

Clinical Spectrum and Etiological Profile of Infantile Cholestasis with low or normal gamma-glutamyl transferase at a North Indian Tertiary Care Centre

Sonali Singh¹, Sanjeev Kumar Verma², Manisha Verma², Prerna Priyadarshini³, Chanchal Rana⁴

¹Pediatrics Department, Saraswati Medical College, Uttar Pradesh, India, ²Pediatrics Department, King George Medical University, Lucknow, Uttar Pradesh, India, ³Pediatrics Department, Hind Institute of Medical Sciences, Ataria, Uttar Pradesh, India, ⁴Pathology Department, King George Medical University, Lucknow, Uttar Pradesh, India.

Abstract

Background: Low and normal γ -glutamyl transferase (GGT) cholestatic liver disorders have a very limited range of differential diagnoses and often require advanced tests for confirmation, posing challenges in diagnosis and management. Thus this study aimed to investigate the prevalence and contribution of low and normal GGT cholestatic disorders among children admitted to a tertiary care centre of Northern India. **Material and Methods:** This prospective observational study was conducted at a North Indian tertiary care centre between January 2020 and August 2021, and included children between 1–36 months with suspected hepatobiliary disorders. All infants with prolonged jaundice and elevated direct bilirubin levels were enrolled in the study. Children with vascular liver disease, indirect hyperbilirubinemia, or acute liver failure were excluded. Detailed clinical evaluation and relevant investigations, including imaging and liver biopsy when indicated, was performed. Data were analyzed using SPSS version 24, applying t-tests, Chi-square/Fisher's exact tests, and ANOVA where appropriate. **Results:** A total of 53 participants with cholestasis (mean age 6.8 ± 8.2 months; 66.7% male) were enrolled, and out of that 34% had low or normal GGT levels. Liver biopsy was performed in 12 cases, and one-third showed liver decompensation. Identified causes included biliary atresia (6), choledochal cysts (4), sepsis (5), TORCH infections (3), PFIC (6), and galactosemia (3), while 26 remained indeterminate. Among the low/normal GGT group, 5 infants showed features of PFIC1/2, 2 had galactosemia, and 11 were indeterminate. Genetic testing confirmed PFIC2 in one case. **Conclusion:** Low and normal GGT cholestatic liver diseases are the third most common cause of infantile cholestasis in Northern India, followed by infections and structural biliary disorders.

Keywords: γ -glutamyl transferase (GGT), hepatobiliary diseases, Northern India.

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INTRODUCTION

Cholestasis is defined as “reduced bile formation or flow, resulting in the retention of biliary substances within the liver normally excreted into bile and destined for elimination into the intestinal lumen”.^[1] The causes of infantile cholestasis in infants and children are myriad and vary according to the age of presentation. Biliary atresia (BA) and choledochal cysts (CC) remain the two most common surgical causes of infantile cholestasis. However, metabolic and genetic causes contribute to a broad spectrum of disorders, including progressive familial intrahepatic cholestasis (PFIC), galactosemia, tyrosinemia, alpha-1 antitrypsin deficiency (A1ATD), Niemann Pick disease type C (NPC), Wolman's disease, bile acid synthesis disorders (BASD), peroxisomal disorders, and mitochondrial respiratory chain defects. Other important causes are neonatal sepsis, paucity of intrahepatic bile ducts, and prolonged total parenteral nutrition.^[2] Worldwide neonatal cholestasis (NC) occurs in approximately 1 out of every 2,500 live births, with this incidence remaining nearly consistent between 1985 and 2017.^[1,3–13] In India, NC represents a significant burden, accounting for around 19–33% of all chronic liver disease

