Original Article

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Clinical and Aetiological Profile of Neonates and Infants with Conjugated Hyperbilirubinaemia- A Cross-sectional Study

Paediatrics Section

ANUJA PATHAK[1], SUNIL ARYA[2], SUMIT KUMAR SINGH[3], JYOTI PRAJAPATI[4]

ABSTRACT

Introduction: Neonatal Conjugated Hyperbilirubinaemia (CHB) poses a significant diagnostic challenge in day to day practice because of its varied aetiologies with non-specific clinical presentations. The rationale of the present study is to better understand the underlying causes, clinical manifestations, and outcomes of CHB in this age group, with the goal of improving early diagnosis, management strategies, and ultimately reducing associated morbidity and mortality.

Aim: To describe the hospital prevalence, clinical and aetiological profile of neonates and infants presenting with CHB.

Materials and Methods: The present cross-sectional study was conducted at Maharana Yeshwantrao Hospital and Sri Aurobindo Institute of Medical sciences, Indore, Madhya Pradesh, India from May 2021 to May 2022. Seventy neonates and infants up to three months of age presenting with CHB, defined as direct bilirubin >1 mg/dL in the presence of elevated total bilirubin, were included in the study. Age at presentation, early (<14 days of life) and late onset (>14 days of life) CHB, clinical findings including syndromic features, were noted, and investigations were done accordingly to find the aetiology. Data was analysed in Microsoft excel sheet and Open Sources Software.

Results: The existing clinical records of 70 neonates were analysed during ongoing admission; the mean age at presentation with CHB was 24.1 days (range 3 to 90 days), and 37 (53%) of the patients had early onset CHB. Male: female ratio was 2.9:1. The clinical features were jaundice in all 70 (100%), pale stools in 21 (30%), failure to thrive in 18 (25%), hepatomegaly in 6 (9%) and liver failure in 8 (11%) neonates. The most common aetiology was sepsis in 24 (34%), followed by blood group incompatibility in 13 (19%), prematurity related factors in 7 (10%), dehydration in 6 (8%) and biliary atresia in 6 (8%) neonates. All patients with CHB due to blood group incompatibilities, dehydration and 13 infants in the sepsis aetiology had early onset disease.

Conclusion: The hospital prevalence of CHB in present study was around 4.6% with almost equal distribution between early and late CHB. Sepsis was the most common aetiology of CHB, with a higher frequency among premature and small-for-gestational-age neonates. This reinforces the importance of early identification and management of infections in at-risk neonates to prevent complications such as cholestasis.

Keywords: Blood group incompatibility, Early onset cholestasis, Neonatal jaundice, Neonatal sepsis

INTRODUCTION

The reported incidence of Neonatal Cholestasis (NC) is approximately 1 in 2500 live births in the United States [1]. However, in Central India, the reported proportion of NC is 1.2 per 1000 patients [2]. CHB is a common laboratory finding among admitted infants. North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition guideline (NASPGHAN, 2016) recommends that any infant noted to be jaundiced after two weeks of age should be considered as NC with measurement of total and direct serum bilirubin, an elevated serum direct bilirubin level (direct bilirubin levels >1.0 mg/dL or >17 mmol/L) warrants further evaluation [3].

The typical clinical findings are prolonged jaundice, scleral icterus, acholic stools, dark yellow urine, and hepatomegaly. Early onset Conjugated Hyperbilirubinaemia (ECHB) is a reported entity among neonates less than 14 days of life, with an aetiology slightly different from NC. Sepsis, poor enteral feeding, perinatal hypoxia, and parenteral nutrition can contribute to its development [4].

The aetiology can be classified into biliary (obstructive) or hepatocellular. Extrahepatic biliary Atresia, Choledochal cyst, Inspissated Bile Syndrome (IBS) and Sclerosing cholangitis are anatomical causes. At the same time, PFIC 1, 2, PFIC 3, Alpha 1 antitrypsin deficiency and idiopathic neonatal hepatitis are hepatocellular diseases that cause CHB [5,6]. Sepsis-induced cholestasis is a kind of hepatocellular cholestasis that occurs during or after sepsis caused by biliary flow obstruction. Major causative organisms are gram-negative bacteria like *Acinetobacter calcoaceticus, Klebsiella pneumonia and Enterobacter aerogenes* [7].

