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Cholestatic Syndromes of Infancy

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Abstract: This study aimed to provide the analysis of clinical presentation, results of laboratory and imaging investigations as well as clinical outcome of children with cholestasis. Infants with neonatal cholestasis referred to Children's Hospital from 2002 to 2007 were participated in the study in a cross-sectional prospective study. Appropriate diagnostic criteria and tests were employed for diagnosis the underlying etiologies of neonatal cholestasis. One year mortality rate was determined. One hundred twenty one infants, 75 males and 46 females, with the mean age of 58.3±15.3 (14-120) days were enrolled in study. Jaundice (94.2%) and hepatomegaly (66.1%) were the most frequent symptom and signs on admission. Idiopathic neonatal hepatitis (36.4%), extrahepatic biliary atresia (24.8%), metabolic disease (20.7%), intrahepatic ductal paucity (10.7%), intrauterine infection (3.3%) were the most frequent causes of neonatal cholestasis. One year mortality was 5.8%. There is still not one effective and specific diagnostic method in differentiating between the causes of cholestasis in the newborns and infants. Some potentially important differences in the disease pattern, initial presentation and long-term outcome are suggested from the present study when compared to previous reports from other parts of the world.

Key words: Cholestasis, conjugated hyperbilirubinemia, newborn, *Biliary atresia*

INTRODUCTION

The saga of Neonatal Cholestasis (NC) continues ever since John Cooke in 1769 referred to mortality occurring in infants due to jaundice (Yachha *et al*., 1996). It is defined as prolonged elevation of serum levels of conjugated bilirubin (> 2 mg dL^{-1} or 20% of the total bilirubin) beyond the first 14 days of life (Yachha *et al*., 1996). NC is the most common liver problem in infants. The main feature is impaired canalicular biliary flow resulting in accumulation of biliary substances in blood and extrahepatic tissues. Infants usually present with prolonged jaundice, pale stool, dark urine and hepatosplenomegaly. Etiologies could be due to infectious, genetic, metabolic, or undefined abnormalities. The incidence of NC in western countries is estimated to be around 1 in 2500 live birth (McKiernan, 2002). The most common causes of NC are Idiopathic Neonatal Hepatitis (INH) and extrahepatic biliary atresia (EHBA). The incidence of EHBA has been estimated to be about 1:15000 (Venigalla and Gourley, 2004) occurring in approximately 1 of 8,000 (Asian countries) to 1 of 18,000 (European countries) live births. Idiopathic neonatal hepatitis comprised up to 30 to 40% of all neonatal cholestasis cases in older series. However, during the past two decades, infants believed to have idiopathic neonatal hepatitis were later found to have newly discovered metabolic and genetic diseases (Sokol *et al*., 2003). The final outcome of many of these causes is dependent on early diagnosis and timely management, while the presenting clinical features are usually alike. More than 80% of cases with EHBA, who undergo Kasai portoenterostomy before 60 days of age become jaundice-free, as compared to 20-35% that was operated in longer time. In the infants with successful biliary drainage, a 15-year survival of 87% has been shown (Mieli-Vergani *et al*., 1989). Subgroups of NC other than EHBA also need early and targeted management. Timely treatment of metabolic causes like galactosemia and tyrosinemia, choledochal cyst and infections and early recognition of disorders like ductal paucity and progressive familial intrahepatic cholestasis will decrease the morbidity due to late presentation (Yachha, 2005). Nowadays, development of sophisticated diagnostic

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modalities and methods makes the diagnosis possible in early stages and the underlying cause could be easily discerned. In spite of this, unfortunately there are limited data about the disease among Asian infants. Etiologies could be different in this area and so this in homogeneity may influence the plan of management approved in western countries. This study aimed at evaluating etiologies and outcome of infants with NC in Northwest of Iran.