(CLD) cases in children.^[4,24] Therefore, every newborn with jaundice beyond 2 weeks of life, should be tested for cholestasis, with total and direct serum bilirubin levels. Gamma glutamyl transferase (GGT) is a microsomal enzyme, involved in secretory and absorptive activities, notably in the bile canaliculi and the brush border of renal tubules.^[5] GGT offers a distinct advantage over alkaline phosphatase (ALP), particularly when plasma ALP levels are elevated but the source of elevation is uncertain.^[6,7] GGT plays a crucial role in differentiating cholestatic liver disorders, particularly in the context of many genetic and metabolic disorders, channelopathies, biliary tract abnormalities,

Address for correspondence: Dr. Prerna Priyadarshini, Assistant Professor, Department of Pediatrics, Hind Institute of Medical Sciences, Ataria, Uttar Pradesh, India.

E-mail: premapriyadarshinisingh@gmail.com

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and infections.^[8,9] Interestingly, serum GGT levels in patients with PFIC and bile acid synthesis disorders are strangely low to normal.^[10,11] However, pediatric literature lacks clarity on the association between low or normal GGT levels and cholestatic liver disorders, as well as its role in uncovering hidden causes. Therefore, this study aimed to identify the prevalence and spectrum of cholestatic liver disorder with low or normal GGT in children admitted to a tertiary care centre of North India.

MATERIALS AND METHODS

This prospective observational study was conducted at a tertiary care centre in Northern India from January 2020 to August 2021. The study population included children from 1 month to 36 months of age, admitted to the department of paediatrics, who were clinically suspected of having hepatobiliary disease. Patients with jaundice beyond two weeks of life (increased direct fraction of bilirubin) with/without features of vitamin A, D, E, K deficiency, with/without firm hepatomegaly or splenomegaly on clinical examination was considered to have hepatobiliary disease. The exclusion criteria comprised children with vascular liver disease, those with indirect hyperbilirubinemia, and those presenting with acute liver failure. Ethical approval was obtained from the Institutional Ethics Committee (Ref: No. 102nd ECM IIB- Thesis/P97).

In all enrolled children, a detailed record of history, immunization, antenatal and perinatal events, dietary patterns, and clinical examination was done, followed by a battery of investigations to determine the aetiology of the disease. Ultrasonography and radionuclear scans were performed when necessary. Admitted children were managed as per consensus guidelines to manage neonatal cholestasis (30). New pediatric percentile for age for liver enzymes by Bussler et al, American association of study in liver disease, 2018, were used (12). Liver biopsy and histopathological examination were conducted in indicated cases.

In the absence of genetic testing, those with histopathologically confirmed PFIC were called PFIC (HPE), and others with low/normal GGT and clinically compatible cases were termed "indeterminate PFIC".

Sample size was calculated according to the formula (Daniel, 1999), where $(n=Z^2x(1-P)/d^2)$

The best known prevalence of infantile cholestasis is 1 per 2500, with 95% confidence level (α error=0.05) and precision of 5%, the calculated minimum required sample size was 59 which was rounded to 60 subjects.^[1,13]

Statistical Analysis: Data was analyzed using SPSS version 24 statistical software (Chicago II, USA). For continuous variables an independent "t" test was used. Chi square test or

Fisher exact test was used to compare the categorical variable. One way ANOVA test was used to compare the means of two or more independent samples simultaneously.

RESULTS

A total of 5338 children were admitted, and 62 were suspected to have hepatobiliary disorders. Seven of the 62 children were excluded due to declined consent, and 2 expired within 6 hours of hospital admission. Finally, the study included 53 patients with a mean age of 6.78 ± 8.08 months, of which 35 (66%) were male. Among these, 23 (43.4%) presented before 3 months of age, while only 6 out of 13 infants with a history of pale stools presented before 3 months of age. Out of the 53 patients, 18 (34%) had low/normal GGT levels, and 35 had high serum GGT levels. Clinical demographics showed that 52 (98.1%) patients had jaundice, 25 (47.2%) had skin/submucosal bleeds, 14 (26.4%) had pruritus, 13 (24.5%) had acholic or fluctuating stool colour, and 25 (16.3%) had a history of sepsis [Table 1]. Consanguinity was present in 3 (5.7%) subjects, while a history of antenatal pruritus was found in 5 (9.4%) subjects, 2 of whom had PFIC (genetically proven) and 3 had PFIC (HPE). Six patients (11.3%) were decompensated with ascites, and 2 out of these had hepatic encephalopathy at presentation. Four patients had dilated anterior abdominal wall veins at presentation reflecting clinical findings of portal hypertension. Other systemic examination findings are detailed in [Table 1].

