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RESEARCH ARTICLE

CLINICAL PROFILE AND OUTCOME OF CONJUGATED NEONATAL HYPER BILIRUBINIMIA IN A TERTIARY PEDIATRIC HOSPITAL

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ABSTRACT

Introduction: Neonatal cholesstasis is a silent emergency (National Biliary Atresia Registry, 1976). In a tertiary care hospital we can diagnose many cases but outcome depends on post natal age, if post natal age crosses 8 weeks of age prognosis is guarded. Very few studies captured clinical profile and outcome which can alert a practicing pediatrician about the nature of severity and long term follow up (Ohkohchi 1989). **Aims and objectives**: Outline the etiology and clinical profile of different cases of Conjugated neonatal hyperbilirubinemia and their outcome over 1year follow up. **Materials and Method**: Babies with conjugated hyperbilirubinimiamore than 20% of total bilirubin presenting at more than 14 days of age at OPD or emergency of Institute of Child Health, Kolkata were admitted in the hospital and started investigation as per standered protocol. Those diagnosed as billary atresia were referred to pediatric surgery and kasai's operation was done as early as possible preferably within 8 weeks of life. Those presenting later than 10 to12 weeks where chance of failed kasai was very high were put on palliative care after discussion with parents.In this prospective cohort study of 46 patients of conjugated hyperbilirubinemia in a neonate is followed up over 12 months and analysed the morbidity and mortality. **Result and analysis**: Ideopathic neonatal hepatitis14 (30.5%) was very high followed by billary atresia BA 11(24%), sepsis 8(17.39%) and hypothyroidism 4 (8.69%). Down syndrome and infant of diabetic mother constitute 6.5% (3) each followed by CMV2 (4.3%) and Galactosemia1 (2.17%).Out of 46 cases 17 cases were died within the follow up period of 8 months. No death is reported within 8 to 12 months. Among 17 cases of death BA were 6 ,r est 11 were due to medical cause. **Conclusion:** The prognosis for intants with neonatal cholestasis syndromespecially due to biliary atresia remains dismal, particularly in our country. It is unfortunate that 35 years after Morio Kasai's first reported success with his portoenterostomy operation our patients still not benefited from the same. Due to delay in diagnosis most babies undergo surgery late and ultimately need a liver transplant.

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INTRODUCTION

Failure of normal amount of bile to reach the duodenum is defined as cholestasis. This may be due to pathology anywhere between the hepatocyte and the ampulla of vater. Sometimes signs and symptoms are so silent in a asymptomatic baby that it remains undiagnosed for a long time. But aggressive necro-inflamation silently destroys the liver and by the time patient is symptomatic, whole liver has reached an irreversible stage. The major difficulty in the management of these babies is that the etiology of cholestasis is multifactorial and the final outcome in many conditions is determined by the early diagnosis and treatment, while the initial presenting symptoms and signs are usually non specific apart from hepatospleenomgaly, mild jaundice and pale stools. In a otherwise well baby caregiver or parents or treating physician does not pay any attention. Recently joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends that any infant noted to be jaundiced after 2 weeks of age be evaluated for cholestasis and an elevated serum direct bilirubin level (direct bilirubin levels >1.0 mg/dL or >17 μmol/L) warrants timely consideration for evaluation and referral to a pediatric gastroenterologist or hepatologist (Fawaz et al., 2017). After 4 weeks of life "every days past is one battle lost" specially in cases of untreated metabolic

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disease like tyrosinemia, galactosemia where accumulated substances due to deficient enzyme causes hepatocellular inflammation leading to progressive hepatis, cholengitis and fibrosis. Due to advent of molecular diagnosis a small sub population of idiopathic neonatal hepatitis are nowadays diagnosed as Allagile, Zellweger or Bylar's disease. Very few studies captured clinical profile and outcome which can alert a practicing pediatrician about the nature of severity. In this prospective cohort study of 46 patients of conjugated hyperbilirubinemia in a neonate, is followed up over 12 months and analysed the morbidity and mortality.

