Research Article

Clinico-etiological Spectrum of Neonatal Cholestasis in the Era of Next Generation Sequencing

Sumit Kumar Singh, Apurva Kawdiya, Gunjan Kela, Priyam Jain*

Background: Neonatal cholestasis (NC) is a complex condition that poses a diagnostic challenge to paediatricians. A significant proportion of NC patients remain idiopathic even after a detailed evaluation. However, with the availability of next-generation sequencing (NGS), the etiological spectrum is changing through the identification of more genetic and metabolic disorders. This study aimed to identify the aetiology and outcomes of NC using NGS.

Method: A prospective cohort study was conducted at the Department of Pediatrics in a tertiary care centre in central India from April 2021 to September 2023. Infants from birth through 1 year of age presenting with cholestasis were included. Details of their history, clinical examinations, and investigations including NGS were recorded in a study proforma.

Result: A total of 106 infants were included, of whom 62 (58%) were male. Biliary atresia was the most common cause, identified in 33 (31%) children, followed by preterm multifactorial causes in 21 (20%) children. NGS was performed on 16 children, and disease-causing mutations were identified in 13 (81%) of them [homozygous in 10 (62.5%), heterozygous in 3 (18.75%), and no mutation in 3 (18.75%)]. A small proportion of patients were found to have idiopathic NC [18 (17%)] and transient neonatal cholestasis [15 (14%)].

Conclusion: Biliary atresia remains the most common cause of NC. A meticulous workup is required to ascertain other causes of the condition. NGS can help identify the causes of NC, providing a definitive diagnosis that aids in determining treatment and prognosis

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Introduction

Neonatal cholestasis (NC) is defined as a prolonged elevation of conjugated bilirubin beyond 14 days of life, specifically where the conjugated fraction exceeds 20% of the total bilirubin. The incidence of neonatal cholestasis ranges from 1 in 2,500 to 5,000 live births [1].

Globally, NC is increasingly recognized as a major cause of chronic liver disease in infants and young children, accounting for nearly 30% of paediatric hepatobiliary diseases that result in infant morbidity and mortality [2]. It encompasses a wide spectrum of clinical conditions, including congenital malformations of the hepatobiliary tree, infections, and inborn errors of metabolism. Early and accurate diagnosis is essential for good clinical outcomes. For instance, the prognosis of biliary atresia depends heavily on the timing of surgical intervention, as delayed diagnosis significantly worsens the outcome. Consequently, a systematic diagnostic approach is key to achieving a rapid diagnosis so that specific, often life-saving therapies can be promptly initiated.

The etiological spectrum of this condition is changing rapidly. Although biliary atresia remains the primary cause of NC across various studies, the proportion of idiopathic hepatitis cases is decreasing due to the increasing recognition of underlying genetic and metabolic disorders [3]. A recent position paper on diagnostic approaches for infants with cholestatic liver diseases by the Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition (FISPGHAN) also emphasized the critical need for genetic testing [4]. Furthermore, preterm birth rates and survival outcomes are constantly rising. In these infants, prolonged neonatal intensive care unit stays and exposure

Department of Pediatrics, Sri Aurobindo Medical College and Postgraduate Institute, Indore, Madhya Pradesh, India

Correspondence to: Apurva Kawdiya, Department of Pediatrics, Sri Aurobindo Medical College and Postgraduate Institute, Indore, Madhya Pradesh, India. E-mail: apurvakav13@gmail.com

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to factors such as sepsis, total parenteral nutrition (TPN), and various medications have established the "preterm multifactorial" group as another critical cause of NC.

Given this evolving landscape, the primary objective of this study was to evaluate the etiological spectrum of NC by integrating advanced genetic testing in form of next-generation sequencing. The secondary objective was to analyze the clinical outcomes associated with the various causes of neonatal cholestasis.

Materials and Methods

This prospective cohort study was conducted in the Department of Pediatrics at a tertiary care centre in central India from April 2021 to September 2023. Infants from birth through 1 year of age diagnosed with cholestasis in either the inpatient or outpatient departments were included. Cholestasis was defined as a serum direct bilirubin level >1 mg/dL if the total bilirubin was <5 mg/dL, or >20% of the total bilirubin if the total bilirubin was >5 mg/dL [2]. Demographic data, clinical history, examination findings, investigations, and outcome data were recorded on a predesigned proforma and analyzed. All children were evaluated by an experienced pediatric gastroenterologist.

