forty infants (up to 1 year of age) with neonatal cholestasis were enrolled. Detailed clinical history, physical examination, laboratory investigations (liver function tests with gamma-glutamyl transpeptidase [GGT], thyroid function, metabolic screening), abdominal ultrasonography, hepatobiliary scintigraphy (HIDA scan), liver biopsy, and clinical exome sequencing (where indicated) were performed.

Results: Of 40 infants, 22 (55%) were male and 18 (45%) were female (M:F = 1.2:1). The mean age at presentation was 68 ± 12.4 days overall. Biliary atresia was the commonest cause (n=14, 35%), followed by progressive familial intrahepatic cholestasis (PFIC; n=12, 30%). Other diagnoses included Alagille syndrome (5%), bile acid synthetic defect (5%), hemophagocytic lymphohistiocytosis (5%), and transient neonatal cholestasis (5%). Eleven cases (27.5%) had a confirmed genetic etiology on clinical exome sequencing; novel pathogenic variants were identified in ATP8B1, ABCB11, and TJP2 genes. A mean diagnostic delay of 30 days was observed across all diagnostic categories.

Conclusion: Biliary atresia remains the leading cause of neonatal cholestasis in this Kashmiri cohort. A notably high prevalence of PFIC (30%)—attributed to high rates of consanguineous marriage—and novel genomic variants highlights the importance of genetic workup in this population. Persistent acholic stools and post-prandial gallbladder ultrasonography are practical discriminating features that should prompt early specialist referral.

Keywords: Neonatal cholestasis; biliary atresia; progressive familial intrahepatic cholestasis; conjugated hyperbilirubinemia; genetic liver disease; Kashmir; India.

INTRODUCTION

Neonatal cholestasis (NC) is defined as conjugated hyperbilirubinemia occurring in the newborn as a consequence of diminished bile flow. Conjugated

hyperbilirubinemia is defined as a serum direct/conjugated bilirubin concentration greater than 1.0 mg/dL when the total serum bilirubin (TSB) is <5.0 mg/dL, or greater than 20% of TSB when TSB is >5.0 mg/dL.^[1]

Unlike physiological jaundice—a common and mostly benign self-limited phenomenon resolving within two weeks—NC is never benign and invariably signals a severe underlying hepatobiliary, metabolic, infectious, or genetic disorder⁽²⁾. NC affects approximately 1 in 2,500 infants in Western populations and constitutes 19–33% of all chronic liver diseases in children referred to tertiary care hospitals in India.^[3,4]

The clinical consequences of untreated cholestasis are significant. Impaired bile flow leads to accumulation of bile components in the liver and extrahepatic tissues, malabsorption of fat-soluble vitamins (A, D, E, K), failure to thrive, cirrhosis, portal hypertension, and end-stage liver disease.^(5,6)

The rapid identification of biliary atresia (BA) is of particular urgency: hepatoportoenterostomy (Kasai procedure) performed before 60 days of age is associated with substantially better long-term bile drainage and reduced need for early liver transplantation compared to later surgery.^[7,8]

The etiological spectrum of NC varies with geography. While idiopathic neonatal hepatitis was historically the most common diagnosis in Western centres, improved diagnostic capabilities have reduced this category significantly.^[3,9] In Asia and India, biliary atresia and genetic causes including PFIC are prominent.^[10,11] Kashmir, with its well-documented tradition of consanguineous marriages, may have a distinct genetic predisposition to inherited cholestatic conditions, yet published data from this region are limited.^[12,13]

The present study was undertaken to prospectively characterize the etiological profile of NC in infants admitted to a tertiary care paediatric hospital in Srinagar, Kashmir, with particular attention to genetic causes and diagnostic delays.