MATERIALS AND METHODS

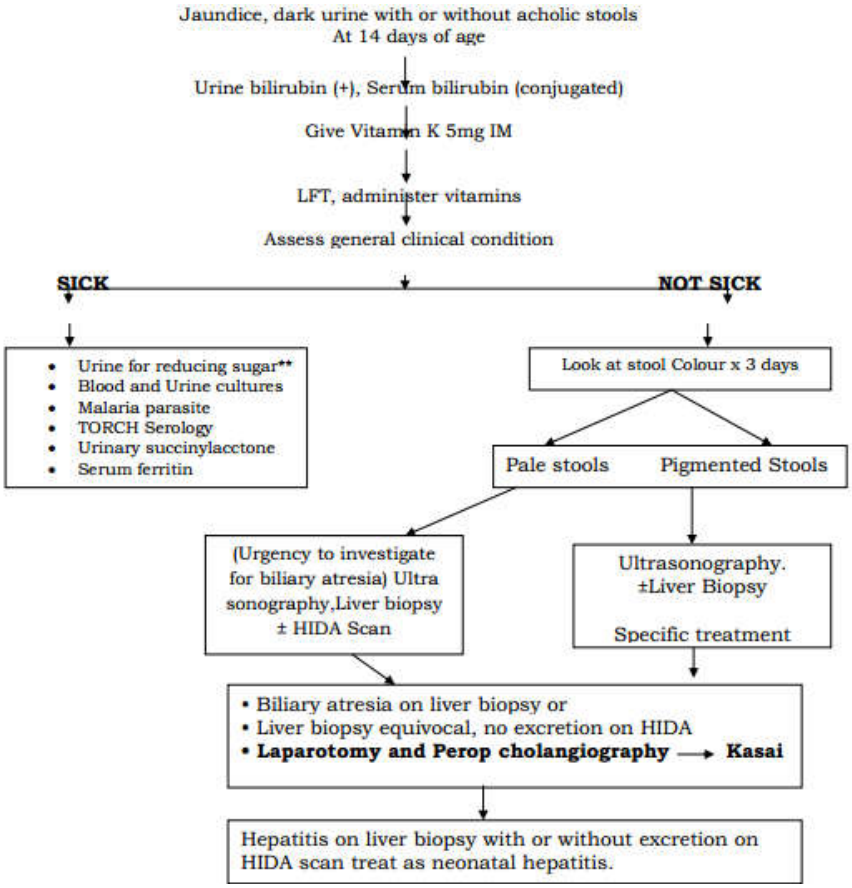
Babies with conjugated bilirubin more than 20% of total bilirub in presenting after 14 days of life at out patient department (OPD) or emergency of Institute of Child Health from March 2010 to April 2011 were included in the study. All patients were admitted in the pediatric ward or neonatal intensive care unit (NICU) of this hospital and started investigation and management as per standered protocol (Bhatia, 2014).

Hep B, HIV, negative sepsis screen, normal coagulation profile ,no clues in metabolic screen were subjected to HIDA scan and liver biopsy with proper consent. Those cases are undisputed billary atresia on liver biopsy were immediately referred to pediatric surgery for portoenterostomy of Kasai.5 In cases of doubtful billary atresia with or without excretion of dye in HIDA scan subjected to laparotomy and peroperative cholangiography. If any conclusion with respect to billary atresia Kasai's operation was done. If liver biopsy showed hepatitis with partial or complete excretion of dye were followed up as neonatal hepatitis. To diagnose suspected metabolic disease we depend on urinary reducing substance and odour. All positive non glucose reducing substance were subjected to ferric chloride test, and if metabolic disease is suspected sample was sent to referral laboratory for Tandem Mass Spectrometry.

RESULTS AND ANALYSIS

A total of 46 babies were included in this study from March 2010 to April 2011, and followed 12 months prospectively at an interval of two month upto April2012.