When contrasting the low/normal GGT group to the high GGT infantile cholestasis group, the frequency of pruritus (8 vs. 6 cases) and low GGT levels (29.6 ± 9.2 vs. 194.9 ± 269.6) were statistically significant ($p = 0.033$ and 0.013 , respectively). Bilirubin, aspartate transaminase (SGOT), and alanine transaminase (SGPT) levels were higher in the high GGT group (7.19 ± 5 vs. 4.71 ± 2.45 , 281.8 ± 215.6 vs. 165.7 ± 171.9 , and 175.2 ± 150.8 vs. 99.7 ± 98.1 , respectively) but not statistically significant. Prothrombin time-INR and albumin levels were lower in the high GGT group (1.54 ± 0.55 vs. 2.19 ± 1.8 and 3.42 ± 0.66 vs. 3.62 ± 0.48 , respectively) but were also not statistically significant [Table 2]. When extrahepatic cholestasis (biliary atresia & choledochal cyst) group was compared with intrahepatic causes of infantile cholestasis, bilirubin, transaminases (SGOT & SGPT) were found to be increased and low GGT was statically significant. On ultrasonography absence/pseudo gall bladder, poor GB contractility post feed, abnormal dilatation and triangular cord sign was seen with biliary tree anomaly group however, altered echotexture of liver was found in the intrahepatic cholestasis group. Liver biopsy was possible in 12 cases and on histopathological examination the biliary tree anomaly group showed major findings of portal tract expansion or dilatation with bile plugging whereas the intrahepatic cholestasis group showed a variety of changes listed in [Table 3].

Table 1: Clinical profile of Infantile cholestasis children (n=53).

Clinical findings- History	Frequency	%
Acholic stools	11	22.6%
Fluctuating stools	2	3.8%
Lethargic	2	3.8%
Skin/mucosal bleeds	25	47.2%
Pruritis	14	26.4%
Fever	25	16.3%

Difficulty in breathing	7	13.2%
Seizure	2	3.8%
Jaundice	52	98.1%
Abdominal distension	9	16.9%
Altered sensorium	1	1.9%
Vomiting	9	16.9%
Diarrhea	4	7.6%
H/O consanguinity	3	5.7%
H/o antenatal pruritis	5	9.4%
Clinical Examination: Pallor	31	58.5%
Icterus	52	98.1%
Generalized edema	2	3.8%
B/L Cataract	1	1.9%
Subconjunctival hemorrhage	1	1.9%
Conjunctival xerosis	2	3.8%
Hepatomegaly or splenomegaly	50	94.3%
Free fluid in abdomen	6	11.3%
Dilated abdominal veins	4	7.5%
Abnormal heart sounds/ murmur	2	3.8%
Added respiratory sounds	5	9.4%
Irritable & bulging AF	3	5.7%

Table 2: Comparison of Clinical & laboratory characteristics of high GGT level patients with low/normal serum GGT level Infantile cholestasis patients.

