Original Article

# Neonatal Cholestasis And Its Various Presentations And Approach To Diagnosis - A Case Series

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## Abstract

**Background:**

Neonatal cholestasis or conjugated hyperbilirubinemia is defined biochemically as prolonged elevation of conjugated bilirubin beyond 14days of life. It is due failure to excrete bile. This may be caused by defects in intrahepatic bile production, defects in transmembrane transport of bile or mechanical obstruction of bile flow. The latest joint recommendation from the North American and European Societies for Pediatric Gastroenterology, Hepatology and Nutrition defines a direct serum bilirubin level >1mg/dl as abnormal[1]. A direct bilirubin level of >20% of the total serum bilirubin is no longer regarded as necessary for the diagnosis of cholestasis[1]. Any infant with jaundice beyond 2weeks needs to be evaluated for Neonatal cholestasis. Rapid diagnosis is important for initiation of essential treatment for the treatable disorders. The most commonly identifiable caues are biliary atresia (BA) (25%–35%), genetic disorders (25%), metabolic diseases (20%), and $a_1$-antitrypsin ($A_1AT$) deficiency (10%). Idiopathic neonatal hepatitis (INH) was the most common non surgical cause of neonatal cholestasis before but with the discovery of more advanced diagnostic methods, the incidence of INH has substantially reduced .

**Case Presentation:**

In this article we describe you a series of 6 cases of neonatal cholestasis presented to a tertiary care centre in Western Mahrashtra.Here we describe the most common causes of neonatal cholestasis, and its presentation and its treatment.

**Conclusion**:

Biliary atresia is found to be most common surgical cause of neonatal cholestasis and its early diagnosis and essential intervention improves the quality of life, Late diagnosis may lead to liver transplant and mortality later in life.

**Keywords**: Neonatal cholestasis, biliary atresia, Kasai, intrahepatic cholestasis.

## Introduction:

Jaundice is a clinical term used to describe yellowish discoloration of the skin, sclera, mucous membranes, and bodily fluids. It is a most common clinical finding in neonates in the first 2 weeks after birth, occurring in 5%-

25% of new-borns [1]. When jaundice persists beyond age 2 weeks after birth cholestasis or conjugated hyperbilirubinemia must be considered in the differential diagnosis. Cholestasis represents an impairment in bile flow and may be caused by either an intrahepatic or extrahepatic obstruction, defects in intrahepatic bile production or defects in transmembrane transport of bile acids.The latest joint recommendation from the North American and European Societies for Pediatric Gastroenterology, Hepatology and Nutrition defines a direct serum bilirubin level >1mg/dl as abnormal [2]. A direct bilirubin level of >20% of the total serum bilirubin is no longer regarded as necessary for the diagnosis of cholestasis [2]. Few physiological conditions like breastfeeding jaundice and breastmilk jaundice causing prolonged jaundice needs to be ruled out before evaluating for conjugated hyperbilirubinemia which is always pathological. Neonatal cholestasis occurs in 0.04 to 0.2 % of live birth[3].The most common presenting complaintsof these neonates would be poor feeding, not gaining weight, yellowish discoloration of skin, acholic stools, and dark coloured urine except in biliary atresia where most of the patients will have normal feeding and adequate weight gain [4] . Of the many conditions that cause neonatal cholestasis, the most commonly identifiable are biliary atresia (BA) (25%–35%), genetic disorders (25%), metabolic diseases (20%), and $a_1$-antitrypsin ($A_1AT$) deficiency (10%), and rapidly identify these causes of cholestasis that can be either treated medically or surgically [5]. Idiopathic neonatal hepatitis (INH) was the most common non surgical cause of neonatal cholestasis before but with the discovery of more advanced diagnostic methods, the incidence of INH has substantially reduced [6,7].

## CASE SERIES:

We have studied a total of 5 cases of neonatal cholestasis presented to us at varying ages with various presentations.

Case1: Is a one month old male child presented with complaints of pale coloured stools and yellowish discolouration of skin and abdominal distension, with normal birth history and adequate weight gain. On examination lft's and coagulation profile were deranged. On Ultrasound Abdopelvis both pre and post prandial suggested paucity of bile ducts and then a serum GGT was sent which was elevated and a liver biopsy was done which confirmed the diagnosis of biliary atresia and the patient underwent kasai procedure and living well now.

