IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 3 Ser. 12 (March. 2019), PP 78-83
www.iosrjournals.org

Study of Frequency of Various Clinical Forms of Neonatal Cholestasis in Jharkhand: A Hospital Based Study

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Abstract:
Background: *Neonatal Cholestasis occurs due to so many causes like- genetic, metabolic, obstructive & less commonly infective. It is never physiological.*
Aims & Objectives: *To describe a stepwise approach for the evaluation of neonatal cholestasis, to understand the importance of early screening for neonatal cholestasis and to understand the frequency of various clinical forms of neonatal cholestasis.*
Methodology: *It is a prospective cohort study, it will include 30 babies diagnosed as having Neonatal Cholestasis at Rajendra Institute of Medical Sciences, Ranchi, Jharkhand from 13 April 2018 to 31 January 2019. In this study descriptive and inferential statistical analysis of data will be done using suitable stastical method.*
Results: *Of the 30 infants investigated, 12 diagnosed as Biliary atresia(40%), 4 with Progressive familial intrahepatic cholestasis(13%), 3 with Premature delivery(10%), 3 with Infectious diseases(10%), 2 with Metabolic & Endocrine disorders(7%), 1 with Alagille syndrome(3%) & 5 cases are Idiopathic neonatal hepatits(17%).*
Conclusion: *Biliary atresia is the most common entity leading to Neonatal cholestasis,It must be differentiated from other causes of cholestasis (PFIC , Infectious diseases,premature delivery, Metabolic & Endocrine disorders and Idiopathic neonatal hepatits) promptly because early surgical intervention before 2 months of age results in a better patient outcome.*
Keywords: *Cholestasis, Hyperbilirubinemia, PFIC, Biliary Atresia*

Date of Submission: 04-03-2019 Date of acceptance: 20-03-2019

I. Introduction

Jaundice, a yellow discolouration of the skin, sclera, mucous membrane & bodily fluids is a common clinical findings in the first 2 weeks after birth, occurring 2.4% to 15% of newborns. Most often, jaundice is, of the indirect or unconjugated variety & resolves spontaneously without intervention. However, persistent jaundice beyond 2 weeks is generally abnormal & can be the presenting signs of serious hepatobiliary or metabolic dysfunction. Cholestasis is defined as – The failure of bile to reach the duodenum, which may be due to pathology anywhere between the hepatocyte & ampula of vater. It may be Intrahepatic or Extrahepatic disorder. Neonatal cholestasis is defined as – persistence of conjugated hyperbilirubinemia for > 14 days in term infants with the direct bilirubin at >20% of total serum bilirubin (TSB}, If TSB is >5mg/dl or direct bilirubin >1mg/dl, if TSB is <5 mg/dl. Cholestasis in infants occurs due to so many causes like- genetic, metabolic, obstructive & less commonly infective. It is never physiological. The typical findings in an infant with cholestasis are- protracted jaundice, acholic stools, dark coloured urine & hepatomegaly. Some infants may present with bleeding or bruising, splenomegaly, neurologic abnormality (like irritability, lethargy, poor feeding, hypotension & seizures) & facial dysmorphism. The incidence of neonatal cholestasis is about 1 in 2500 live births, of which Biliary atresia (BA) represents the most common cause (35% - 41%), followed by Progressive familial intrahepatic cholestasis, PFIC (10%), Premature delivery (10%), metabolic & endocrine disorder (9-17%), Alagille syndrome (2-6%), Infectious diseases (1-9%), Mitochondriopathy (2%) & Idiopathic cases (13-30%). Once Neonatal Cholestasis is confirmed, a systemic approach should be applied for the rapid diagnosis & specific treatment. This strategy is most important to identify & treat infants with Biliary atresia, the most common cause of Neonatal cholestasis, as this require- Hepatoportoenterostomy (kasai procedure) as soon as possible. My study is to provide a detailed & systematic work up to know : The frequency of various clinical forms of neonatal cholestasis in Jharkhand.

II. Methodology

Thirty neonates having Neonatal Cholestasis are included in this study at Rajendra Institute of Medical Sciences, Ranchi, Jharkhand from 13 April 2018 to 31 January 2019. The neonates incuded in this study are: Infants < 28 days of life, persistent hyper bilirubinemia for > 14 days, increased levels of direct bilirubin >20% of total serum bilirubin, presence of clay coloured stool, infants with evidence of liver cell failure & jaundice, infants with dysmorphic features with jaundice & infants with features of sepsis & jaundice.

