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Case Series

Paediatrics Section

Varied Aetiologies and Outcome of Neonatal Cholestasis: A Series of Four Cases

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ABSTRACT

Neonatal cholestasis is a significant cause of chronic liver disease in infants. However, lack of awareness among parents and primary care physicians often leads to delayed diagnosis and management of these children. In this series, the authors discussed four cases of neonatal cholestasis (48 days term female, 3 months term male, 73 days old female, 33 days old term male) that presented in the outpatient department with the chief complaint of yellowish discolouration of the eyes and pale-coloured stools. Clinical and histochemical findings in all cases were suggestive of neonatal cholestasis. The neonates were treated with Ursodeoxycholic Acid (UDCA), vitamin ADEK, and followed-up. Fortunately, in all the babies, symptoms resolved after management, except for a three-month-old male baby who unfortunately succumbed to liver failure after two weeks of hospitalisation. Early identification of Progressive Familial Intrahepatic Cholestasis (PFIC) disorders is crucial as it enables effective management and potential definitive therapy. Additionally, prompt implementation of a galactose-free diet is critical for preventing acute toxicity and minimising tissue damage in galactosemia. Late presentation of biliary atresia can lead to increased morbidity and mortality. Therefore, it is crucial to include stool and urine charts in the discharge summary of every newborn and provide parental education on recognising the signs of cholestasis in the Paediatric Outpatient department.

Keywords: Biliary atresia, Hyperbilirubinemia, Kasai procedure, Progressive familial intrahepatic cholestasis

INTRODUCTION

Neonatal cholestasis is a common presenting feature of neonatal hepatobiliary dysfunction that affects normal biliary metabolism. Neonatal cholestasis is defined as conjugated hyperbilirubinemia occurring in newborns as a consequence of diminished bile flow. Cholestasis is categorised into biliary (obstructive, involving large extrahepatic or small intrahepatic bile ducts) or hepatocellular (resulting from defects in membrane transport, embryogenesis, or metabolic dysfunction) in origin [1]. It should be suspected in any newborn who has jaundice, dark-coloured urine, or pale-coloured stool beyond the age of two weeks. Conjugated hyperbilirubinemia in a newborn is defined as a direct bilirubin level >1 mg/dL when the total bilirubin is less than 5 mg/dL or >20% of the total bilirubin if the total bilirubin is >5 mg/dL [2]. The recent definition states that at any age, conjugated hyperbilirubinemia is pathological and requires evaluation using a stepwise evidence-based approach to arrive at a diagnosis [1]. Early diagnosis and identification of the aetiology are essential, and appropriate medical support and nutritional supplementation can be lifesaving, while a delayed diagnosis can be detrimental.

Case 1

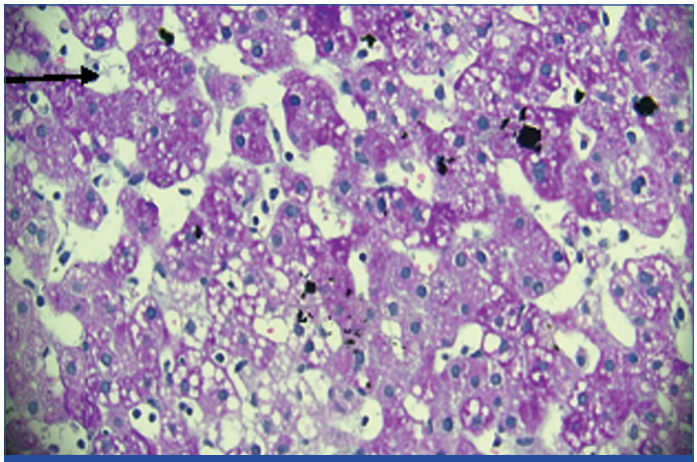
A 48-day-old term female infant, the firstborn to non-consanguineous parents, was brought to the Paediatric Outpatient Department with yellowish discolouration of the eyes since day 3 of life. The baby was on direct breastfeeding and formula feeds since birth. The baby had been passing intermittent pale-coloured stools and normal urine. There was no significant antenatal history. On physical examination, the baby appeared icteric and had hepatomegaly (liver 3 cm below the right costal margin). During the evaluation for neonatal cholestasis, the baby was found to have conjugated hyperbilirubinemia with mildly elevated alkaline phosphatase and normal liver enzymes [Table/Fig-1].