Case 2:

A 4 day old male infant brought by parents with complaints of increased work of breathing and yellowish discolouration of skin. On admission the baby was icteric, abdominal distension was present and oxygen requirement was present. Sepsis screen was positive and was being treated with IV antibiotics and Covid screen was also positive and IVIG was given, the baby was transfused with prbc and ffp. After 14 days of antibiotic therapy also the oxygen requirement was not reduced, then a serum GGT was sent which was mildly elevated and then got screened for neonatal hemochromatosis, biliary atresia, neonatal hepatitis and the ultrasound abdopelvis was suggestive of liver parenchyma disease. A liver biopsy was done suggestive of biliary atresia , the baby was discharged on liver supportive medication like vitamin A, D, E and K , and ursodeoxycholic acid. The baby is doing well now without any operative management.

Case 3:

A 14 day old male child born extreme preterm with very low birth weight admitted in NICU , recieved prolonged parenteral nutrition, antibiotics and was discharged. Following which the baby started refusing feeds at home, increased work of breathing and was admitted in Picu. Then baby was having oxygen requirement, deranged lfts and coagulation profile and the supportive treatment was given and the metabolic screen was positive for galactosemia, unfortunately the baby succumbed death during the Picu stay.

Case 4:

4 month old male child brought by parents with yellowish discolouration of skin with normal birth history and adequate weight gain and was evaluated with ultrasound abdopelvis which confirmed the diagnosis of biliary atresia and the patient is planned for liver transplant and is now on supportive management. Case 5:

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Age at presentation | 1 month | 4 days | 14 days | 4 months | 21days |
| Sex | Male | Male | Male | Male | Male |
| Complaints | Pale colored stools | Breathing difficulty | Breathing difficulty | Yellowish discoloration Of skin | Yellowish discoloration of skin |
| Clinical features | Yellowish discoloration of skin Abdominal distension | Abdominal distension, Increased WOB | Yellowish discoloration Increased WOB | Yellowish discoloration of skin | yellowish discolouration of skin |
| Antenatal history | Mother had history of fever at 7$^{th}$ Month of gestation | NS | PIH on tab labetalol 1 month | Mother had history of fever in 3rd trimester and was diagnosed to have torch positive titres posnataly | Elderly primi 3rd trimester scan suggestive of mild IUGR |
| Birth history | FT/NVD/3.2kg/BCIAB | FT/NVD/2.8kg/BCIAB | EPT/1.2kg/VLBW/BCIAB | FT/NVD/3kg/BCIAB | FT/NVD/2.4kg/DNCAB |
| Consanguinity | NIL | NIL | NIL | NIL | NIL |
| Signs of failure to thrive | No | NO | YES | No | No |
| Clinical sepsis | NO | Yes | Yes | No | Yes |
| Mother History | Torch +ve | NO | Torch +ve | Torch +ve | ND |
| Hepatomegaly | Present | Present | Present | hepatomegaly | Present |

Table 1: Description of cases

21day old male child admitted in NICU for prematurity and low birth weight , who was ventilated for 3 days and then slowly weaned off oxygen started having yellowish discolouration and oxygen requirement on day 14 of life , the sepsis screen was positive and the baby is being treated for Klebsiella sepsis and the reason for neonatal cholestasis.