The Infants with hyperbilirubinemia > 2 weeks, will get evaluated in a step wise approach, to identify the underlying etiology & the frequency of different clinical forms of Neonatal Cholestasis will be approached. The Infants are followed up every 2 weeks to know the status of disease & outcome after treatment. The investigations done as per facilities available in our Institutions are: complete blood count including peripheral blood smear, sepsis screen, baby & mother blood group with Rh type, direct coomb`s test, liver function test {including serum bilirubin (total, direct & indirect), SGOT, SGPT, Alk. phosphatase, GGT & PT} G-6 PD assay serum electrolytes(sodium. potassium, calcium), serum albumin, Thyroid function test (mainly TSH) , screening for TORCH infection, HIV, HbsAg, Ultrasonography & Echocardiography. Infants > 28 days of life, history of ABO blood group or Rh type incompatibility, hyperbilirubinemia for < 14 days or direct bilirubin < 20% of total serum bilirubin, & infants having undergone the procedure of exchange transfusion for severe indirect hyperbilirubinemia are excluded from this study.

III. Results

Out of 30 neonates, having Neonatal Cholestasis, 16 neonates are male babies, while 14 neonates are female babies, showing no sexual predominance . Of the 30 neonates investigated, 12 diagnosed as Biliary atresia(40%), 4 with Progressive familial intrahepatic cholestasis ,PFIC(13%), 3 with Premature delivery(10%), 3 with Infectious diseases(10%), 2 with Metabolic & Endocrine disorders(7%), 1 with Alagille syndrome(3%) & 5 cases are Idiopathic neonatal hepatits(17%). So the extrahepatic causes of neonatal cholestasis accounts for 12 cases, while intrahepatic causes acconts for 18 cases of the total of 30 neonates diagnosed as having neonatal cholestasis. The distribution of clinical signs and symptoms for the neonates shows, that they all presented with jaundice. Significantly more neonates with extrahepatic cholestasis had clay-coloured stools ($P < 0.01$) and a tendency to bleed ($P < 0.05$) than those with intrahepatic cholestasis. There were no other significant differences in clinical signs and symptoms between the two groups. Liver function test shows, no significant difference in total serum bilirubin levels between the two groups. Neonates with extrahepatic cholestasis had significantly higher levels of direct serum bilirubin ($P < 0.05$), ALP ($P < 0.01$), GGT ($P < 0.01$), PT ($P < 0.01$), ALT ($P < 0.05$) and AST ($P < 0.05$) and significantly lower levels of albumin ($P < 0.05$) compared with the neonates with intrahepatic cholestasis. . Ultrasonographic reports indicates that , Significantly more extrahepatic than intrahepatic cholestasis neonates had dilated biliary radicals ($P <0.01$). None of the intrahepatic cholestasis neonates had a positive triangular cord sign compared with 17.9% of the extrahepatic cholestasis neonates ($P < 0.01$).

Table 1: Frequency of various clinical forms of neonatal cholestasis:

Intrahepatic cholestasis(18 cases)			
Diagnosis	**No. of cases**	**Frequency (%)**	**Frequency (%) among all cases**
PFIC	4	22	13
Infection	3	17	10
Premature Delivery	3	17	10
Metabolic & Endocrine Disorders	2	11	7
Alagille syndrome	1	5	3
Idiopathic Neonatal Hepatitis	5	28	17
Extrahepatic cholestasis(12 cases)			
Biliary Atresia	12	100	40

FIG. 1:

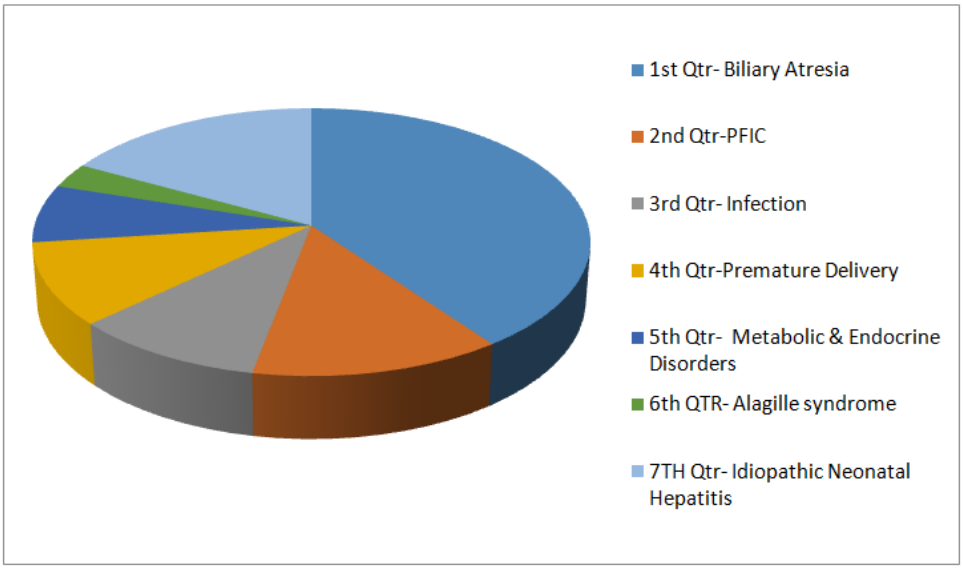

Table 2: Clinical signs and symptoms of the infants with intrahepatic and extrahepatic cholestasis who participated in this study