The diagnostic workup for infants with NC was divided into two tiers. All participants underwent Tier 1 investigations, which comprised a complete blood count, liver function tests including gamma-glutamyl transferase (GGT) levels prothrombin time, thyroid-stimulating hormone levels, and an abdominal ultrasound. Tier 2 investigations were individualized based on the likely etiology suggested by Tier 1 results, as well as test availability and cost. These secondary investigations included a sepsis screen (comprising blood and urine cultures), metabolic screen (arterial blood gas, blood sugar, lactate, ammonia, urinary ketones, urine for non-glucose reducing substances, urine gas chromatography-mass spectrometry, and blood tandem mass spectrometry), serum alpha-fetoprotein (AFP), serum ferritin, Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes Simplex Virus (TORCH) IgM serology, skeletal X-rays, 2D-echocardiography, next-generation sequencing (NGS), and liver biopsy. NGS was planned for a subset of patients with advanced liver disease presenting with coagulopathy, ascites, and failure to thrive. Additional inclusion criteria included a history of parental consanguinity, unexplained or liver-disease-related sibling death, and an otherwise inconclusive diagnostic workup.

Clinical outcome measures were defined as follows:

Resolved cholestasis

Complete resolution of icterus and normalization of liver function tests.

Persistent cholestasis

Persistence of icterus and elevated serum bilirubin with no decreasing trend by the last follow-up.

Resolving cholestasis

A decreasing trend in icterus and bilirubin levels, without reaching complete normalization by the last follow-up.

Written informed consent was obtained from the parents or legal guardians of each study subject. The study protocol was approved by the Institutional Ethics Committee (RC/IEC/2021/87).

Statistical analysis

Descriptive statistics were used to summarize the features and characteristics of the collected data. Continuous variables are presented as medians and ranges. All statistical analyses were performed using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 106 infants were included in the present study, of whom 62 (58.5%) were male. The mean age at presentation was 2.3 months, and the median follow-up duration was 14 months (range: 1–22). Sixty-four children (60%) presented with pale stools, while the remaining 42 (40%) had pigmented stools. The etiologies of NC are summarized in Table 1.

Biliary atresia (BA) was diagnosed in 33 of the 64 children who presented with pale stools, representing the most common cause of NC in the present study (31%). Of the 33 children diagnosed with BA, only 14 (42%) presented before 2 months of age, and 7 of these underwent Kasai portoenterostomy (KPE). Following surgery, cholestasis resolved in three of these seven children over a median follow-up of 3 months. The remaining four children had persistent cholestasis over a median follow-up of 9 months (range: 4–14).

Preterm birth was the second most common etiology in our cohort, affecting 21 infants. All 21 preterm infants presented with concomitant sepsis, and TPN was administered to 8 (38%) of them. While 11 (52%) of these children initially presented with pale stools, treatment with ursodeoxycholic acid (UDCA) resulted in a complete transition to pigmented stools in all cases. Cholestasis successfully resolved in all 21 infants, with a median

Table 1: Etiologies of neonatal cholestasis

Etiology	*Number of patients (n=106)*
Biliary atresia	33 (31%)
Pre-term multifactorial	21 (20%)
Transient neonatal cholestasis	15 (14%)
Genetic disorders	13 (12%)
Idiopathic	18 (17%)
Sepsis	5 (5%)
Metastasis to liver	1 (1%)

time to resolution of 1.5 months (range: 1–3). There was no recurrence of cholestasis at a median follow-up of 3 months (range: 2-5).

A genetic etiology, including inherited metabolic disorders, was suspected in 31 infants. These children exhibited a more severe clinical presentation characterized by failure to thrive in 21 (68%) and uncorrectable coagulopathy in 22 (71%). A history of consanguineous marriage was present in 16 (52%) cases, and previous unexplained or liver disease-related sibling death occurred in 6 (19%) infants. However, due to financial constraints, only 16 children underwent NGS. Of these, 10 (62.5%) had a definitive genetic diagnosis, and 3 (18.8%) harbored a heterozygous mutation for an autosomal recessive disorder matching their clinical phenotype, as summarized in Table 2. No pathogenic variants were identified in the remaining 3 (18.8%) children.

The infant diagnosed with galactosemia was started on a galactose-free formula, resulting in the resolution of cholestasis within 2 months and cataracts within 7 months; the child remained asymptomatic throughout 15 months of follow-up. Three children (one with progressive familial intrahepatic cholestasis (PFIC) type 4 and two with PFIC type 7) showed an excellent response to UDCA, achieving complete resolution of cholestasis. Conversely, the infant with Alagille syndrome showed a reduction in jaundice, but pruritus remained poorly controlled during 5 months of follow-up. Five children with advanced presentation died after their families declined liver transplantation. Among the three children with a heterozygous mutation, cholestasis resolved by 6 months of age in two infants, who were subsequently classified as having transient neonatal cholestasis. The third child developed progressive liver disease and was referred for liver transplantation. A flowchart showing the evaluation pathway of neonatal cholestasis and indications for NGS testing is shown in Figure 1.