Variables	Case 1	Case 2	Case 3	Case 4
SBR Direct bilirubin	4.01 mg/dL 2.02 mg/dL	4.67 mg/dL 2.91 mg/dL	11.09 mg/dL 9.67 mg/dL	14.68 mg/dL 12.34 mg/dL
SGOT/SGPT (U/L)	44/23	498/469	1019/516	283/128
ALP/ GGT (U/L)	263/102	329/102	376/41	252/59
Sr Albumin (gm/dL)	3.3	3.89	4.49	3.1
PT/ INR	13/1.24	11/1	15/1.07	120/>10
USG	Normal	Hepatomegaly with increased echotexture non visualisation of intrahepatic biliary radicals and common bile duct prominent hepatic artery	Normal	Normal
HIDA	Normal hepatocyte and bilio enteric drainage	-	-	-
Liver biopsy-refer case reports				
Miscellaneous lab investigations	Sr Ferritin: 520 AFP: 10850	Nil	Sr.TSH: 3.04 uIU/L Sr.Ferritin: 846 ng/mL AFP: 3710 ng/mL S.Bile acids: 305.7 umol/L	-
Enzyme assay	Nil	-	-	GALT assay - Normal

Clinical exome	Normal	-	Compound Heterozygous variant involving ABCB11 gene	Normal
Aetiology	Progressive Familial Intrahepatic Cholestasis (PFIC)	Biliary atresia	Progressive Familial Intrahepatic Cholestasis (PFIC)	Conjugated hyperbilirubinemia with acute liver failure, bilateral cataract and hypoglycaemia seizures, suggestive of galactosemia
Outcome	Baby was discharged and on follow-up, there was no sign/ symptoms of the disease	Baby died due to liver failure after 2 weeks of hospitalisation	On follow-up, LFT were normal but baby had pruritis, which was managed	On follow-up, Jaundice had resolved with normalisation of biochemical values

[Table/Fig-1]: Laboratory values, imaging results at presentation of four cholestasis cases.

Urine reducing substance was negative, serum ferritin was 520 ng/mL, and Alpha Fetoprotein (AFP) was 10,850 ng/mL, which was normal for the age. Abdominal Ultrasonography (USG) revealed a partially distended gall bladder with no other significant abnormalities. Ophthalmology evaluation was normal. Hepatobiliary iminodiacetic acid testing revealed normal hepatocyte function and bilio-enteric drainage. Liver biopsy showed normal hepatic architecture, bile ducts, a normal cord pattern, mild inflammation with eosinophilic and mononuclear infiltrates in the portal tract. Cytoplasmic changes included panzonal feathery degeneration, more pronounced in Zone 3, with occasional giant cell transformation. Dilated sinusoids with hemosiderin-laden macrophages were seen, canaliculi were visualised, and cholestasis was noted [Table/Fig-2].



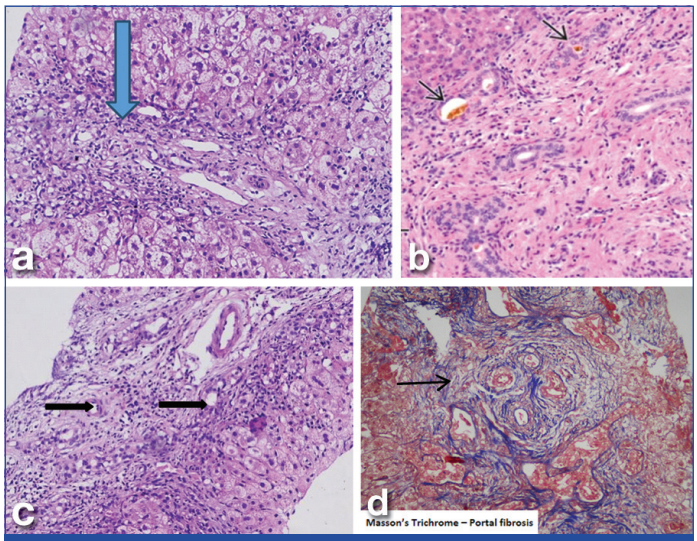
[Table/Fig-2]: Photograph showing eosinophilic and mononuclear infiltrates with ballooning degeneration. {Haematoxylin and Eosin (H&E) stain 10x}.