Signs and symptoms	Intrahepatic (18 cases)	Extrahepatic (12 cases)	Statistical significance
Jaundice	18 (100%)	12 (100%)	No significance(NS)
Clay-coloured stools	1 (6%)	10 (83%)	P< 0.01
Bleeding tendency	3 (17%)	7 (58%)	P< 0.05
Failure to thrive	4 (22%)	1 (8%)	NS
Abdominal distension	3 (17%)	3 (25%)	NS
Diarrhoea	1 (6%)	0	NS

Table 3: Comparison of liver function tests in the infants with intrahepatic and extrahepatic cholestasis who participated in this study

Test	Intrahepatic (18 cases)	Extrahepatic (12 cases)	Statistical significance
Total serum bilirubin (mg/dl)	14.2 ± 4.7	17.5 ± 6.8	NS
Direct serum bilirubin (mg/dl)	8.3 ± 3.3	10.8 ± 5.2	*P* < 0.05
Albumin (mg/dl)	3.3 ± 0.5	2.8 ± 0.8	*P* < 0.05
Alkaline phosphatase (IU/dl)	115.4 ± 26.8	236.3 ± 14.0	*P* < 0.01
□ □ □Glutamyl transpeptidase (U/l)	32.1 ± 11.9	99.2 ± 91.0	*P* < 0.01
Alanine transaminase (U/l)	154.7 ± 26.8	178.5 ± 21.2	*P* < 0.05
Aspartate transaminase (U/l)	207.4 ± 23.5	245.2 ± 19.7	*P* < 0.05
Prothrombin time (s)	12.2 ± 1.7	30.6 ± 2.7	*P* < 0.01

Table 4: Comparison of ultrasonography findings in infants with intrahepatic and extrahepatic Cholestasis

Ultrasonography finding	Intrahepatic (18 cases)	Extrahepatic (12 cases)	Statistical significance
Hepatomegaly	12 (67%)	9 (75%)	NS
Splenomegaly	9 (50%)	7 (58%)	NS
Ascites	2 (11%)	4 (33%)	NS
Visualized gall bladder	15 (83%)	4 (33%)	*P* < 0.01
Dilated common bile duct	0	5 (42%)	*P* < 0.01
Dilated Biliary radicals	0	4 (33%)	*P* < 0.01
Positive triangular cord sign	0	3 (25%)	*P* < 0.01

IV. Discussion

Infantile cholestasis, characterized by persistent conjugated hyperbilirubinaemia,has remained a major diagnostic challenge despite continued improvements in diagnostic tests and increasing knowledge regarding its pathogenesis. It is important that infants with biliary atresia are identified early because the success of the Kasai procedure is inversely related to age and outcomes are best when performed during the first 2 months of life.2 No single test or imaging modality can reliably define the causes of infantile cholestasis. The prognosis of

infantile cholestasis, either intrahepatic or extrahepatic, depends on the region of study, the severity of the disease and whether the parents are aware of the symptoms of the disease. The objectives of the present study were to assess the relative accuracy and role of abdominal ultrasonography, and other investigations in differentiating the diverse causes of infantile cholestasis, and to propose the best diagnostic approach. In total, 30 infants classified as having either intrahepatic or extrahepatic causes for their cholestasis were investigated.
Biliary atresia(BA) is the most common cause of neonatal cholestasis and progresses to end-stage liver disease in up to 80% of patients within the first two decades after birth. Early identification and Hepato-Porto-Enterostomy(HPE) are essential to establish bile flow and avoid liver transplantation within the first 2 years. A loss of stool pigmentation (acholic stools) may be one of the earliest clinical indicators of BA and is not confounded by breastfeeding, as is relying solely on the presence of jaundice. Lai et al found that 95% of infants who have BA had acholic stool in early infancy. In Taiwan, a national stool color screening system was implemented in 2004 through which an infant stool color card was placed into the child health booklet given to the mother of every newborn. Mothers were to notify a care provider if the infant had an acholic stool before age 1 month and brought the stool color card into the 1-month health supervision visit to show the provider the color of the stools. This program reduced the average age at diagnosis of BA, increased the national rate of the HPE operation performed before age 60 days, increased the 3-month jaundice-free rate after HPE, and increased the 5- year overall survival rate .