MATERIALS AND METHODS

In a cross-sectional descriptive study, we evaluated 121 infants with NC refereed to Children Hospital, Tabriz, Iran during a five-year period from 2002 to 2007. The parents or main care provider were personally interviewed by the author upon or soon after admission. Referral letter from the referring clinician and other inpatient record, where appropriate, was screened for additional information. Through physical examination was performed in all patients on admission and during hospital stay. The patients were followed for one year after admission and the mortality rate was calculated. As our hospital is the main referral center of pediatric disease in the Northwest region, this conclusion could be drawn that the results of current study may be attributable to the population living in this area. The present study was approved by the ethical committee of Tabriz University of Medical Sciences (TUMS). Patients' parents or person in-charge signed the consent for this study. NC was defined as the onset of clinically apparent jaundice within the first 4 months of life, with the conjugated bilirubin greater than 17 μmol L^{-1} (1 mg dL^{-1}) if the total bilirubin was less than 85 μmol L^{-1} (5 mg dL^{-1}), or the conjugated portion of plasma bilirubin more than 20% of the total bilirubin if the total bilirubin was more than 85 μmol L^{-1} (Moyer *et al*., 2004). Liver biopsy and histopathological study of extracted specimen was carried out in all patients. Radiological study, abdominal ultrasonography, hepatobiliary scintigraphy, chromatography, cholangiography, enzyme-linked immunosorbent assay (ELISA) and other different lab studies were carried out where appropriate to confirm the diagnosis of any probable underlying etiology of NC according to guidelines and instructions recommended in authoritative sources (Maclin, 2004).

Data were analyzed with the SPSS statistical software package (version 15.0; SPSS Inc., Chicago). Continuous variables were expressed as mean Standard Deviation (SD) and categorical data were shown as frequency and percent.

RESULTS AND DISCUSSION

One hundred twenty one infants with definite neonatal cholestasis were studied. They were 75 (62%) males and 46 (38%) females, with the mean age of 58.3±15.3 (14-120) days at the time of admission. The mean birth weight of the patients was 2824.5±587.6 (1975-3950) g. The mean levels of serum total and direct bilirubin on admission were 9.3±3.8 and 6.2±1.5 mg dL^{-1}, respectively. The signs and symptoms on admission and their rates are shown in Table 1. Based on the final diagnosis, extrahepatic and intrahepatic underlying causes were identified in 32 (26.4%) and 89 (73.6%) cases, respectively (Table 2). After a one year follow-up, 7 (5.8%) patients expired due to the disease. Extrahepatic biliary atresia (5 cases), idiopathic neonatal hepatitis (1 case) and histiocytosis X (1 case) were the underlying etiologies of neonatal cholestasis in died patients. Parents of 4 expired patients (all with extrahepatic biliary atresia) had not allowed their children to be operated.

Table 1: Signs and symptoms of the patients with neonatal cholestasis on admission

Sign and symptom	No.	%
Jaundice	114	94.2
Hepatomegaly	80	66.1
Acholic stool	68	56.2
Dark urine	67	55.4
Splenomegaly	53	44.0
Vomiting	24	20.0
Failure to thrive	22	18.2
Seizure	3	2.5
Edema	2	2.0
Neural deficit	2	2.0

Table 2: Causes of neonatal cholestasis

Cause	No.	%
Extrahepatic	32	26.4
EHBA	30	24.8
Choledochal cyst	2	1.7
Intrahepatic	89	73.6
INH	44	36.4
Metabolic disease	25	20.7
Galactosemia	10	8.3
GSD	7	5.8
Tyrosinemia	4	3.3
Niemann-pick syndrome	3	2.5
ISD	1	0.8
IDP	13	10.7
TORCH syndrome	4	3.3
CMV hepatitis	2	1.7
Toxoplasmosis	2	1.7
CF	1	0.8
Alagille syndrome	1	0.8
PFIC	1	0.8
Histiocytosis X	1	0.8