Most similar studies conducted in India, have individually focused on newborns with early onset cholestasis or preterms, or newborns that fit the criteria of NC after 14 days of life [2,4,8,9]. The current study is unique in the fact that it includes clinical and aetiological profile of neonates right from early neonatal period (<14 day of life) upto three months of life. The cause of CHB rapidly changes across this age group, with early onset being related with non-hepatic causes and infantile onset being related with surgical causes. The present study will enhance the existing knowledge on the profile of neonates with early onset cholestasis, thus preventing time-consuming or invasive investigations towards a primary liver disease and shift the focus on preventing and treating non-hepatic causes.

Hence, present study was conducted to estimate the hospital prevalence and to describe the clinical and aetiological profile of neonates with CHB.

MATERIALS AND METHODS

The present cross-sectional study was conducted at the Department of Paediatrics, Maharana Yeshwantrao Hospital and Sri Aurobindo Institute of Medical sciences, Indore, Madhya Pradesh, India, over one year (from May 2021 to May 2022) after approval from the Institutional Scientific and Ethical Commitees (Approval Number EC/MGM/Dec-21/17).

Inclusion criteria: All the neonates and infants up to three months of age who presented with CHB during the one year of study period were included, after obtaining written informed consent from parents.

Exclusion criteria: Neonates having significant congenital anomalies were excluded from the study.

Study Procedure

During the study period total 2201 subjects admitted, among them 102 patient presented with CHB. On admission to the hospital, basic patient details such as age, gender, address and date of admission were entered in a predesigned proforma. Blood samples were collected and analysed during the presentation after taking informed consent from parents. Conjugated Bilirubin was measured using an automated diazo dye reaction method from venous blood obtained by venipuncture in all patients. Blood samples were sent promptly to the laboratory in covered specimen tubes to decrease the effect of light on the samples. Infants with CHB underwent various 1st, 2nd 3rd line investigations according to IAP standard treatment guidelines 2022 [10] and investigations available to our hospital, including complete blood counts, liver function tests, blood and urine cultures, coagulation profile, thyroid functions, hepatobiliary ultrasonography. Whenever indicated, 2nd and 3rd line investigations like Hepatobiliary Iminodiacetic Acid (HIDA) scan, tests for Inborn Errors of Metabolism (IEM), serum ferritin and transferrin saturation levels were done. Investigations not available to the hospital were also provided to needy patients with the help of non-government organisations, free of cost whenever possible, although liver biopsy was not available in our set-up. After analysis of the complete available investigations, various aetiologies of CHB were decided with the opinion of a pediatric gastroenterologist. These patients were investigated and treated as per protocol. Patients were followed-up till discharge from the hospital or death. Various definitions and terms used in the study have been cited in [Table/Fig-1] [3,4,8,10-16].

Term	Definition	Reference
Conjugated Hyperbilirubinaemia (CHB)	Direct bilirubin >1 mg/dL in the presence of elevated total bilirubin.	[3]
Early Onset Conjugated Hyperbilirubinaemia (ECHB)	CHB in neonates presenting before 14 days of life.	[4]
Sepsis	A cause of CHB when a bacterial or fungal agent is isolated or when a neonatal sepsis screen is positive, along with improvement in CHB after antibiotics and antimicrobial treatment.	[10]
Cytomegalovirus (CMV) hepatitis	Diagnosed based on raised serum IgM titers and positive urine for CMV PCR.	[11]
Isoimmune haemolysis	Determined in infants with RH and ABO incompatibilities showing severe unconjugated Hyperbilirubinaemia requiring exchange transfusion, with CB levels >1 mg/dL, features of haemolysis, and biliary sludge in USG.	[12]
Prematurity-related causes of liver injury	Considered in preterm babies after ruling out sepsis and Urinary Tract Infection (UTI), when no definitive cause for CB can be identified.	[8]
Gestational Alloimmune Liver Disease causing Neonatal Hemochromatosis (GALD-NH)	Considered in neonates with features of neonatal liver failure, raised serum ferritin, and response to Intravenous Immunoglobulin (IVIG).	[13]
Dehydration	Considered in full-term, clinically well infants who showed CHB after receiving phototherapy, with gall bladder sludge in hepatobiliary Ultrasonography (USG) and no other identifiable cause.	[14]
Biliary atresia	Diagnosed with hepatobiliary USG, Hepatobiliary Iminodiacetic Acid scan (HIDA) scan, and intraoperative cholangiograms.	[15]
Neonatal liver failure	Defined by coagulopathy despite Vitamin K administration, low serum albumin, recurrent hypoglycaemia, and ascites.	[16]
Idiopathic CHB	Considered when no cause is identified after all available investigations.	–