Clay-coloured stools were significantly more common among infants in the present study with extrahepatic cholestasis than with intrahepatic cholestasis ($P < 0.01$). This is a very important sign in differentiating extrahepatic biliary atresia from neonatal hepatitis and must be taken into consideration during the evaluation of infantile cholestasis. Lai *et al*. stated that the diagnostic accuracy of persistent clay coloured stools was 80.2% in the diagnosis of extrahepatic biliary atresia. Bazlul Karim and Kamal26 noted, in 63 cholestatic infants, that 13/16 (81.3%) who had extrahepatic biliary atresia and 16/37 (43.2%) infants with neonatal hepatitis had clay coloured stools. Abdel-kawy21 found that claycoloured stools were observed in 94% of surgical causes (including extrahepatic biliary atresia), which was significantly higher than that due to other causes (48%). They also reported that the appearance of clay-coloured stools in patients diagnosed with extrahepatic biliary atresia gave a diagnostic accuracy for extrahepatic biliary atresia in 73% of cases, with a sensitivity of 94% and a specificity of 52%.

All patients in the present study were subjected to abdominal ultrasonography, and laboratory investigations. Infants with extrahepatic cholestasis showed significantly lower serum albumin, higher serum ALP, higher GGT, higher direct serum bilirubin and prolonged PT compared with those with intrahepatic cholestasis. Serum GGT is a very important test for differentiating extrahepatic biliary atresia from other causes of cholestasis. The findings presented here are in accordance with those of Roberts, in terms of being elevated several-fold above the normal level in extrahepatic biliary atresia. Badawy in their study of 981 patients, found the mean elevation of GGT in extrahepatic biliary atresia was 10.6-fold, with the smallest rise in idiopathic neonatal hepatitis (7.1-fold). Roberts also stated that PT may be normal in cholestatic infants, although 10 – 15% of patients may present with vitamin K responsive coagulopathy.

Comparison of abdominal ultrasonography in the present study revealed that the sensitivity, specificity, positive predictive value and negative predictive value of abdominal ultrasonography for intrahepatic cholestasis were 95.0%, 50.0%, 90.0% and 50.0%, respectively, whereas for extrahepatic cholestasis they were 76.4%, 54.5%, 72.2% and 60.0%, respectively, and for all cholestatic infants they were 86.0%, 50.0%, 81.5% and 58.3%, respectively. Lin *et al*. demonstrated a sensitivity, specificity and accuracy of abdominal ultrasound for biliary atresia of 86.7%, 77.1% and 79.4%, respectively, and similar data were reported by Park *et al*., with values of 85%, 100% and 95%, respectively. Kotb *et al*. found 25/65 cholestatic infants identified with the triangular cord sign had extrahepatic biliary atresia . After abdominal ultrasonography of 55 infants with cholestatic jaundice, which focused on the triangular cord sign, Kanegawa *et al*. reported that the diagnostic accuracy for biliary atresia was 95%, the sensitivity was 93% and the specificity was 96%. In a study of 65 infants, Dehaghni *et al*. found abdominal ultrasonography had a sensitivity and specificity for extrahepatic biliary atresia of 52.6% and 76.1%, respectively.

In a recent study by Harpavat et al, direct bilirubin and conjugated bilirubin levels that were obtained within the first 72 hours after birth were retrospectively reviewed from 34 infants who had BA and a number of controls. All direct or conjugated bilirubin levels in the BA infants exceeded laboratory norms and were significantly higher than those of the control subjects ($P < .0001$). However, total bilirubin remained below the American Academy of Pediatrics' recommended phototherapy levels, and the ratio of direct bil-irubin:total bilirubin was less than 0.2, the current level at which the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommends further evaluation. Additional studies will be needed to confirm these findings; however, this study suggests that if all newborns were to be screened for elevated direct bilirubin levels in the first 96 hours after birth regardless of clinical appearance, that it might be possible to identify those who have BA and cholestasis at a young age, potentially improving the outcomes for BA and

possibly other conditions. Of course, a cost-effectiveness analysis would need to be conducted to determine the rate of false-positive findings and the costs of such a recommendation for essentially universal screening of total and direct or conjugated bilirubin levels before a newborn is discharged from the hospital.