CF: Cystic fibrosis, CMV: Cytomegalovirus, EHBA: Extrahepatic biliary atresia, GSD: Glycogen storage disease, IDP: Intrahepatic ductal paucity, INH: Idiopathic neonatal hepatitis (giant cell hepatitis), ISD: Iron storage disease, PFIC: Progressive familial intrahepatic cholestasis (Byler syndrome), TORCH: Toxoplasmosis and other infections and rubella and cytomegalovirus and herpes simplex

Table 3: Causes of neonatal cholestasis in different studies

Study	Patients (No.)	Location	INH (%)	EHBA (%)	Metabolic disorders (%)	IDP (%)	Infection (%)
Present study	120	Iran	36.4	24.8	20.7	10.7	3.3
Aanpreung *et al.* (2005)	252	Thailand	23.0	22.2	6.0	-	9.9
Yachha (2005)	60	India	23.0	55.0	-	3.0	11.0
Bazlul Karim and Kamal (2005)	62	Bangladesh	24.2	25.8	-	-	12.0
Mowat *et al.* (1976)	137	England	52.0	23.0	-	-	-
Mieli-Vergani *et al.* (1989)	50	England	30.5	34.7	-	-	-
Stormon *et al.* (2000)	205	Australia	25.0	20.0	23.0	3.0	9.0

EHBA: Extrahepatic biliary atresia, IAP: Indian academy of pediatrics, IDP: Intrahepatic ductal paucity, INH: Idiopathic neonatal hepatitis (giant cell hepatitis)

In this prospective study, we evaluated 121 infants with Neonatal Cholestasis (NC). Majority of patients in our study were male (m/f = 1.6). The male predominance of infants with NC has been reported in a few other Asian studies; with a male to female ratio ranging from 1.2 to 4.5 (Aanpreung *et al*., 2005; Najafi, 2006; Yachha *et al*., 1996). NC, as a general term, comprises many diverse pathological entities, each one with its specific characteristics including gender difference. However; it seems that there is a gender preference of the disease in Asian infants. The mean age of infants was 58.3 days (1.9 month) when they were evaluated by our staff for the first time. Late referral of infants with NC is considered to be one the main problems in dealing with these patients; especially in developing countries. In two reports (Yachha *et al*., 1996) the mean referral age of Indian infants with NC was 3 to 3.9 months. The mean age of referral in Najafi's series (2006) carried out in capital of Iran was 4 month. The optimal age for the Kasai portoenterostomy is up to two months (Maclin, 2004). Our patients met this recommended age and they are in better position comparing other studies. Distinguishing between different underlying etiologies of NC is of great importance because the plan of treatment could literally vary. While idiopathic neonatal hepatitis and extrahepatic biliary atresia, two major causes of NC, the latter must be managed operatively as soon as possible; the preferred treatment of less common metabolic and infectious causes is medical (Najafi, 2006). Liver biopsy, is introduced as a gold-standard method in distinguishing between diverse etiologies of NC (Bazlul Karim and Kamal, 2005; Kelly and Stanton, 1995; Nayak and Vasdev, 2002; Moyer *et al*., 2004) hence we did a liver biopsy in all infants. In current study, idiopathic neonatal hepatitis (36.4%), extrahepatic biliary atresia (24.8%), metabolic disease (20.7%), intrahepatic ductal paucity (10.7%) and infection (3.3%) were the most frequent causes of NC. As shown in Table 3, idiopathic neonatal hepatitis and extrahepatic biliary atresia are the most common underlying cause of NC in infants in all studies. Apparently, the main difference regarding the prevalence of etiologies of NC is related to infectious causes. In areas with tropical-like climate (India, Malaysia, Bangladesh and Thailand), the role of infectious causes are more prominent. On the other hand, inborn errors of metabolism such as alpha-1 antitrypsin deficiency in particular, are more frequent in western countries (Lee, 2008; Mieli-Vergani *et al*., 1989; Mowat *et al*., 1976; Stormon *et al*., 2001). There was not such a case in this study. Najafi (2006) supposed that this may be attributed to lack of a routine evaluation for detecting the phenotype of alpha-1 antitrypsin deficiency in infants with NC. It was a retrospective study. We fully evaluated the suspected patients regarding alpha-1 antitrypsin deficiency; however no positive result attained. Present result as well as the reports from Asian countries lacks a significant share of alpha-1 antitrypsin deficiency in infants with NC. It seems that alpha-1 antitrypsin deficiency is a point of discrimination between the Asian and non-Asian patients, possibly due to racial variation. The one-year mortality rate in our series was 5.8%. This mortality rate is higher than 2.8% of mortality rate in Aanpreung *et al*. (2005). It should be noticed that four expired infants with extrahepatic biliary atresia did not go under operation due to their parents' noncompliance. So the true mortality rate (2.5%) is comparable with theirs. High mortality rate in our study indicates a comprehensive educational program for parents of infants with NC.