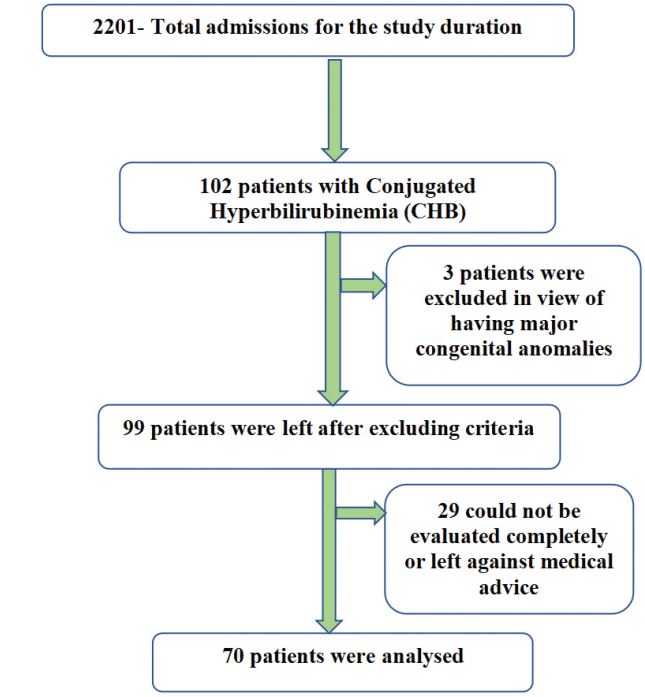
[Table/Fig-1]: Definitions used in the study [3,4,8,10-16]

STATISTICAL ANALYSIS

Data were entered into a Microsoft excel sheet and analysed using Open Sources Software. Continuous data were expressed in terms of mean and SD. Categorical data were represented in the form of proportions and percentages.

RESULTS

The hospital prevalence of CHB was 4.63 % among 2201 admitted infants up to three months of age. The hospital prevalence of CHB for the study duration was 102 (4.6 %) as shown in [Table/Fig-2] Of the 102 patients with CHB, three were excluded due to major congenital anomalies, 29 patients could not be evaluated completely as per standard protocols followed for the study and a total of 70 neonates were included in the final sample size at the end of study period.



[Table/Fig-2]: Sampling of study.

A total of 70 patients with complete data were included for analysis in present study. The mean age at presentation with CHB was 24.1 days (range 3 to 90 days) and majority of them were male (2.9:1). Majority of the children were term with a median gestational age of 36 weeks. Baseline neonatal clinical and biochemical characteristics are described in [Table/Fig-3].

Baseline characteristics	N	Percentage
Age		
<14 days	37	52.85%
≥14 days	33	47.14%
Mean age (days)	24.1±14.67	
Sex		
Male	54	77.14%
Female	16	22.85%
Birth weight		
1-1.5 kg	18	25.71%
1.59-2.5 kg	41	58.57%
>2.5 kg	11	15.71%
Gestation		
Preterm	29	41.42%
Term	41	58.57%
Mean gestational age	35.91±3 weeks	
Syndromic features Down's facies	3	4.28%
Dysmorphism (undiagnosed)	1	1.42%

[Table/Fig-3]: Baseline neonatal clinical and biochemical characteristics at the onset of Conjugated Hyperbilirubinaemia (CHB).

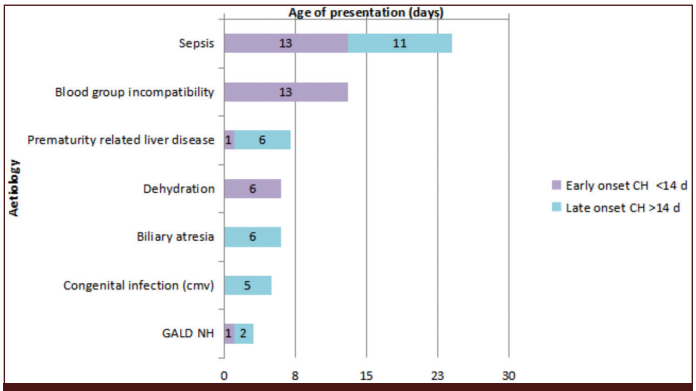
Four children had syndromic features. Early onset CHB was seen in 37 (53%) of the patients. Icterus was seen in all 70 (100%) followed by dark coloured urine in 36 (51%) pale stools in 21 (30%), failure to thrive and lethargic in 18 (25%), hepatomegaly in 6 (11%) and liver failure in 8 (11%) patients [Table/Fig-4].