Approach to a Case of Neonatal Cholestasis (Standered Protocol)



According to that all the babies were subjected to complete blood count with malarial parasite, sepsis screen, blood culture, urine routine and culture, blood gas, liver function test, thyroid profile, selective TORCH screen, serology for HIV, hepatitis Band ultrasonography of whole abdomen. Sick babies were treated for sepsis with intravenous fluid, antibiotics, vitamin k and with or without parentral nutrition. The non sick looking babies with pale stool, negative serology of TORCH,

Out of 46 babies 25 were male and 21 female. Mean age of presentation to hospital with cholestasis was 42 days. All cases of trisomy 21 had maternal age less than 35 yrs and were nondysjuction of 21st chromosome on karyotype. Cardiac defect was universally present and was picked up early, so no case went to heart failure and subsequent rise of bilirubin by passive venous stasis in liver. All the babies were not sick looking and liver enzymes were proportionately raised with visualization of extrahepaticbillary tract on ultrasound of liver.

Table 1. Clinical Profile and outcome

1)	Hypothyroidism	4	3 → Normal growth and development after treatment 1→ Lost in follow up
2)	TORCH Infection(CMV)	2	Both died in the hospital
3)	Metabolic disorder(Galactosemia)	-1	Died→ due to septicemica
4)	Down's Syndrome	3	1 → died after 6 months 1→resolution of jaundice and are growing well with anticongestive medications 1→Resolution of cholestasis.
5)	Sepsis	8	2 →died due to fulminant sepsis 6→ responded to antibiotics
6)	Choledochal cyst	1	Operated doing well at 12 month
7)	Infant of Diabetic mothers	3	All of them survived and are doing well at12 month follow up.
8)	BillaryAtresia	10	2→ died after 3 days of admission due to liver failure 6→ Undergone Kasai's operation a)2 → died in post operative period b)3→Mild to Mod. Symptom at 12month. c)1 → No follow up 2 →Did not gave consent for kasai died at 6 month follow up.
9)	IdeopathicNeonatal Hepatitis(INH)	14	3 → died due to liver failure at 3month. 3→ developed cirrhosis at 9months. 3 → Jaundice resolved doing well. 2→Died due to liver failure at 6--8 months 3→ Lost in follow up.

Tabel 2. Clinical and Laboratory profile of Down syndrome with cholestasis

Number of cases	Age at presentation	Karyotype	Age Mother	Cardiac defect	TSH	Bilirubin Total/direct	SGPT	SGOT	Alk. PO4	γGT
Case1	32days	47 XY(Trisomy 21)	32	Tiny ASD	8.6	16.2/4.3	434	233	546	187
Case2	24days	,,	28	Small ASD	5.9	21.4/6.7	343	287	654	212
Case3	36days	,,	29	Small VSD	9.7	13.5/3.8	256	322	756	267

Table 3. Clinal and Laboratory profile of Hypothyroid cases

Number of cases	Age at presentation	Dry skin	Constip ation	TSH	FT4	FT3	Bilirubin Tot/Direct	SGPT	SGOT	Alk PO4	γGT
1	23 days	++	++	24	2.3	1.2	17.5/7.8	138	154	435	112
2	28days	+	++	18	1.2	0.7	13.6/5.6	189	132	443	96
3	34days	+++	++	31.5	0.9	0.8	16.8/6.5	123	166	564	134

Table 4. Clinical and Lab profile of infant of diabetic mother

Sl. no	SGA/LGA	Polycythemia PCV<60	Hypoglyc emia	Hypocalce mia	Cong. Anomaly	SGPT	SGOT	Alk PO4	TSH	Asymetricseptal Hypertrophy
1	LGA	Hb 20	++	++	Nil	433	343	432	<10	Mild
2	LGA	HB19.7	++	++	Nil	534	445	456	<10	Moderate
3	LGA	HB18.75	++	++	Nil	328	298	387	<10	Moderate