On immunohistochemistry, there was a complete loss of BSEP canalicular staining. The overall morphological, histochemical, and immunohistochemical features were consistent with PFIC type 2. Clinical exome sequencing revealed no pathogenic variants. The baby was started on UDCA (15 mg/kg/day) and vitamin A, D, E, K supplements (Vitamin A 5000 U/day, Vitamin D 1200 IU/day, Vitamin E 50 IU/kg/day, Vitamin K 5 mg per week orally) and continued for three months after the resolution of jaundice. The baby was followed-up until 11 months of age without any significant complications.

Case 2

A three-month-old term male baby, the secondborn to non-consanguineous parents, was brought to the paediatric OPD with yellowish discolouration of the eyes and passing pale-coloured stools since birth. The baby was on direct breastfeeding and formula feeds since birth. There was no significant antenatal history or family history. On physical examination, the baby appeared icteric and had hepatosplenomegaly. During the evaluation for neonatal cholestasis, the infant was found to have conjugated hyperbilirubinemia with elevated liver enzymes, with predominance of alkaline phosphatase and gamma glutamyl transpeptidase [Table/Fig-1].

Fasting abdominal Ultrasonography (USG) revealed hepatomegaly with increased echotexture, non-visualised intrahepatic biliary radicals and common bile duct at the porta hepatis region, and a prominent hepatic artery with non-visualised gall bladder, suggestive of biliary atresia. In the liver biopsy, hepatocytes showed panzonal feathery degeneration, and portal tracts showed inflammation, ductular proliferation, bile duct plugs, and portal-portal bridging fibrosis. The overall morphological and histochemical features were consistent with the diagnosis of biliary atresia [Table/Fig-3a-d].



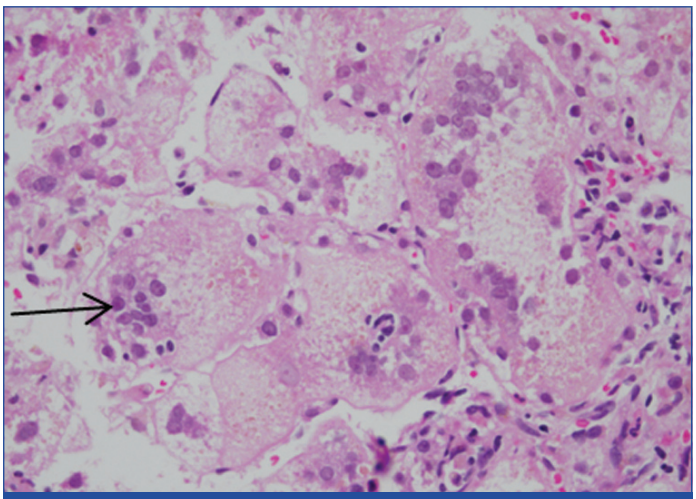
[Table/Fig-3]: Photograph showing eosinophilic and mononuclear infiltrates with ballooning degeneration. {Haematoxylin and Eosin (H&E) stain 10x}. a) Portal inflammation- H&E stain 10x; b) Bile duct plugs- H&E stain 10x; c) Bile ductular proliferation- H&E stain 10x; d) Portal fibrosis-Masson's trichrome stain, 40x.

Unfortunately, this infant presented late to the healthcare facility due to a lack of awareness among parents. The baby succumbed to death due to liver failure after two weeks of hospitalisation.

Case 3

A 73-day-old term female infant, the firstborn to non-consanguineous parents, presented to the paediatric OPD with a history of yellowish discolouration of the eyes, pale-coloured stools, and dark yellow-coloured urine since one month. The baby was on direct breastfeeding and formula feeds since birth. There was no significant antenatal history or family history. On examination, the baby had icterus and hepatomegaly (liver 4 cm below the right costal margin). During the evaluation for neonatal cholestasis, the infant was found to have conjugated hyperbilirubinemia and elevated liver enzymes [Table/Fig-1]. Urine reducing substances were negative, urine succinylacetone was not detected, and total bile acids were elevated at 305.7 µmol/L. Serum ferritin, TSH, and AFP were normal for age (serum ferritin was 846.3 ng/mL, TSH was 3.04 µIU/L, AFP was 23,710 ng/mL). Abdominal Ultrasonography (USG) and ophthalmology evaluation were normal. The liver biopsy revealed normal hepatic architecture, hepatocytes showed lobular inflammation and diffuse giant cell transformation, and portal tracts showed inflammation, ductular proliferation, and a few damaged bile ducts, which are features suggestive of giant cell hepatitis [Table/Fig-4]. Clinical exome sequencing revealed a compound heterozygous variant involving the ABCB11 gene, suggestive of PFIC [Table/Fig-5]. The baby was started on UDCA and vitamin A, D, E, K supplements, which were continued for four months after