Consequently, 18 (17.0%) infants (comprising 15 who did not undergo genetic testing and 3 with a negative NGS yield) were classified as having an idiopathic etiology of NC. Of these 18 children, 4 died from advanced liver disease, while the remaining 14 had persistent cholestasis at a median follow-up of 3.5 months (range: 1.5–6).

A total of 15 (14%) clinically stable infants who presented with a mild phenotype and had an inconclusive initial etiological evaluation were followed conservatively. All 15 infants achieved complete resolution of cholestasis within a 6-month follow-up period, and this cohort was subsequently classified as having transient neonatal cholestasis (TNC). No recurrence of cholestasis was observed in this group over a median follow-up of 10 months (range: 8–14).

Culture-proven Gram-negative sepsis was identified as the etiology of NC in five term-born infants, all of whom presented within the first 3 months of life. Klebsiella pneumoniae was isolated from the blood culture of one infant, whereas Escherichia coli was isolated from the urine cultures of the remaining four infants. Cholestasis resolved completely in all five infants following targeted antibiotic therapy for sepsis. Additionally, one infant presented with neuroblastoma complicated by liver metastasis, which directly resulted in cholestasis.

Discussion

The present study prospectively evaluated 106 infants with NC at a single tertiary care center, with a male predominance (58.5%). The mean age at presentation was 2.3 months, consistent with findings from previous Asian cohorts [5-7]. Biliary atresia (BA) emerged as the most common etiology, accounting for nearly one-third of the cases (31.1%), which closely aligns with existing literature [5-7]. However, fewer than half of the infants with BA presented to our center before 2 months of age, underscoring a pervasive issue of delayed referral in the majority of patients. Thus, there is need for early detection