MATERIALS AND METHODS

Study Design and Setting: A prospective observational study was conducted at the Postgraduate Department of Pediatrics, GB Pant Children's Hospital—an associated hospital of Government Medical College, Srinagar, Kashmir, India—over a period of 18 months. Ethical clearance was obtained from the Institutional Ethics Committee, and written informed consent was obtained from parents/guardians of all enrolled infants.

Participants: Forty newborn infants up to one year of age admitted with neonatal cholestasis were enrolled by non-probability purposive sampling.

Inclusion criteria

Infants presenting with (i) icterus with acholic stools; (ii) icterus with high-coloured (dark) urine; or (iii) laboratory evidence of cholestasis (conjugated bilirubin >1.0 mg/dL if TSB <5.0 mg/dL, or >20% of TSB if TSB >5.0 mg/dL).

Exclusion criteria

Age >1 year; refusal of parental consent.

Clinical Assessment: A standardized questionnaire captured detailed antenatal, perinatal, and postnatal history, including family history of cholestasis, consanguinity, stool and urine colour, and nutritional history. Physical examination—with particular attention to scleral icterus, stool colour, hepatomegaly, splenomegaly, dysmorphic features, and neurological status—was recorded at admission and followed daily.

Laboratory Investigations: All infants underwent complete blood count, liver function tests (total and direct bilirubin, alanine aminotransferase [ALT/SGPT], aspartate aminotransferase [AST/SGOT], alkaline phosphatase [ALP], gamma-glutamyl transpeptidase [GGT], prothrombin time), thyroid-stimulating hormone (TSH), and urine testing for non-glucose reducing substances (Benedict's test). Where indicated, TORCH serology, galactose-1-phosphate uridylyltransferase (GALT) assay, serum ferritin, triglycerides, fibrinogen, and tandem mass spectrometry/gas chromatography-mass spectrometry (TMS/GCMS) of urine and stool were performed.

Imaging: Fasting abdominal ultrasonography (USG) was performed in all infants, with post-prandial gallbladder assessment to evaluate contraction. Hepatobiliary scintigraphy (HIDA scan) was performed after intravenous administration of 3 mCi of mebrofenin (BrIDA) following phenobarbitone pre-treatment (5 mg/kg/day orally in two divided doses for ≥5 days). Absence of radiotracer in the small bowel at 24 hours was defined as absent excretion.^[4,14]

Liver Biopsy: Percutaneous liver biopsy was performed in infants with prolonged prothrombin time that corrected with parenteral vitamin K and in cases where parental consent was obtained. Histological examination focused on ductal proliferation, bile plugs, portal fibrosis, hepatocyte necrosis, giant cell transformation, and ductopenia.

Genetic Testing: Clinical whole-exome sequencing (clinical exome) was performed in infants with a suspected genetic aetiology, particularly those with a history of consanguinity, recurrent cholestasis of pregnancy, or atypical biochemical profiles (e.g., normal GGT with elevated bile acids).^[15,16]

Statistical Analysis: Data were recorded in Microsoft Excel and analysed using SPSS version 23. Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean ± standard deviation (SD) or median with interquartile range. Group comparisons for continuous variables used ANOVA; chi-square test was used for categorical comparisons. A p-value <0.05 was considered statistically significant.

RESULTS

Demographic Profile: A total of 40 infants were included. Of these, 22 (55%) were male and 18 (45%) were female (M:F ratio 1.2:1). The overall mean age

at presentation was 68 ± 12.4 days. Biliary atresia patients presented earlier (mean 50 ± 14.8 days) compared to intrahepatic cholestasis (IHC) patients (mean 80 ± 10.2 days).

Etiological Profile: Biliary atresia (BA) was the most common aetiology, accounting for 14 cases (35%), followed by progressive familial intrahepatic cholestasis (PFIC) in 12 cases (30%). The remaining diagnoses are detailed in [Table 1].