discharge. The infant is being followed-up periodically. It's good to know that the patient's Liver Function Tests (LFT) were within normal limits, despite experiencing pruritus during their last visit at 10 months of age. The management approach for their pruritus included the use of Hydroxyzine and UDCA.



[Table/Fig-4]: Photograph showing the main histological findings of Giant cell hepatitis (H&E stain Stain, 40x).

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance
ABCB11 (-) (ENST00000650372.1)	Exon 8	c.747C>4 (p.Ser249Arg)	Heterozygous	Progressive familial intrahepatic cholestasis-2	Autosomal recessive
	Exon 8	c.749C>T (p.Pro250Leu)	Heterozygous		

[Table/Fig-5]: Clinical Exome report.

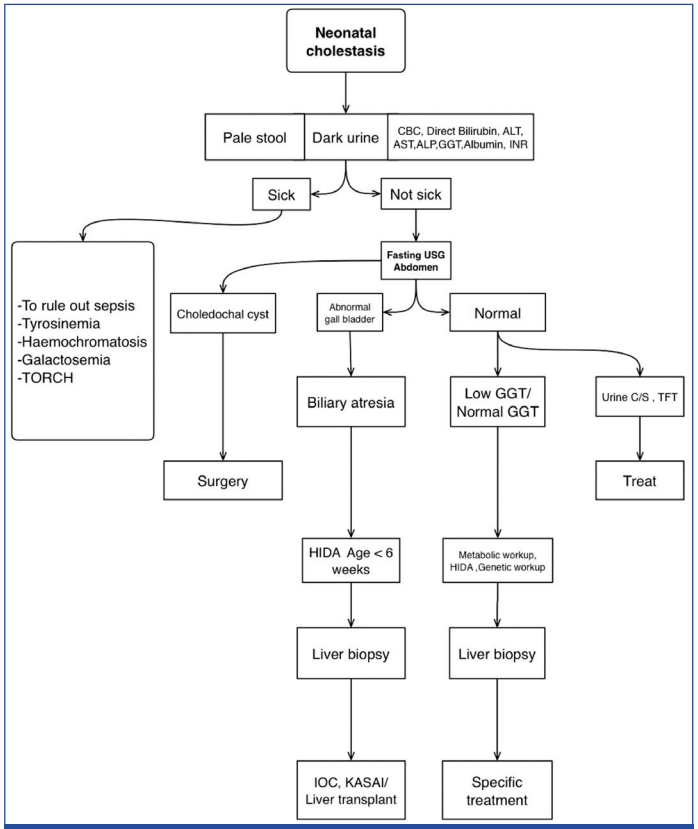
Case 4

A 33-day-old term male infant, the firstborn to non-consanguineous parents, was noticed to have yellowish discolouration of the eyes, pigmented stools, and dark yellow-coloured urine since day 3 of life. The baby was on direct breastfeeding and formula feeds since birth. There was no significant antenatal or family history. The baby had recurrent hypoglycaemic seizures since day 3 of life, for which he was evaluated elsewhere and found to have conjugated hyperbilirubinemia. The baby was managed conservatively with intravenous fluids and UDCA. On day 31, the baby developed features of pneumonia and progressive deterioration of general condition, and hence was referred to our department. He was managed with oxygen therapy at 2 liters/min through nasal prongs and intravenous Cefotaxime at 100 mg/kg/day and Amikacin at 15 mg/kg/day for five days, which were stopped as the culture was found to be sterile. On examination, the baby had icterus and hepatomegaly (liver 4 cm). The baby was further evaluated for cholestasis. Routine biochemistry showed the presence of defective coagulation (PT 120 sec, INR >10) not corrected by vitamin K, elevated direct bilirubin, modest hypertransaminasemia (AST 238 U/L; ALT 128 U/L), low serum albumin, and a transient hyperammonemia (128 mcg/dL) [Table/Fig-1].