REFERENCES

Aanpreung, P., M. Laohapansang, R. Ruangtrakool and J. Kimhan, 2005. Neonatal cholestasis in Thai infants. J. Med. Assoc. Thai, 88: S9-15.

Bazlul Karim, A.S. and M. Kamal, 2005. Cholestatic jaundice during infancy: Experience at a tertiary-care center in Bangladesh. Indian J. Gastroenterol., 24: 52-54.

Kelly, D.A. and A. Stanton, 1995. Jaundice in babies: Implications for community screening for biliary atresia. Br. Med. J., 310: 1172-1173.

Lee, W.S., 2008. Pre-admission consultation and late referral in infants with neonatal cholestasis. J. Paediatr. Child Health, 44: 57-61.

Maclin, V.A.B.W.F., 2004. Approach to Neonatal Cholestasis. In: Pediatric Gastrointestinal Disease, Walker, W.A. (Ed.). BC Decker Inc., Ontario, pp: 1080-1093.

McKiernan, P.J., 2002. Neonatal cholestasis. Semin. Neonatol., 7: 153-165.

Mieli-Vergani, G., E.R. Howard, B. Portman and A.P. Mowat, 1989. Late referral for biliary atresia-missed opportunities for effective surgery. Lancet, 25: 421-423.

Mowat, A.P., H.T. Psacharopoulos and R. Williams, 1976. Extrahepatic biliary atresia versus neonatal hepatitis. Review of 137 prospectively investigated infants. Arch. Dis. Child., 51: 763-770.

Moyer, V., D.K. Freese, P.F. Whitington, A.D. Olson, F. Brewer, R.B. Colletti and V.A.B.W.F. Maclin, 2004. Guideline for the evaluation of cholestatic jaundice in infants: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J. Pediatr. Gastroenterol. Nutr., 39: 115-128.

Najafi, M., 2006. Prevalence of different etiology in neonatal cholestasis. Iranian J. Pediatric., 16: 289-294.

Nayak, N.C. and N. Vasdev, 2002. Neonatal cholestasis syndrome: Identifying the disease from liver biopsy. Indian Pediatr., 39: 421-425.

Sokol, R.J., C. Mack, M.R. Narkewicz and F.M. Karrer, 2003. Pathogenesis and outcome of biliary atresia: Current concepts. J. Pediatr. Gastroenterol Nutr., 37: 4-21.

Stormon, M.O., S.F. Dorney, K.R. Kamath, E.V. O'Loughlin and K.J. Gaskin, 2001. The changing pattern of diagnosis of infantile cholestasis. J. Paediatr. Child Health, 37: 47-50.

Venigalla, S. and G.R. Gourley, 2004. Neonatal cholestasis. Semin. Perinatol., 28: 348-355.

Yachha, S.K., 2005. Cholestatic jaundice during infancy. Indian J. Gastroenterol., 24: 47-48.

Yachha, S.K., A. Khanduri, M. Kumar, S.S. Sikora, R. Saxena, R.K. Gupta and J. Kishore, 1996. Neonatal cholestasis syndrome: An appraisal at a tertiary center. Indian Pediatr., 33: 729-734.