Table 1: Etiological Profile of Neonatal Cholestasis (n=40)

Etiology	No. of Patients (n)	Percentage (%)
Biliary Atresia	14	35.0
Progressive Familial Intrahepatic Cholestasis (PFIC)	12	30.0
Alagille Syndrome	2	5.0
Bile Acid Synthetic Defect	2	5.0
Hemophagocytic Lymphohistiocytosis (HLH)	2	5.0
Transient Neonatal Cholestasis	2	5.0
Bile Acid Malabsorption	1	2.5
Congenital Hepatic Fibrosis	1	2.5
Paucity of Intrahepatic Bile Ducts (PILBD, non-syndromic)	1	2.5
Neonatal Hemochromatosis	1	2.5
Niemann-Pick Disease (Type C)	1	2.5
Galactosemia	1	2.5
Total	40	100.0

Genetic Diagnoses: Eleven infants (27.5%) received a confirmed genetic diagnosis on clinical exome sequencing. PFIC was the most frequent genetic category (5 cases), with mutations identified in ABCB11 (PFIC2, n=3), ATP8B1 (PFIC1, n=1), and TJP2 (PFIC4/familial hypercholanemia, n=1). Three novel pathogenic variants were identified: a truncating variant in ATP8B1 (p.Thr732Ala), a truncating variant in ABCB11 (p.Val195Met), and a heterozygous splice-donor variant in TJP2. Additional genetic diagnoses included bile acid

synthetic defects (HSD3B7 mutation—CBAS1; ACOX2 mutation—CBAS6), bile acid malabsorption (SLC10A2 heterozygous variant), familial HLH (STXBP2 homozygous missense variant), Niemann-Pick type C (NPC1 mutation), and Alagille syndrome (NOTCH2 heterozygous variant). Consanguinity was present in all 9 patients with homozygous variants.

Sex Distribution: Among BA cases, sex distribution was equal (7 males, 7 females). Among IHC cases, 15 (57.7%) were male and 11 (42.3%) were female.

Table 2. Sex Distribution by Diagnosis Category

Sex	Biliary Atresia n (%)	IHC n (%)	Total
Male	7 (50.0)	15 (57.7)	22
Female	7 (50.0)	11 (42.3)	18
Total	14	26	40

Age at Presentation and Diagnostic Delay: The mean age at onset of jaundice in BA was 20.1 ± 2.7 days, with mean age at admission of 50 ± 14.8 days, yielding a mean diagnostic delay of 30 days. In IHC, the mean age at onset was 50 ± 2.8 days, with mean age at admission of 80 ± 10.2 days—again a 30-day delay.

Clinical Features: Jaundice and dark urine were present in all 40 cases (100%). Persistent acholic stools were pathognomonic of BA (100% sensitivity, 100% specificity in this cohort), while intermittent acholic stools were universal in IHC. Hepatomegaly was present in all BA cases (100%) with a firm-to-hard consistency, compared to 33% of IHC cases. Splenomegaly occurred exclusively in IHC cases (25%). Coagulopathy was identified in 1 IHC case (3%).

Biochemical Profile: In BA, mean total serum bilirubin was 12.8 ± 3.6 mg/dL, SGOT 320 ± 80 U/L, SGPT 310 ± 97 U/L, and GGT markedly elevated at 410 ± 121 U/L. In PFIC, mean bilirubin was 14.8 ± 2.6 mg/dL, SGOT 306 ± 90 U/L, SGPT 290 ± 79 U/L, but GGT was characteristically low (48 ± 31 U/L), consistent with PFIC1 and PFIC2 subtypes.

Ultrasonography: All BA infants showed a small or absent gallbladder with non-visualized biliary channels and absent post-prandial gallbladder contraction. All IHC infants demonstrated a normal gallbladder with patent biliary channels and normal post-prandial contractility.

Liver Biopsy: Liver biopsy was performed in 30 infants. All 14 BA cases showed characteristic ductular proliferation, bile plugs, and intraportal fibrosis with preserved lobular architecture. The 16 IHC biopsies demonstrated inflammation, hepatocyte necrosis, giant cell transformation, and variable degrees of fibrosis. Biopsy was deferred in 10 infants due to prolonged prothrombin time or parental refusal.