	High GGT	Low/Normal GGT	P value
No of patients (n=53)	35	18	
Etiology	Biliary atresia-6, choledochal cyst-4, PFIC 3-1, Galactosemia- 1, Sepsis- 5, TORCH-3, Idiopathic-15	PFIC-5, galactosemia-2, Idiopathic- 11	
Age <1 year	31	18	0.287
Median age (months)	4.5 (1-48)	6.5 (1-36)	0.233
Males	23	13	0.631
Growth failure	28	12	0.285
Jaundice	35	17	0.341
Pale or fluctuating colour stools	13	0	0.008
Pruritis	6	8	0.033
Skin/mucosal bleed	15	10	0.381
Hepatomegaly	32	18	0.543
Splenomegaly	13	09	0.368
Vit A/D/E/K def	15	10	0.381
Lethargic/comatose/seizure/irritable	3	2	1.000
Laboratory findings			
	Mean	Mean	
Bilirubin total (mg/dl)	11.35±7.51	7.64±3.66	0.054
Bilirubin direct (mg/dl)	7.19±5.00	4.71±2.45	0.053
SGOT(IU/L)	281.80±215.64	165.7±171.9	0.054
SGPT(IU/L)	175.2±150.8	99.7±98.1	0.060
ALP(IU/L)	1043.3±701.7	892.2±411.8	0.405
GGT(U/L)	194.9±269.6	29.6±9.2	0.013
Albumin(gm/dl)	3.42±0.66	3.62±0.48	0.261
INR	1.54±0.55	2.19±1.80	0.053

Table 3: Comparison of Clinico-laboratory profile, radiological, histopathological features & outcome of children between structural malformations/extrahepatic & intrahepatic cholestasis (n=53).

	Structural Malformations/ Extrahepatic Cholestasis (N=10)	Intrahepatic Cholestasis (N=43)	P value
Etiology	6 BA 4 CC	5 sepsis 3 TORCH 6 PFIC 3 Galactosemia 26Indeterminate	NA
Age< 1 year	9	37	0.739
Age(median) months	7.9 (1-48)	6.5 (1-36)	0.236
Male gender	7	28	0.769
Growth failure	5	19	0.639
Jaundice	10	42	1
Pale colored stool	10	1	<0.001
Fluctuating stool	0	2	1
Pigmented stool	0	39	<0.001

Pruritis	1	13	0.191
Skin/mucosal bleed	5	20	0.842
Hepatomegaly	10	40	1
Splenomegaly	5	17	0.545
Vit A/D/E/K def	5	20	0.842
Lethargic/irritable/ Seizure/comatose	1	4	1
Labs	Mean	Mean	P Value
Bilirubin total	15.78±8.26	8.79±5.8	0.003
Bilirubin direct	9.35 ± 4.81	5.73±4.22	0.021
SGOT	392.26±242.84	207.5±184.91	0.01
SGPT	261.11±192.95	123.65±110.91	0.004
ALP	1563.88±774.2	859±499.29	0.001
GGT	273.7±456.48	107.41±128.91	0.04
Albumin	3.27±0.34	3.54±0.65	0.209
INR	1.47±0.53	1.83±1.26	0.384
Histopathological Examination (n=12)			
Portal tract dilatation	3	2	0.046
Bile plugs	2	1	0.127
Feathery degeneration	-	3	NA
Focal necrosis	-	5	NA
Ballooning degeneration	-	4	NA
Giant cells	-	4	NA
Extramedullary hematopoiesis	-	2	NA
USG findings	3-Triangular Cord Sign, 5- Non-Visualization of Gb/Small Gb, 1-Echogenic Tissues at Porta Hepatis, 1-Lack of Post Feed Gb Contraction Types of Choledochal Cyst F-1b, III, IVa, V	7- Coarse Liver Echotexture, 40- Hepatomegaly 17- Splenomegaly 4- Ascites 5-Cystitis 1-Portal Cavernoma	
Outcome	Alive-4 Expired-4 Loss to follow up-2	Alive-27 Expired-5 Loss to follow up-11	

(BA Biliary Atresia, CC Choledochal Cyst, TORCH Toxoplasmosis Rubella Cytomegalovirus Herpes Others, PFIC Progressive Familial Intrahepatic Cholestasis)