Urine reducing substances were negative, and urine succinylacetone was not detected. Total galactose and GALT enzyme were normal. Possibilities of GALD, mitochondrial hepatopathy, and inborn errors of metabolism were considered and evaluated. Minor salivary gland biopsy was normal, and abdominal Ultrasonography (USG) was normal. Urine ketones were not detected. Tandem mass spectrometry and urine gas chromatography mass spectrometry were normal. Ophthalmology evaluation revealed bilateral cataracts, and the baby was operated on for the same. Conjugated hyperbilirubinemia with acute liver failure, bilateral cataracts, and hypoglycaemic seizures were suggestive of galactosemia, and lactose-free formula was started. However, clinical exome sequencing turned out to be normal. After five months, on follow-up, the baby was thriving well. Jaundice had resolved, and normalisation of biochemical values was noticed (serum bilirubin 0.10 mg/dL, direct bilirubin 0.05 mg/dL, SGPT 25 U/L, SGOT 39 U/L, ALP 264 U/L, serum albumin 4.6 g/dL, GGT 10 U/L, PT/INR 12/1).

DISCUSSION

Earlier, idiopathic neonatal cholestasis was considered the most common cause, accounting for 30% of cases of neonatal cholestasis. The availability of genetic analysis for metabolic liver disorders has made the diagnosis more definite. Conjugated hyperbilirubinemia is defined as a direct bilirubin level >1 mg/dL when the total bilirubin is less than 5 mg/dL or >20% of the total bilirubin if the total bilirubin >5 mg/dL [1]. The work-up profile of an infant with neonatal cholestasis must include complete liver function tests, thyroid function tests, and a sepsis screen, followed by specific biochemical, radiological, and histopathological tests [Table/Fig-6]. Most infants with neonatal cholestasis are underweight and will need nutritional support. The goal is to provide adequate calories to compensate for steatorrhea and manage malnutrition. The calorie requirement is approximately 125% of the Recommended Dietary Allowance (RDA) based on ideal body weight [3].



[Table/Fig-6]: Diagnostic algorithm for evaluating neonatal cholestasis [3,4].

The incidence of neonatal cholestasis was found to be 1 in 2500 live births [1]. There are two major categories: hepatocellular and obstructive. Hepatocellular dysfunction (infection, metabolic causes) accounts for 45-69% of all cases, while obstructive causes (biliary atresia and choledochal cyst) account for 19% to 55% [4]. The most common cause is biliary atresia. In this case series, there was one child with biliary obstruction, and all others had hepatocellular dysfunction. Tyrosinemia, herpes simplex infection, hemochromatosis, and sepsis have to be considered in sick babies.

Liver function tests will help guide us to differentiate between hepatocellular and biliary cholestasis. If transaminases (SGOT and SGPT) are raised more, it is more likely hepatocellular aetiology. If alkaline phosphatase and GGT are raised more, then it is more probably biliary cholestasis.

Abdominal ultrasonography may provide findings suggestive of biliary atresia and can also be used to confirm other surgically treatable

conditions like choledochal cyst and inspissated bile plug syndrome. Findings described in biliary atresia include the triangular cord sign, abnormal gallbladder morphology, or absence of the gallbladder. However, these findings cannot be reliably used to diagnose biliary atresia as they are neither highly sensitive nor specific [5,6].

A HIDA scan presence of tracer in the duodenum rules out biliary atresia. But absence of tracer in the duodenum does not necessarily mean biliary atresia; it may indicate either bile duct obstruction or severe inability of the hepatocyte to secrete [7].

Liver biopsy is an essential investigation in the evaluation of neonatal cholestasis. Early recognition of Biliary Atresia (BA) by liver biopsy can avoid unnecessary laparotomy [2]. The characteristic histopathological features of BA are bile duct proliferation, bile plugs in ducts, fibrosis, and lymphocytic infiltrates in the portal tracts, which were observed in presently discussed case 2. In several studies, it has been found that a diagnosis of biliary atresia was possible after liver biopsy in approximately 85-95% of patients [3,8,9]. Intraoperative Cholangiogram (IOC) remains the gold standard for the diagnosis of BA [1,4].