Table 5. Outcome of Kasai operation

Case number	Age at presentation	Day of operation	Post operative complication Leading to death, n=2		12 month outcome
			Infection	Perforated stoma	
1	63days	73days	+++	No	Death at 88days
2	65days	76 days	No	+++	Death at 86days
3	37days	45days	No	No	Asymptomatic
4	35days	42days	No	No	Mod symptom
5	33days	40days	No	No	Minimal symptom
6	39days	47days	No	No	Lost in follow up

Table 6. Analysis of Symptom at 12 month post Kasai

Case number	Wt. for age Centile	Length for age. Centile	Portal HTN	Palmer Erythema	Digital Clubbing
3	50^{th}	50^{th}	Regressed	No	No
4	30th	30th	Same at 6m	No	GradeII
5	40-50th	$40\text{-}50^{th}$	Same at 6m	Yes	GradeII

Table 7. Age of death due to different causes of Neonatal Cholestasis

Cause	Age of death
1) CMV	32 days
2) CMV	59 days
3) Galactosemia	49 days
4) Down syndrome	7 months
5) Sepsis	21 days
6) Sepsis	29 days
7) BA(Before Kasai, delayed refer)	80 days
8) BA(Before Kasai, delayed refer)	93 days
9) BA(Post operativePd)	63 days
10)BA(Post operativePd)	65 days
11)BA(No consent for Kasai)	180days
12)BA(No consent for Kasai)	172days
13) INH	90 days
14) INH	119 days
15) INH	120 days
16)INH	240days
17)INH	210days.

Case 2 was doing well died at 6 month due to massive pneumonia All the hypothyroid cases presented within three weeks of life with classical signs of dry skin, constipation, lathergy, poor cry, excessive sleepiness and jaundice. TSH was disproportionally high with respect to FT4 and FT3. Liver enzymes were universally raised but after starting Thyroxin to all 3 babies showed good response in clinical features as well as resolution of cholestasis. All the three cases of infant of diabetic mother who presented after 2weeks of life with conjugated hyperbilirubinimia had large body mass as compared to gestational age, needed intravenous glucose and calcium for first seven days of life.On full oral feed these babies were doing well with calcium supplementation and frequent feed. Moderate septal hypertrophy noted in two cases ,did well on follow up. Liver enzymes and cholesstasis resolved at 6 and 12 month follow up. From the above table it is concluded that survival depends on age of operation, but there may be other determinants in cholestasis free life. Inspite of early operation within 6 weeks of life our case number 4 and 5 has some symtoms of cholestasis.

In this very small cohort, inspite of post operative success two cases showed signs of liver failureat 12 months follow up. More follow up data is required to comment on slowly evolving progressive liver disease even if billarycanaliculi is patent initially. All death cases were analysed and their mode of death were due to chronic liver failure complicated with portal hypertension, ascitis ,encephalopathy and coagulopathy. Medical management could support the failing liver to some extent but without hepatic replacement therapy there is no hope.

Conclusion

Misdiagnosis of cholestasis as physiologic jaundice delays the identification of severe liver diseases. In the majority of infants, prolonged physiologic jaundice represent benign cases of breast milk jaundice, but few among them are masked and caused by neonatal cholestasis that requires a prompt diagnosis and treatment. Extra hepatic billary atresia is a surgically correctable anatomical defect which can be operated surgically by an expert pediatric surgeon. But we the practicing pediatrician as well as community physicians lack adequate knowledge and awareness for early detectection, early intervention and early surgical referral. In the year 1992 ,the department of Pediatric surgery of LTMG Hospital, Sion, Mumbai correctly recommended inclusion of "Neonatal jaundice with particular reference to biliary atresia" in all maternal and child health programmes and Launching of a media and poster campaign aimed at patients, health workers and family practitioners to increase the awareness on this issue and stressing the importance of prolonged jaundice in newborn, yellow urine and white stools as signs of a hepatobiliary disorders. All consensus report, case series, case report in the existing literature identified one common variable for the successful treatment of neonatal cholestasis syndrome is “early referral”.

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