Clinical features	n	Percentage
General condition on presentation		
Icterus	70	100.00%
Failure to thrive	18	25.71%
Lethargic	18	25.71%
Signs of dehydration	4	5.71%
GI features		
Pale stools	21	30.00%
Dark coloured urine	36	51.42%
Hepatomegaly	6	8.57%
Features of neonatal liver failure	8	11.42%
CNS features		
Hypotonia	15	21.42%
Hypertonia	3	4.28%
Convulsions	8	11.42%
Dysmorphic features/Syndromic	4	5.71%

[Table/Fig-4]: Clinical features at the onset of Conjugated Hyperbilirubinaemia (CHB).

The most common aetiology of CHB in present study was sepsis in 24 (34%), followed by blood group incompatibility in 13 (19%), prematurity related factors in 7 (10%), dehydration in 6 (8%), biliary atresia in 6 (8%) patients [Table/Fig-5].

Maximum mortality (n=5) was also observed in the sepsis category, followed by that in blood group incompatibilities, biliary atresia and idiopathic causes. In the present study, all neonates with CHB due to blood group incompatibilities, i.e., isoimmune haemolysis, dehydration, and non-immune haemolysis, had presentation before 14 days of life. Neonates with biliary atresia, congenital CMV infection, and one neonate with Down syndrome presented after 14 days of life. Thirteen (54%) neonates with CHB due to sepsis had an early presentation, while 11 (45%) with sepsis, developed features of CHB after 14 days of life. One neonate with CHB due to prematurity-related factors presented before 14 days of life, and the other 6, presented after 14 days of life [Table/Fig-5].



[Table/Fig-5]: Aetiology of neonatal Conjugated Hyperbilirubinaemia (CHB) related to the time of presentation in days.

One male baby with Down syndrome presented at 24 days of life had jaundice and hypotonia but no apparent history of pale stools or organomegaly on examination. He had total bilirubin of 13 mg/dL, the direct component being 5.6 mg/dL with normal liver enzymes, thyroid profile and screening USG. No other cause apart from downs syndrome was found attributable. He was started on ursodeoxycholic acid and fat-soluble vitamin supplements, discharged at 10 days of life and observed on subsequent follow-ups. He remained well at last follow-up and CHB had gradually decreased.

Another full-term male baby presented to us on the 4 day of life with a total bilirubin of 23, direct component 3.4. The cause of jaundice was found to be G6PD deficiency on workup; the aetiology of CHB was considered non-immune haemolysis. His jaundice decreased with phototherapy and was discharged at day 9 of life.

DISCUSSION

The hospital prevalence of CHB was 4.63 % among 2201 admitted infants up to three months of age. The incidence is one in 2500 live births in the United States [1]. In India, limited studies have been done to report the incidence [2,15,17]. Jain M et al., reported the proportion of NC to be 1.2 per 1000 [2]. The higher prevalence in present study is probably due to inclusion of newborns of <14 days of life.

Thirty-seven (53%) patients had Early onset CHB (<14 days of life), the mean age at presentation being 20.5 days. Tiker F et al., reported their mean age at presentation be ten days [4]. Jain M et al., reported it as 78 days in central India [2]. This is variable from present study as both, early and late presentations of CHB are included. Male: Female ratio is 3.3:1. It was 1.17:1 in a similar study in central India [2]. The male preponderance could be due to the admission bias in developing countries since females are often neglected [18].

The clinical presentation is similar to those reported by Ahmad M et al., i.e., jaundice, listlessness, organomegaly, failure to thrive and feeding difficulty [19].

The most common aetiology of CHB in present study was Sepsis, similar to findings of Tiker F et al., where culture-proven sepsis was the most common cause of early onset CHB (35.7% of total), followed by perinatal hypoxia-ischemia (n=7), blood group incompatibility (n=5), down syndrome (n=3), cholestasis associated with parenteral nutrition (n=3), neonatal hepatitis (n=2) [4] In another study, the aetiology of CHB was as follows- biliary atresia (41.41%), neonatal hepatitis (20,20%), idiopathic neonatal hepatitis (18.18%), sepsis (14.14%) and others (7.7%) [2].