Table 2: Investigations and outcome

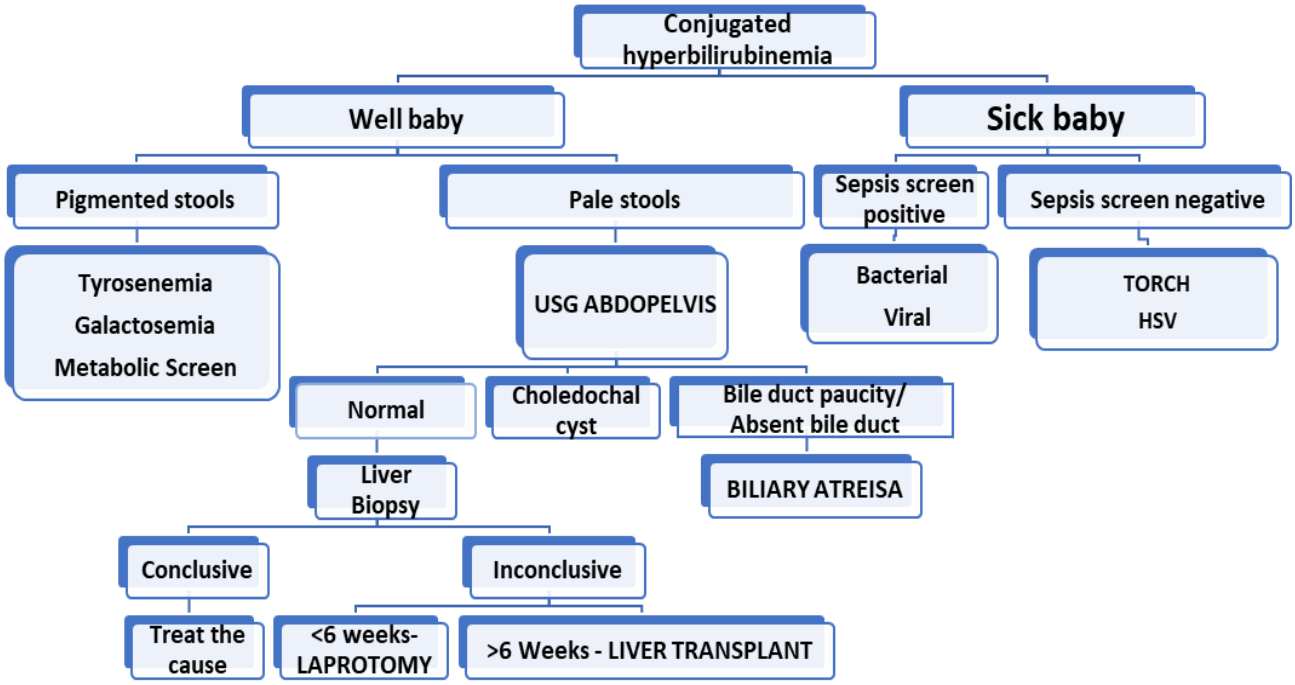
| Investigation | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| CBC | Normal | Pancytopenia | Anemia with leucocytosis | Normal | Bicytopenia with leucocytosis |
| LFT(D)<br>LFT(I) | 5.56<br>2.26 | 19.46<br>10.09 | 15.5<br>6.8 | 6.61<br>2.13 | 13.09<br>9.11 |
| CRP | Negative | Positive | Positive | Negative | Positive |
| Blood culture | Negative | Negative | Negative | Negative | Positive (klebsiella pneumoniae) |
| PT/ INR | Deranged | Deranged | Deranged | Deranged | Normal |
| USG | Normal | Liver parenchymal disease with gallbladder wall Triangualar cord sign seen | Gross ascites with early changes of cystitis | Gall bladder is small and collapsed, mildly thickened wall and peri cholecystic fibrosis of thickness around 5 mm , main pancreatic duct is not dilated | Biliary sludge present with gall bladder edema |
| GGT | 308 | 17 | 120 | 713 | ND |
| TORCH Titres | IgG +ve Rubella, CMV, HSV | Negative | IgM CMV +ve IgG CMV,Rubella +ve | IgM CMV +ve IgG CMV,Rubella +ve | ND |
| HIDA | ND | ND | ND | ND | ND |
| Metabolic screen | ND | Negative | Galactosemia +ve | ND | ND |
| Liver Biopsy and HPE | S/o Biliary Atresia | Biliary Atresia | ND | Biliary atresia | ND |
| OUTCOME | Porto enterostomy done | Patients bilirubin level decreased gradually and was adviced for 2nd liver biopsy after 6 weeks | Succumbed to death | Adviced for liver transplant | Being treated for sepsis |

ND - not done , NS -not significant, IgM- Immunoglobulin M, IgG - Immunoglobulin G, CMV- cytomegalovirus, HSV- HerpesSimplex Virus, NVD- Normal Vaginal Delivery, LSCS- Ceserean Section , BCIAB-Baby Cried Immediately After Birth, DNCAB- Did Not Cry After Birth, FT- Full Term, EPT- Early Preterm, WOB- Work Of Breathing.

## Discussion:

Any infant with prolonged jaundice needs beyond 2weeks after birth to be evaluated for Neonatal cholestasis. In majority of infants, prolonged physiological jaundice needs to be ruled out as it occurs due to breast feeding or breast milk, hemolysis, Gilbert syndrome, Criggler Najar syndrome. Upto 15% of breastfed infants develop Breastfeeding jaundice lasting for more than 3 weeks due to inadequate feeding[8], it usually appears between 24-

72hrs of age, peaks by 5-15 days of life. It usually disappears by 3rd week of life. The mother should be encouraged to breast feed the baby frequently and exclusive for atleast 8 - 12 times a day with no top feeds. Parents should be counselled to bring the baby to the hospital if there is resolution and also if the colour of the leg looks as yellow as the face. Sometimes a very large amount of bilirubin rarely accumulates in the blood and can cause kernicterus[9]. Breastmilk jaundice occurs in about 2.4% of infants possibly due to **β** Glucoronidase a factor in human milk that deconjugates the intestinal bilirubin and promotes its absorption. If breastfeeding is interrupted bilirubin will fall rapidly within 48hrs and the bilirubin levels gradually dalls down[10]. Parents needs to be adviced not to stop breastfeeding as it is harmless. Thus there is a tendency to ignore jaundice until 6 weeks (the first health surveillance check). The consequent delay in diagnosis of cholestatic jaundice can adversely affect the outcome of the treatment.[11,12,13]. Hence these condition needs to be rules out before evaluating for Neonatal Cholestasis. Once Neonatal cholestasis is confirmed systematic approach is the key to promptly identify the specific diagnosis and promptlife saving treatment can be initiated for the better outcome.