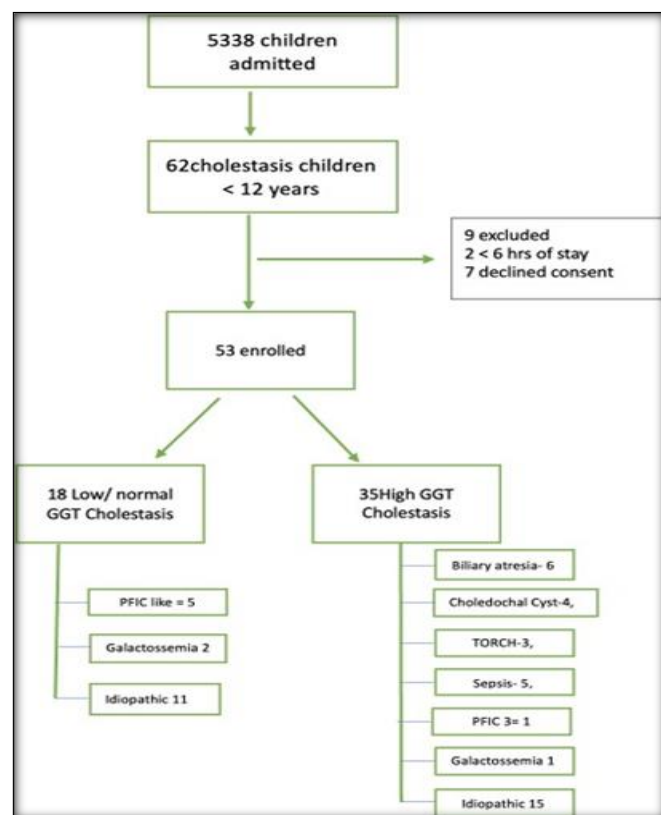


Figure 1: study flow chart

for India's healthcare system, accounting for 19–33% of all paediatric hepatobiliary disorders (4, 12). A prospective study conducted in Europe reported that the overall incidence of hepatobiliary disorders in the first year of life was approximately 1 per 2,500 live births, a figure that remained stable over time.^[13] Similarly, a hospital-based retrospective study from central India, spanning five years, found the prevalence of infantile cholestasis to be 1.2 cases per 1,000 patients.^[14] In our study, the prevalence of infantile cholestasis was 11.6 per 1,000 patients and the average age at which infants presented to the hospital was 6.78 ± 8.08 months, significantly higher than that reported in other Indian studies. This delay in presentation is alarming, particularly in cases of biliary atresia, where delay in diagnosis is significantly related to poor surgical outcomes.^[9] A study by Poddar et al. (2009) showed a reduction in the average age of presentation to 2.76 ± 1.67 months.^[15] The male-to-female ratio was 2.1:1 (67.9% male), consistent with other Indian studies, likely reflecting regional gender bias.^[14-16] Raising awareness among primary healthcare providers about the use of stool colour charts could help improve early detection of neonatal cholestasis.

In our study, amongst the 53 infantile cholestasis cases, 10 cases were diagnosed with surgical conditions including biliary atresia or choledochal cyst, 6 with PFIC (HPE), 5 with sepsis or infection, 3 with galactosemia, and 3 with TORCH infections, and 26 remained unidentified. A total of 19 PFIC indeterminate cases, including 6 diagnosed with PFIC, accounted for over one-third of the infantile cholestasis pool.