In the present study, 24 (34.2%) of the neonates were diagnosed with sepsis, of which, 62.5% were premature, and 71% were small for gestational age. Similar findings have been reported by Bachtiar KS et al., Preterm and low birth weight neonates with immature immune systems are more susceptible to infectious causes of CHB [20].

In present study, 41.6% of neonates had culture-proven sepsis, (*E. coli, Klebsiella, Pseudomonas* and *Streptococcus*). Similar organisms in blood culture are reported by Tiker F et al., [4]. Bacterial endotoxin and lipopolysaccharides induce hepatocellular injury by biliary flow obstruction [7]. Six (25%) neonates in present study had associated UTI. Previous studies show that UTI in newborns is known to present as isolated cholestasis [9,21]. Five infants (7.1%) with CMV hepatitis presented with icterus, hepatomegaly and raised liver enzymes. This is the usual presentation [22]. Severe jaundice and granulomatous hepatitis are also seen in CMV infection [23].

Haemolytic Disease Of Newborns (HDN) is a risk factor for cholestasis, prevalence being 13-60% [21]. In the present study, 13 (18.5%) cases had CHB due to Isoimmune haemolysis caused by RH/ABO incompatibilities. All presented before 14 days of life (mean age 4.3 days). Five patients of 13 (38%) showed biliary or gall bladder sludge in ultrasonography. It is known that excessive haemolysis can densify bilirubin as calcium bilirubinate sludge, leading to cholestasis (IBS) [24,25].

Thirteen cases (18%) in the present study had hepatitis on lab parameters, of which two had isolated hepatitis after all causes of sepsis ruled out. However, they could not be sent for liver biopsy and were labelled idiopathic neonatal hepatitis. Wu H et al., has reported few cases of cholestatic giant cell hepatitis in their study [26].

Seven (10%) cases in this study were considered CHB due to prematurity when no other cause was attributable (mean gestational age of 30 weeks). There was a gradual decline of bilirubin unrelated to medical treatment indicating that as the inflammation slowly resolved, bilirubin declined. Several studies have reported prematurity as a cause of cholestasis. Risk factors include parenteral feeding, intestinal injury, and sepsis [8].

In 6 (8.5%) neonates cause of CHB was attributed to dehydration after phototherapy for physiological jaundice. All were term male babies with early onset CHB with a marginal rise in direct bilirubin that improved spontaneously after adequate feeding. Three showed gall bladder sludge in hepatobiliary USG. Other case series have reported similar findings [27]. The estimated incidence of Irritable Bowel Syndrome (IBS) is 1 in 175,000 live births [27]. Risk factors include prematurity, parenteral nutrition, and dehydration. Biliary sludge may resolve independently or with UDCA treatment. Some cases may require surgical intervention [28].

Six infants (8.5%), were diagnosed with extrahepatic biliary atresia. In the United States, Biliary Atresia (BA) is the most common cause of NC (25-35%) [17]. In an Indian study, biliary atresia was reported as a cause of NC in 41, 41% of patients [2]. In the present study, cases of BA were lower than expected, probably due to direct admission in paediatric surgery department or presentation later than three months.

Out of the three cases diagnosed as NH GALD, only one presented early (<14 days), and all three had features of acute liver failure. Serum ferritin was highly raised (>1500) Extrahepatic siderosis is needed for diagnosing NH GALD, demonstrated by iron staining of tissues affected by siderosis by MRI [29,30]. Although oral mucosal biopsy could not be performed, a T2-weighted liver Magnetic Resonance Imaging (MRI) was done in one of three babies demonstrating liver iron overload. There was slow decline of direct bilirubin after receiving IVIG. The published experience IVIG shows marked improvement in survival [31].

Of the three cases of Down syndrome with CHB, two had causes attributable to sepsis and ABO incompatibility. In the third baby, no other cause was found attributable. Kotb MA et al., studied 55 babies with Downs syndrome and found the aetiology of cholestasis to be neonatal hepatistis and paucity of intrahepatic bile ducts, but not extra hepatic biliary atresia [32]. Arnell H et al., have reported the outcome of Down syndrome-associated NC to be variable, with most severe forms associated with bone marrow disease [33]. Cholestasis affects 3.9% of Down syndrome infants due to small bile acid pool, lower synthesis, reduced recirculation of bile acids and immature function of the canalicular bile acid transporting system [34].