*Metabolic Screen: GCMS/TMS

Schematic approach to investigations in order:

1. CBC and CRP to rule out sepsis
2. LFT's: To rule out unconjugated hyperbilirubinemia
3. RBC morphology and retic count- to rule out hemolysis
4. TFT to r/o hypothroidism and G6PD deficiency
5. Serum GGT: >200IU

Abnormal GGT and increase in conjugated hyperbilirubinemia with pale stools gives the most probable diagnosis of biliary atresia which when diagnosed earlier improves the Quality of life by early intervention and surgical management. Biliary atresia is the most common surgical cause of neonatal cholestasis.

6. Serum ferritin to rule out neonatal hemochromatosis
7. USG Abdomen And Pelvis.
8. HIDA scan now not commonly used [14]
9. Metabolic Screening
10. Liver biopsy and Histopathological examination
11. Genetic Workup

Ultrasonography interpretation: ultrasonography of a patient with neonatal cholestasis will show features suggestive of EHBA. Most specific finding for EHBA is the Triangular cord sign seen due to fibrosis of porta hepatis and the bifurcation of portal vein, which is not seen in other types of cholestatic jaundice [15] collapsed Gall bladder with non visualisation of biliary tracts in post prandial scan is also suggestive of BA

Histopathological Examination Interpretation:

If HPE shows widened portal tracts with prominent, distorted, elongated, angulated bile ducts, increased fibrosis and inflammatory cell infiltrates with preserved hepatic architecture it is suggestive of BA. If HPE shows prominent hepatocellular necrosis, disorganised liver cord, giant cell transformation and inflammatory cell infiltrates are suggestive of hepatitis.[16]

The diagnosis of Biliary Atresia was finally made by either cholangiography or histopathologic examination. BA is a rare disease characterised by a biliary obstruction of unknown origin that manifests in the neonatal period[17]. Inflammatory damage to the intra-and extrahepatic bile ducts, along with sclerosis, constriction, or even obliteration of the biliary tree, make up the usual histological appearance [18]. If left untreated, this condition causes cirrhosis and mortality within the first few years of life [19]. Surgical treatment typically begins with an effort to reestablish bile flow: the Kasai portoenterostomy [20]. The outcome of children with biliary atresia also is related to the caseload of the surgical centre where they undergo their primary surgery [21].

## CONCLUSION

Out of the cases enrolled of the study 3 cases were found to have Biliary Atresia and out of 3 patients with biliary atresia one patient underwent kasai procedure and the other one is planned for liver transplant, and the other patient is being followed up. Identification of Neonatal cholestatic jaundice is very important and reffering them to a pediatric gastroenterologist or hepatologist is very essential for further management of the patient. BA is one of the common causes of Neonatal Cholestatic Jaundice that should be promptly diagnosed early and treated early before 45 days of life for kasai procedure otherwise the patient requires Liver Transplant for the better outcome. The most common non surgical cause is Neonatal Hepatitis Syndrome. Hence a careful history, thorough physical examination and fractionation of serum bilirubin are recommended in any neonate/infant with jaundice seen beyond 2 weeks after birth.

## REFERRENCES:


1) Narang, A., Gathwala, G., & Kumar, P. (1997). Neonatal jaundice: an analysis of 551 cases. Indian pediatrics, 34(5), 429–432.
2) Fawaz, R., Baumann, U., Ekong, U., Fischler, B., Hadzic, N., Mack, C. L., McLin, V. A., Molleston, J. P., Neimark, E., Ng, V. L., & Karpen, S. J. (2017). 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. Journal of pediatric gastroenterology and nutrition, 64(1), 154–168. https://doi.org/10.1097/MPG.0000000000001334
3) Mushtaq, I., Logan, S., Morris, M., Johnson, A. W., Wade, A. M., Kelly, D., & Clayton, P. T. (1999). Screening of newborn infants for cholestatic hepatobiliary disease with tandem mass spectrometry. BMJ (Clinical research ed.), 319(7208), 471–477. https://doi.org/10.1136/bmj.319.7208.471
4) Feldman, A. G., & Sokol, R. J. (2013). Neonatal Cholestasis. NeoReviews, 14(2), 10.1542/neo.14-2-e63. https://doi.org/10.1542/neo.14-2-e63
5) Balistreri WF, Bezerra JA. Whatever happened to "neonatal hepatitis"? Clin Liver Dis. 2006 Feb;10(1):27-53, v. doi: 10.1016/j.cld.2005.10.008. PMID: 16376793.