V. Conclusion

Cholestatic jaundice, defined as conjugated hyperbilirubinemia, must be considered in any infant presenting with prolonged jaundice longer than 2 weeks (or with hepatomegaly, failure to thrive, acholic stools, or dark urine before or after age 2 weeks) because it can be the first sign of liver disease. Early detection of cholestasis and subsequent prompt diagnostic evaluation by a pediatric hepatologist is essential to successful treatment and optimal prognosis. Delayed diagnosis of neonatal cholestasis (and particularly of BA) remains a problem. Further investigation and development of evidence will be necessary to know the frequency of different clinical forms of Neonatal Cholestasis in the health facility.

Fig 2: Diagnostic Algorithm of Neonatal Cholestasis

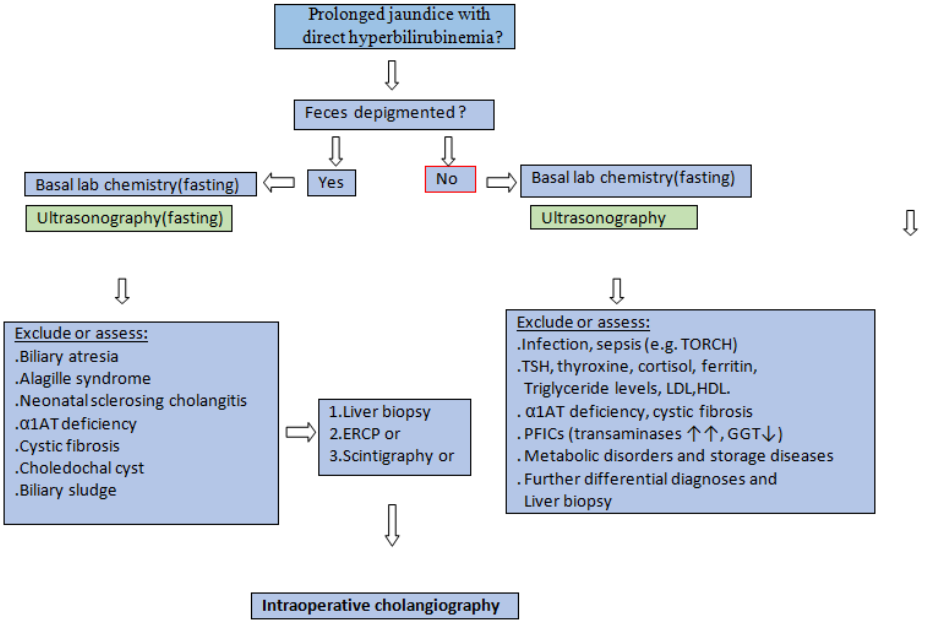

Table 5: Key Clinical and Laboratory pointers to Diagnosis of Neonatal Cholestasis

Acholic stools	Biliary atresia, Choledochal cyst, Neonatal sclerosing cholangitis, inspissated bile duct syndrome, Spontaneous perforation of bile duct, Ductal paucity (PILBD)
Sick infant	Metabolic liver disease (Galactosemia, Tyrosinemia, Neonatal hemochromatosis, Fatty-acid transport and mitochondrial oxidation, FATMO defects), Sepsis, Urinary tract infection, TORCH infections
Pruritus	PFIC types 1, 2 and 3, PILBD (Alagille's syndrome and Non-syndromic)
Ascites	MLD (Galactosemia, Tyrosinemia, Neonatal hemochromatosis), Late presentation of biliary atresia (>6 mo), End-stage liver disease due to any cause, Spontaneous perforation of bile duct
Dysmorphism	Alagille's, Down's syndrome, Williams syndrome, Peroxisomal defects, TORCH infections
Cardiac defect or murmur	Alagille's syndrome (Peripheral pulmonary artery stenosis), Congenital rubella (Patent ductus arteriosus, Tetralogy of Fallot, Ventricular septal defect), Biliary atresia (VSD, Atrial septal defect)
Eye findings	Galactosemia (Cataract), Alagille's syndrome (Posterior embryotoxon), TORCH infections (Chorioretinitis), Niemann-Pick disease type C (Cherry red spot)
Vertebral defects	Alagille's syndrome
Lymphedema	Aagenes syndrome
Rickets + Renal tubular acidosis	Galactosemia, Tyrosinemia
Low GGT	Progressive familial intrahepatic cholestasis (PFIC) types 1 & 2, Bile acid synthetic defects
Hyperammonemia	Neonatal intrahepatic cholestasis caused by citrin deficiency(NICCD), Advance liver failure due to any cause

Hypoglycemia	MLD (Galactosemia, Tyrosinemia, Neonatal hemochromatosis, FATMO defects, Advance liver failure due to any cause

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