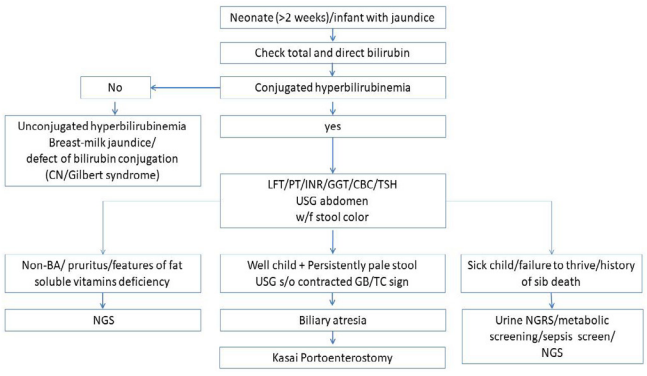

Figure 1: Flow chart for evaluation of neonatal cholestasis

Table 2: Genetic causes of neonatal cholestasis

S. No.	*Age/sex*	*Clinical presentation*	*Gene*	*Variant*	*Zygosity*	*Final diagnosis*	*Follow-up duration*	*Outcome*
1.	2m/M	Cholestatic Jaundice, Cataract	GALT+	C.958G>A (P.Ala320Thr) C.997C>T (P.Arg333Trp)	Homozygous	Galactosemia	15 months	Resolved cholestasis
2.	4m/M	Cholestatic Jaundice, failure to thrive, coagulopathy	CYP27A1+	C.1184+1g>A (5'splice Site) C.526 Del (P.Asp176metfster6)	Homozygous	Cerebrotendinous Xanthamatosis	2 months	Expired
3.	2m/M	Cholestatic Jaundice, ascites	ADK+	C.680T>C (P.Leu227Ser)	Homozygous	Hypermethionemia	7 months	Expired
4.	6m/F	Cholestatic Jaundice, Pruritus, Low GGT Levels	USP53+	C.829dup (P.Tyr277leufster2)	Homozygous	PFIC-7	11 months	Resolved cholestasis
5.	2m/M	Cholestatic Jaundice, Failure to thrive	AMAC (-)	C.779C>T (P.Thr260lle)	Homozygous	Congenital Defect In Bile Acid Synthesis -4	5 months	Expired
6.	11m/M	Cholestatic Jaundice, Pruritus, Low GGT	TJP2+	C.1796G>A (P.Arg599Gln)	Homozygous	PFIC-4	9 months	Resolved cholestasis
7.	2m/M	Cholestatic Jaundice, massive splenomegaly	NPC1 (-)	c.3591+1G>T (5' splice variant)	Homozygous	Niemann-Pick disease type C1 or type D	6 months	Expired
8.	5m/M	Cholestatic Jaundice, Pruritus, high GGT	JAG1	Chr20;g (10639956_10640782)_ (10664015_10672700)del	Heterozygous	Alagille Syndrome	5 months	Persistent cholestasis
9.	9m/F	Cholestatic Jaundice, Pruritus, low GGT	USP53(+)	c.144+4A>T (3'splice variant)	Homozygous	PFIC-7	14 months	Resolved cholestasis
10.	1m/M	Cholestatic Jaundice, failure to thrive, coagulopathy	CYP27A1(+)	c.785G>A (p.Arg262His)	Homozygous	Cerebrotendinous Xanthamatosis	1 month	Expired
11.	3m/M	Cholestatic Jaundice with low GGT	ABCB11 (-) KIF12 (-)	c.1694A>C (p.Gln565Pro) c.946C>T (p.Pro316Ser)	Heterozygous Heterozygous	PFIC-2 PFIC-8	11 months	Persistent cholestasis
12.	4m/M	Cholestatic Jaundice with Low GGT	ABCB11 (-) TJP2 (+)	c.720del (p.Lys240AsnfsTer2) c.2884A>G (p.Ile962Val)	Heterozygous Heterozygous	PFIC-2 PFIC-4; Familial hypercholanemia-1	3 months	Resolved cholestasis
13.	2m/M	Cholestatic Jaundice with low GGT	AMACR (-)	c.779C>T (p.Thr260Ile)	Heterozygous	Congenital defect in bile acid synthesis-4	5 months	Resolved cholestasis

Abbreviations: PFIC- progressive familial intrahepatic cholestasis; GGT- gamma-glutamyl transferase

and timely referral of BA for KPE to have good clinical outcome.

Premature infants constituted the second most common etiology in our study, accounting for approximately one-fifth (20%) of the total cohort. These infants possess an anatomically and functionally immature biliary tract, which intrinsically predisposes them to cholestasis. This is frequently compounded by a high incidence of sepsis—particularly Gram-negative infections—and the prolonged use of TPN, both of which further increases the risk of developing cholestasis. Notably, none of the preterm infants in our cohort exhibited clinical features of liver failure or hepatic decompensation. All preterm infants achieved complete resolution of cholestasis within 3 months of initiating medical management. This favorable outcome underscores the clinical importance of identifying this transient, benign etiology and preventing unnecessary, invasive diagnostic procedures. Similarly, all five full-term infants who developed cholestasis secondary to sepsis achieved complete resolution following targeted antimicrobial therapy. This signifies that infection-induced cholestasis carries an excellent prognosis once the infection is treated.

Genetic disorders, particularly inherited metabolic liver diseases, represent a critical subset of NC that demands urgent clinical evaluation and prompt treatment. In our cohort, the majority of infants suspected of having an underlying genetic etiology presented with severe phenotypes, characterized by failure to thrive, uncorrectable coagulopathy, reflecting significantly compromised hepatic synthetic function. Similarly, a history of parental consanguinity and previous liver disease-related or unexplained sibling deaths served as strong clinical indicators of an underlying metabolic or monogenic hepatic disorder.

Out of 16 infants who underwent NGS in our study, a definitive genetic diagnosis was found in 10 (62.5%), successfully establishing the underlying etiology. This diagnostic yield closely aligns with the findings of Nicastro et al., who reported a 60% detection rate utilizing an integrated clinical and genetic algorithm for infantile cholestasis [3]. Similarly, a comparable diagnostic yield of 61% was observed by in a cohort study from Saudi Arabia by Shagrani et al. [8]. The clinical imperative for early genetic testing is further underscored by the fact that five of the ten molecularly confirmed infants already presented with advanced, decompensated liver disease. Nonetheless, establishing a precise diagnosis remains vital to initiating life-saving, targeted therapies; for instance, the infant diagnosed with galactosemia achieved complete resolution of cholestasis simply after transitioning to a galactose-free formula.