Biliary atresia needs to be considered and evaluated immediately in all non-sick newborns with neonatal cholestasis. The time of Kasai portoenterostomy surgery (within 60 days of age) and the expertise of the surgeon determine the outcome of biliary atresia [2]. Hence, the earliest diagnosis is essential for timely management. A case series by Fontenele JPU et al., also highlights the importance of this unusual differential diagnosis in infants with a cholestatic syndrome [10].

Galactosemia should be ruled out in newborns with culture-proven sepsis because it is easily treatable. Galactosemia is usually the result of Galactose-1-phosphate Uridyl Transferase (GALT) deficiency. Affected infants present with conjugated hyperbilirubinemia after the introduction of human or cow's milk (galactose-containing feedings). Associated features like sepsis, coagulopathy, hypoglycaemia, vomiting, diarrhoea, failure to thrive, and cataracts are also common. Early elimination of galactose from the diet may prevent further progression of galactosemia. The diagnosis is suggested by the presence of reducing substances in the urine and supported by GALT assay. Diagnosis is confirmed by genetics. Treatment requires galactose-free formula. In the present study, the fourth case presented with liver failure, cataract, and recurrent hypoglycaemia, and a probable diagnosis of galactosemia was made. The authors started the infant on lactose-free formula, and the infant improved dramatically. INR normalised over a period of time. In a case report by Nesrin C et al., a newborn with galactosemia and abnormal presentation has been presented [11]. Mutational analysis of the GALT gene from Indian subjects has revealed heterogeneity in the structure of the gene and the presence of novel mutations [12,13].

Progressive Familial Intrahepatic Cholestasis (PFIC) is a group of unrelated monogenic disorders in which mutations in one of the genes involved in canalicular hepatobiliary transport result in progressive cholestasis and liver injury. Alkaline Phosphatase (ALP) and Gamma-Glutamyl Transpeptidase (GGTP) are considered markers for biliary cholestasis. GGTP is elevated in most cholestatic disorders; paradoxically low or normal levels are found in patients with PFIC 1,2 and disorders of bile acid synthesis [14]. The presently discussed cases 1 and 3 have low GGT cholestasis. Case 3 had a ABCB11 gene involvement, which is a compound heterozygous variant suggestive of PFIC II, and the infant developed pruritus during follow-up. In infants with pruritus due to severe cholestasis, depending on severity and response to previous agents, an add-on drug can be considered in the following order: UDCA (20 mg/kg/d), rifampicin (5-10 mg/kg/d), naltrexone, and ondansetron [15]. Surgical methods like partial internal biliary diversion and partial external biliary diversion may be effective in symptomatic children without decompensated cirrhosis in PFIC [16].

CONCLUSION(S)

Early identification and appropriate evaluation of the cause of a medical condition or disease are indeed crucial for achieving a favourable outcome. It involves a combination of various diagnostic methods, including biochemical tests, imaging studies, and histopathology interpretation. India has made significant progress in establishing major centres equipped with the necessary infrastructure and personnel to conduct these investigations. The outcome of infants with cholestasis is adversely affected by malnutrition, hence adequate nutritional and vitamin supplements should be continued for atleast three months after the resolution of jaundice. Sick infants with suspected metabolic liver disorders and intriguing diagnosis require early dietary changes and appropriate monitoring for clinical improvement. Biliary atresia is still a challenging disease to diagnose. Any infant with cholestasis needs early identification and referral to appropriate centres, which remains the cornerstone of proper management.

REFERENCES

[1] 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. Journal of Pediatric Gastroenterology and Nutrition. 2017;64(1):154-68.

[2] Dani C, Pratesi S, Raimondi F, Romagnoli C, Task force for hyperbilirubinemia of the Italian Society of Neonatology. Italian guidelines for the management and treatment of neonatal cholestasis. Ital J Pediatr [Internet]. 2015;41(1):69. Available from: http://dx.doi.org/10.1186/s13052-015-0178-7.

[3] Suchy FJ, Sokol RJ. Medical and nutritional management of cholestasis in infants and children. In: Liver Disease in Children. Cambridge University Press; 2021. Pp. 116-46.

[4] Bhatia V, Bavdekar A, Matthai J, Waikar Y, Sibal A. Management of neonatal cholestasis: Consensus statement of the Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics. Indian Pediatr [Internet]. 2014;51(3):203-10. Available from: http://dx.doi.org/10.1007/s13312-014-0375-2.