Worldwide, biliary atresia (BA) remains the leading cause of neonatal cholestasis, accounting for 35–41% of all infantile

DISCUSSION

Cholestatic liver disorders represent a significant challenge

cholestasis cases, followed by genetic and metabolic causes.^[17] Gotze et al. (2014) also observed that BA is the leading cause of NC, reported in 35–41% of the cases.^[18] A Bangladeshi study by Karim et al. reported BA in 42.5% and choledochal cysts in 7.5% of cases of neonatal cholestasis.^[19] Poddar & Jain also found BA in 34–41% of cases, reinforcing its prevalence in India, where it constitutes over one-third of neonatal cholestasis cases. Other notable intrahepatic causes include urinary tract infections, sepsis, and galactosemia.^[15] In the current study, 26 (49.1%) patients were classified as idiopathic; however, nearly half of these showed features suggestive of PFIC. Due to inconsistent histopathological findings and overlapping sepsis, they were grouped under an idiopathic group. Hence, the idiopathic group may shrink to 24.5% (n=13). In this study, following the indeterminate group, patients with low or normal GGT levels accounted for 34% of cases, most of whom exhibited features suggestive of PFIC. A total of 19 patients, 6 with histologically confirmed PFIC and 13 with PFIC-like characteristics based on clinical and laboratory features were classified under PFIC-like etiology. Histopathological confirmation was achieved in 6 out of the 12 liver biopsies performed.

The PFIC-like etiology group consisted of children with histologically confirmed PFIC and those with clinical and laboratory features consistent with PFIC.

Although the exact prevalence of PFIC is unknown, it is thought to affect between 1 in 50,000 to 1 in 100,000 newborns, with an equal impact on both genders [24]. Arora et al. (2010) performed a study on subjects aged 3 months to 15 years (n=410) and found that PFIC constituted 3.9% of all NC cases.^[25] A recent study from South India also reported 10% overall PFIC in NC cases.^[9] Chen et al. (2018) showed that among 135 Taiwanese infants with intrahepatic cholestasis, 14% had low/normal GGT PFIC, and 8% had elevated GGT.^[26] Agarwal et al. reported a PFIC prevalence of 8% among neonatal cholestasis cases and 34% in older children, with PFIC 1 presenting earlier (median age 3 months) than PFIC 2 (5.5 months).^[20]

In the current study, all 19 patients with a PFIC-like profile (low/normal GGT and/ favourable histopathology) presented with jaundice. Other common symptoms included skin or mucosal bleeding (57.9%), fever (52.6%), pruritus (52.6%), and hepatosplenomegaly (52.6%). Antenatal pruritus was noted in 26.3% of cases, and hepatic decompensation was present in 15.8% at the time of diagnosis. Growth failure was present in 10 out of 19 (52.6%) patients.

Agarwal et al. also reported growth failure in 18 out of 24 (75%) children, similar to our observation. Clinical or laboratory evidence of fat-soluble vitamin deficiency was present in 14 out of 24 (58%) children, while in our study, 66.7% of low or normal GGT cholestasis patients had fat-soluble vitamin deficiency.^[20]

Genetic studies by Wanty and Davit Spraul et al., involving 49 and 62 PFIC patients respectively, identified jaundice, pruritus, and hepatomegaly as the main clinical features as observed in our case. PFIC 1 and 2 typically presented at a median age of 2 months, while PFIC 3 appeared slightly later at 3 months. The primary clinical distinction among subtypes was the severity of pruritus. Davit-Spraul et al. (2010) found

that almost all PFIC patients with low GGT levels had pruritus with or without jaundice.^[22] Wanty et al. (2004) also found that pruritus was a major complaint of PFIC patients, with the only clinical variation between PFIC subtypes being the degree of pruritus.^[21] In our study, pruritus was prominently seen in patients with PFIC etiology, distinguishing PFIC from infective causes of cholestasis.