Three infants in our cohort harbored heterozygous variants for autosomal recessive conditions that were phenotypically consistent with their clinical presentations. Interpreting heterozygous mutations in autosomal recessive disorders remains challenging, as patients often manifest vastly divergent clinical outcomes. This phenotypic heterogeneity is determined by two main phenomena: incomplete penetrance, wherein individuals carrying a pathogenic variant fail to develop clinical disease, and variable expressivity, where affected individuals show diverse disease severity and symptom profiles. Although the precise molecular mechanisms underlying this variability remain poorly understood, it is widely hypothesized to be driven by a complex interplay of modifier genes, specific mutation types, and epigenetic, hormonal, or environmental influences [9]. Furthermore, the clinical interpretation of single heterozygous variants can be confounded by the presence of another co-existing mutation that was missed in the NGS. Also, NGS possess inherent diagnostic limitations; they frequently fail to detect copy number variations (such as large-scale deletions or duplications), repeat expansions, structural chromosomal rearrangements, or pathogenic variants located deep within intronic or promoter regions. Intriguingly, two of our infants (Cases 11 and 12, Table 2) harbored a single heterozygous pathogenic variant in ABCB11, accompanied by an additional pathogenic variant in KIF12 and TJP2, respectively. These multi-locus findings support the emerging framework of digenic heterozygosity, a phenomenon increasingly documented across other hereditary disorders [10-12]. This theory is further supported by a recent case report identifying compound heterozygous digenic mutations in ABCB4 and ABCB11 in an infant presenting with low phospholipid-associated cholelithiasis (LPAC) and TNC, who achieved symptomatic resolution following UDCA therapy [13]. Indeed, TNC has been mechanistically linked to heterozygous pathogenic variants in critical bile acid transport genes, specifically ATP8B1, ABCB11, and ABCB4 [14]. Consistent with these reports, two of our three patients with heterozygous variants demonstrated complete clinical resolution and normalization of hepatic biochemical parameters. Conversely, the remaining infant developed progressive, end-stage liver disease and required referral for liver transplantation.

Overall, genetic conditions account for 25% to 50% of all NC etiologies, particularly following the exclusion of BA [3]. Early diagnosis guides targeted therapies in conditions such as galactosemia, tyrosinemia, bile acid synthesis defects, and select PFIC variants. It also predicts long-term clinical prognosis, and offers essential recurrence risk counseling—including prenatal diagnosis—for affected families. The recent FISPGHAN guidelines also recommend stratifying and prioritizing patients for advanced genetic testing in resource-limited clinical environments [4].

A small proportion of infants in our study (17%) exhibited persistent cholestasis despite an exhaustive diagnostic evaluation and were consequently classified as idiopathic. This subset of patients represents a key population that should ideally undergo NGS, as they may harbor underlying, unidentified genetic variants—further highlighting the critical diagnostic value of genetic testing in the workup of NC. Ultimately, our study demonstrated a high diagnostic yield of 62.5% for NGS among infants suspected of having a genetic etiology, emphasizing the robust clinical utility of this test.

The principal strengths of the present study include its prospective design and good sample size, particularly given the rare nature of the disease under investigation. Nonetheless, several limitations must be acknowledged. First, because this was a single-center, tertiary care-based study, possibility of an inherent referral bias cannot be entirely excluded. Second, this purely descriptive study lacked a comparison among various NC subgroups. Third, due to financial constraints, we were unable to perform NGS in all infants with NC who clinically required it. Furthermore, the standard turnaround time for NGS ranged from 3 to 4 weeks, occasionally missing the optimal clinical window for initiating the targeted medical therapies. Therefore, the development of rapid, highly cost-effective NGS panels is an urgent clinical necessity to maximize the real-world utility of genetic testing in NC.

In conclusion, biliary atresia remains the most common etiology of NC, particularly among infants presenting with persistent pale stools. However, a meticulous and systematic diagnostic workup is essential to accurately delineate alternative etiologies. Infants with underlying inherited metabolic liver diseases frequently exhibit advanced, severe clinical presentations. Next-generation sequencing serves as important tool in this diagnostic algorithm, providing definitive confirmation of genetic and metabolic causes which is vital to optimizing patient treatment and outcomes.

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Conflict of Interest

All authors declare that there is no conflict of interest.

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Author's Contribution

Sumit K Singh: Concept and design of study, interpretation of data, drafting and revising the article for important intellectual content and final approval of the version to be published.

Apurva Kawdiya: Concept and design of study, interpretation of data, revising the article for important intellectual content and final approval of the version to be published.

Gunjan Kela: Concept and design of study, revising the article for important intellectual content and final approval of the version to be published.

Priyam Jain: Concept and design of study, acquisition of data or analysis of data, drafting the article and final approval of the version to be published

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