DISCUSSION

This prospective study provides a comprehensive etiological characterisation of NC in a Kashmiri paediatric population and highlights several regionally important findings.

Biliary Atresia: BA remained the commonest single diagnosis (35%), consistent with data from other

Indian tertiary centres (25–41%)^[4,11,17] and comparable to reports from Bangladesh (47.4%),^[10] Germany (41%),^[18] and Thailand (11.5–22.2%).^[19,20] BA presented earlier than IHC (mean 50 vs. 80 days), but a 30-day delay from onset of jaundice to admission was noted—a persistent problem reported across South Asia.^[2,13] Early referral, guided by the universally present triad of persistent acholic stools, hepatomegaly, and elevated GGT, is critical since Kasai portoenterostomy before 60 days of age offers the best long-term outcome.^[7]

Progressive Familial Intrahepatic Cholestasis: The high prevalence of PFIC (30%) in this cohort markedly exceeds figures from most published series (typically 10–15%)⁽¹⁶⁾ and likely reflects the high background rate of consanguinity in the Kashmiri Muslim population. Consanguinity was documented in 75% of PFIC patients. A low or normal GGT with high bilirubin and pruritus should prompt early genetic evaluation in this setting.^[16,21] Novel variants in ATP8B1, ABCB11, and TJP2 identified in this study expand the known mutational spectrum of PFIC in Indian patients, supporting the hypothesis that PFIC variants in the North Indian Kashmiri population differ from those in Caucasian populations.^[15]

Genetic Diagnoses: Overall, 27.5% of infants had a confirmed genetic aetiology, underscoring the clinical utility of whole-exome/clinical exome sequencing in unexplained neonatal cholestasis, particularly in consanguineous families.^[15] Genetic diagnoses spanned multiple pathways: bile salt transport (PFIC),^[16,21] bile acid synthesis (CBAS1, CBAS6),^[22] intracellular lipid trafficking (NPC1),^[23] and tight-junction proteins (TJP2).^[24]

Comparison with Published Literature: The etiological distribution in this study differs from Western series, in which TPN-associated cholestasis and idiopathic neonatal hepatitis are more prominent, reflecting differences in neonatal intensive care practices and genetic background.^[9,20] The absence of idiopathic neonatal hepatitis as a major category in our cohort may partly reflect improved genetic diagnostic yield from clinical exome sequencing.^[15]

Diagnostic Delay: The consistent 30-day delay between symptom onset and admission observed for both BA and IHC is clinically important.^[25] Acholic stool colour cards, post-prandial gallbladder ultrasound, and fractionated bilirubin measurement at the 2-week visit are feasible primary care interventions that could substantially reduce this delay.^[26]

CONCLUSION

Biliary atresia is the most common cause of neonatal cholestasis in this Kashmiri cohort, with a notably high prevalence of PFIC reflecting regional consanguinity. A genetic aetiology was confirmed in over one quarter of infants, with novel variants identified in key cholestatic genes. Persistent acholic

stools and characteristic post-prandial gallbladder ultrasonographic findings are practical clinical discriminators accessible to primary care providers. Standardised stool-colour card programmes and fractionated bilirubin assessment at the 2-week visit are recommended to reduce the 30-day diagnostic delay documented in this study. Future studies with larger sample sizes and whole-genome sequencing will be needed to fully characterise the genetic landscape of PFIC and other inherited cholestatic conditions in this population.

Limitations: The principal limitations of this study are the modest sample size (n=40) imposed by the 18-month postgraduate study period, the absence of long-term follow-up outcomes data, and the unavailability of whole-genome sequencing for non-coding and intronic variant detection. Selection bias inherent to a tertiary referral centre may over-represent complex and rare diagnoses.

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