The studies conducted by Wanty and Davit Spraul et al., also emphasized that serum GGT levels and liver histology are useful in differentiating PFIC 3 from PFIC 1 and 2. Histological findings in PFIC cases included giant cell transformation, hepatocyte ballooning, and cholestasis, while PFIC 3 showed additional ductular proliferation, portal inflammation, and fibrosis.^[22] Agarwal et al. (2015) also found that HPE of low GGT PFIC patients had giant cell transformation, cholestasis, and fibrosis, whereas HPE of elevated GGT PFIC patients had ductular proliferation, cholestasis, and fibrosis.^[20] Wanty et al. (2004) found a similar histopathological pattern in patients with low and high GGT levels, respectively.^[21] Gaur et al. (2017) reported liver tissues provide useful insights for PFIC diagnosis. PFIC1 biopsies are characterized by a maintained lobular architecture and bland canalicular cholestasis without inflammation.^[23]

Children with cholestatic liver diseases are prone to sepsis and similarly sepsis can lead to cholestasis. Niazi et al. (2018) found that sepsis might cause an increased direct fraction of bilirubin in infancy, with UTI being the most common cause.^[4,27] *E. coli* is the leading organism causing sepsis related jaundice and gram negative pathogens are responsible for the majority of cases. The ATP-dependent transporter MDRP 2, part of the bile salt-independent bile export system, exhibits a marked decrease under oxidative stress caused by lipopolysaccharide (LPS) endotoxins from bacterial outer membranes, leading to cholestasis in urosepsis. Poor excretion leads to bile stasis and indirectly harms hepatocytes.^[28] Among our cohort of 53 patients, 2 were diagnosed with blood culture positive sepsis, while 6 presented with culture-positive urinary tract infections, with jaundice as the primary clinical symptom. The most frequently identified organisms in urine cultures were *Escherichia coli* and *Candida albicans*.

Poddar et al. (2009) reported that galactosemia contributes to 10.9% to the cholestatic pool and, together with sepsis, is one of the most important and prevalent causes of intrahepatic cholestasis in India.^[15] In our study, 3 patients (5.7%) were diagnosed with galactosemia and two out of these exhibited signs of hepatic decompensation. The strengths of this study included its prospective design, adequate sample size, and sufficient statistical power, along with well-defined inclusion and exclusion criteria. Currently, there are no established screening strategies to effectively categorize patients with infantile cholestatic disorders. A unique strength of this study lies in its approach to classify cholestatic disorders based on their gamma-glutamyl transferase (GGT) profile. It underscores the significance of serum GGT levels and their association with specific metabolic conditions, elevated in most cholestatic disorders, except in cases such as PFIC types 1 and 2 and bile acid synthesis defects (BASD). However, a major limitation of the study is its resource constrained setting, which restricted access to genetic testing (e.g., Next Generation Sequencing) and

comprehensive metabolic evaluations for all patients. As a result, a substantial proportion of cases remained of indeterminate etiology. Additional limitations of the study include potential bias and the inability to conduct long-term follow-up or serial monitoring of liver enzymes, cholestasis markers, and treatment response primarily due to poor patient compliance. A considerable number of cases remained unclassified or idiopathic. To better understand the diverse etiologies of infantile cholestasis and the genetic spectrum of cholestatic liver diseases associated with low and high GGT levels, further well-structured, population-based studies are essential.

What this study adds to:

- Low or normal gamma-glutamyl transferase (GGT) cholestasis in infants is predominantly attributable to genetically driven infantile cholestatic disorders.
- A high prevalence of low/normal GGT cholestatic disorders in the Indian subcontinent suggests a strong genetic predisposition to cholestasis in this population.

CONCLUSION

Low and normal GGT cholestasis constituted a substantial proportion of infantile cholestatic disorders in this North Indian cohort and was predominantly associated with PFIC-like or genetic etiologies. Serum GGT, combined with clinical features such like growth failure, pruritus and signs of fat-soluble vitamin deficiencies, can serve as a useful initial marker for identifying children who require evaluation for inherited cholestatic disorders. Early recognition of this biochemical phenotype may facilitate timely referral particularly in resource-poor settings. Larger multicentric studies are needed to define the etiological spectrum and establish the true burden of low or normal GGT cholestasis in Indian children.

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Conflicts of interest

There are no conflicts of interest.

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