Comparison of the findings in present study with contrast studies are shown in [Table/Fig-6] [2,4,9,19,20].

Study aspect	Present study	Ipek MŞ et al., [9]	Jain M et al., [2]	Tiker F et al., [4]	Bachtiar KS et al., [20]	Ahmad M et al., [19]
Year/Place of the study	2025, Indore, India	2013, Ankara, Turkey	2016, Indore, India	2006, Adana, southern Turkey.	2008, Jakarta, Indonesia	2006, Rawalpindi. Pakistan
Hospital prevalence of CHB	4.63% among 2201 admitted infants (up to 3 months)	4.3% among 1230 neonates	3.8%	4.5% prevalence (among early-onset cases)	6.6% of neonates in NICU	7.1% among 1129 neonates with jaundice
Mean age at presentation	20.5 days (with early & late onset included)	12 days (mean age for early-onset CHB)	78 days	10 days (for early-onset CHB)	Not specified	18 days
Male: female ratio	3.3:1	2.7:1	1.17:1	Not specified	Not specified	3.2:1
Most common aetiology	Sepsis (34%) including UTI, CMV infection	Biliary atresia (38.4%), Sepsis (32.4%)	Neonatal hepatitis (41.4%), biliary atresia (20.2%)	Sepsis (35.7%)	Sepsis (40%), prematurity	Neonatal hepatitis (35.7%), biliary atresia (26.4%)
Prematurity & low birth weight	62.5% of sepsis cases were premature, 71% small for gestational age	61% of neonates with CHB were premature	Not reported	Premature infants (62%) more susceptible to sepsis-induced CHB	70% of neonates with cholestasis were preterm	58.8% of neonates with neonatal cholestasis were preterm

Cholestasis due to extrahepatic biliary atresia	8%	38.4%	41.41%	15% of early-onset cases of CHB	Biliary atresia was not a major contributor	26.4%
Neonatal hepatitis	18% had associated hepatitis, of which 2 were idiopathic.	22.8% of cases	20.2% of cases	Not specified	35.7% of cases	Not specified
Down Syndrome & CHB	3 cases, 2 with sepsis and ABO incompatibility	4.5%	Not specified	Not specified	Not specified	Not specified
Ultrasonographic findings	Gall bladder sludge in some cases (including HDN and dehydration)	Gall bladder sludge in 20% of cases	Gall bladder sludge in some cases with biliary atresia	Gall bladder sludge in 25% of early-onset sepsis cases	Gall bladder sludge observed in some cases with sepsis	Gall bladder sludge in some cases
Limitations	Lack of follow-up, insufficient information on long-term outcomes	Small sample size, retrospective study design	Lack of follow-up and incomplete data on long-term outcomes	Small sample size, focus on early-onset cases	Lack of long-term follow-up, small sample size	Limited follow-up, sample size may not represent all cases

[Table/Fig-6]: Comparative findings of present study with similar studies [2,4,9,19,20].

Limitation(s)

This study was limited by lack of follow-up, leading to insufficient information on long-term outcomes. Many cases presented in terminal stage and could not be investigated.

CONCLUSION(S)

The hospital prevalence of CHB in present study was just below 4.6%. There was equal distribution between early and late CHB. This highlights a notably high occurrence (53%) of early-onset CHB, which is a significant finding compared to other studies. This could help refine neonatal screening protocols in Neonatal intensive care units. Sepsis was the most common aetiology (34%) of NC in this cohort, with a higher frequency among premature and small-for-gestational-age neonates. This reinforces the importance of early identification and management of infections in at-risk neonates to prevent complications such as cholestasis. Further multicentric studies are required to describe these aetiologies and outcome in greater details.

Authors' contributions: Conception and design: AP, SA, SKS and JP; Acquisition, analysis and interpretation of data: AP, SKS and JP; Drafting the article: AP, SKS and JP; Revising it critically for important intellectual content: SA and SKS; Approved final version of the manuscript: AP, SA, SKS, and JP.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Paediatrics, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India.
2. Associate Professor, Department of Paediatrics, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India.
3. Assistant Professor, Department of Paediatrics, Aurobindo Medical College and Postgraduate Institute, Indore, Madhya Pradesh, India.
4. Assistant Professor, Department of Paediatrics, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Sumit Kumar Singh,
Department of Paediatrics, Sri Aurobindo Medical College and Postgraduate Institute, Indore, Madhya Pradesh, India.
E-mail: drsumitkgmu@gmail.com

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