[5] Nievelstein RA, Robben SG, Blickman JG. Hepatobiliary and pancreatic imaging in children-techniques and an overview of nonneoplastic disease entities. Pediatr Radiol. 2011;41(1):55-75.

[6] Mittal V, Saxena AK, Sodhi KS, Thapa BR, Rao KLN, Das A, et al. Role of abdominal sonography in the preoperative diagnosis of extrahepatic biliary atresia in infants younger than 90 days. AJR Am J Roentgenol [Internet]. 2011;196(4):W438-45. Available from: http://dx.doi.org/10.2214/AJR.10.5180.

[7] Kianifar HR, Tehranian S, Shojaei P, Adinehpoor Z, Sadeghi R, Kakhki VRD, et al. Accuracy of hepatobiliary scintigraphy for differentiation of neonatal hepatitis from biliary atresia: Systematic review and meta-analysis of the literature. Pediatr Radiol [Internet]. 2013;43(8):905-19. Available from: http://dx.doi.org/10.1007/s00247-013-2623-3.

[8] Russo P, Magee JC, Boitnott J, Bove KE, Raghunathan T, Finegold M, et al. Design and validation of the biliary atresia research consortium histologic assessment system for cholestasis in infancy. Clin Gastroenterol Hepatol [Internet]. 2011;9(4):357-62.e2. Available from: http://dx.doi.org/10.1016/j.cgh.2011.01.003.

[9] Russo P, Magee JC, Anders RA, Bove KE, Chung C, Cummings OW, et al. Key histopathologic features of liver biopsies that distinguish biliary atresia from other causes of infantile cholestasis and their correlation with outcome: A multicenter study. Am J Surg Pathol [Internet]. 2016;40(12):1601-15. http://dx.doi.org/10.1097/PAS.0000000000000755.

[10] Fontenele JPU, Schenka AA, Hessel G, Jarry VM, Escanhoela CAF. Clinical and pathological challenges in the diagnosis of late-onset biliary atresia: Four case studies. Braz J Med Biol Res [Internet]. 2016;49(3):01-04. Available from: http://dx.doi.org/10.1590/1414-431X20154808.

[11] Nesrin C, Nihat D, Erdal P, Oguz T, Murat D, Kaan M. An unusual presentation of galactosemia in the newborn: Liver failure and hyperammonemia. Journal of Contraceptive Studies. 2016;1(3):01-03. Available at: https://contraceptivestudies.imedpub.com/an-unusual-presentation-of-galactosemia-in-the-newborn-liver-failure-and-hyperammonemia.php?aid=9091.

[12] Singh R, Thapa BR, Kaur G, Prasad R. Biochemical and molecular characterization of GALT gene from Indian galactosemia patients: Identification of 10 novel mutations and their structural and functional implications. Clin Chim Acta [Internet]. 2012;414:191-96. Available from: http://dx.doi.org/10.1016/j.cca.2012.09.017.

[13] Singh R, Kaur G, Thapa BR, Prasad R, Kulkarni K. A case of classical galactosemia: Dentification and characterization of 3 distinct mutations in galactose-1- phosphate uridyl transferase (GALT) gene in a single family. Indian J Pediatr. 2011;78(7):874-76.

[14] Amer S, Hajira A. A comprehensive review of progressive familial intrahepatic cholestasis (PFIC): Genetic disorders of hepatocanalicular transporters. Gastroenterology Res [Internet]. 2014;7(2):39-43. Available from: http://dx.doi.org/10.14740/gr609e.

[15] Agarwal S, Lal BB, Rawat D, Rastogi A, Bharathy KGS, Alam S. Progressive familial intrahepatic cholestasis (PFIC) in Indian children: Clinical spectrum and outcome. J Clin Exp Hepatol [Internet]. 2016;6(3):203-08. Available from: http://dx.doi.org/10.1016/j.jceh.2016.05.003.

[16] Sharma D, Shah UH, Sibal A, Chowdhary SK. Cholecystoappendicostomy for progressive familial intrahepatic cholestasis. Indian Pediatr [Internet]. 2010;47(7):626-28. Available from: http://dx.doi.org/10.1007/s13312-010-0122-2.

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