6) Dick MC, Mowat AP. Hepatitis syndrome in infancy--an epidemiological survey with 10 year follow up. Arch Dis Child. 1985 Jun;60(6):512-6. doi: 10.1136/adc.60.6.512. PMID: 3874604; PMCID: PMC1777358.
7) Mandelia A, Lal R, Mutt N. Role of Hepatobiliary Scintigraphy and Preoperative Liver Biopsy for Exclusion of Biliary Atresia in Neonatal Cholestasis Syndrome. Indian J Pediatr. 2017 Sep;84(9):685-690. doi: 10.1007/s12098-017-2408-z. Epub 2017 Jul 8. PMID: 28687948.
8) Winfield, C. R., & MacFaul, R. (1978). Clinical study of prolonged jaundice in breast- and bottle-fed babies. Archives of disease in childhood, 53(6), 506–507. https://doi.org/10.1136/adc.53.6.506
9) Trikalinos, T. A., Chung, M., Lau, J., & Ip, S. (2009). Systematic review of screening for bilirubin encephalopathy in neonates. Pediatrics, 124(4), 1162–1171. https://doi.org/10.1542/peds.2008-3545
10) Maruo, Y., Nishizawa, K., Sato, H., Sawa, H., & Shimada, M. (2000). Prolonged unconjugated hyperbilirubinemia associated with breast milk and mutations of the bilirubin uridine diphosphate- glucuronosyltransferase gene. Pediatrics, 106(5), E59. https://doi.org/10.1542/peds.106.5.e59
11) Mowat, A. P., Davidson, L. L., & Dick, M. C. (1995). Earlier identification of biliary atresia and hepatobiliary disease: selective screening in the third week of life. Archives of disease in childhood, 72(1), 90–92. https://doi.org/10.1136/adc.72.1.90
12) Mieli-Vergani, G., Howard, E. R., Portman, B., & Mowat, A. P. (1989). Late referral for biliary atresia--missed opportunities for effective surgery. Lancet (London, England), 1(8635), 421–423. https://doi.org/10.1016/s0140-6736(89)90012-3
13) Serinet, M. O., Wildhaber, B. E., Broué, P., Lachaux, A., Sarles, J., Jacquemin, E., Gauthier, F., & Chardot, C. (2009). Impact of age at Kasai operation on its results in late childhood and adolescence: a rational basis for biliary atresia screening. Pediatrics, 123(5), 1280–1286. https://doi.org/10.1542/peds.2008-1949
14) Choi SO, Park WH, Lee HJ. Ultrasonographic "triangular cord": the most definitive finding for noninvasive diagnosis of extrahepatic biliary atresia. Eur J Pediatr Surg. 1998 Feb;8(1):12-6. doi: 10.1055/s-2008-1071111. PMID: 9550270.
15) http://dx.doi.org/10.1136/adc.51.10.763
16) Suchy FJ. Neonatal cholestasis. Pediatrics in review. 2004 Nov;25(11):388-96.
17) Alagille D. Extrahepatic biliary atresia. Hepatology. 1984 Jan;4(S1):7S-10S.
18) Gautier M, Eliot N. Extrahepatic biliary atresia. Morphological study of 98 biliary remnants. Archives of Pathology & Laboratory Medicine. 1981 Aug 1;105(8):397-402.
19) Dick MC, Mowat AP. Hepatitis syndrome in infancy--an epidemiological survey with 10 year follow up. Arch Dis Child. 1985 Jun;60(6):512-6. doi: 10.1136/adc.60.6.512. PMID: 3874604; PMCID: PMC1777358.
20) Kasai M, Kimura S, Asakura Y, Suzuki H, Taira Y, Ohashi E. Surgical treatment of biliary atresia. Journal of pediatric surgery. 1968 Dec 1;3(6):665-75.
21) McKiernan, P. J. , Baker, A. J. & Kelly, D. A. (2000). The frequency and outcome of biliary atresia in the UK and Ireland. The Lancet, 355 (9197), 25-29.