

Neonatal Cholestasis in Thai Infants

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The objective of this study was to study etiologies and outcome of neonatal cholestasis in Thai infants.

The medical records of infants aged less than 3 months with the diagnosis of neonatal cholestasis in Department of Pediatrics, Siriraj Hospital from 1993 to 2004 were retrospectively reviewed. The etiologies were diagnosed by history, physical examination, and proper investigations.

There were 252 infants, including 135 males (53.6%) and 117 females (46.4%). The etiologies of cholestasis were idiopathic neonatal hepatitis (INH) 23%, extrahepatic biliary atresia (EHBA) 22.2%, total parenteral nutrition (TPN)-related cholestasis 18.3%, infection 9.9%, endocrine causes 6%, choledochal cyst 5.6%, Down syndrome 4.4%, hemolytic anemia 1.6%, and miscellaneous causes 9.1%, respectively. TPN-related cholestasis was increasingly found due to advance management of critically ill premature infants. Inborn error of metabolism were suspected in 8 patients (3.2%). Seventeen cases (6.7%) developed cholestasis during the first week of life due to hemolytic anemia, intrauterine infection, hypoxia and others. During the 3 month follow-up period, 6 cases died of progressive dysfunction of liver and one case with idiopathic neonatal hepatitis died from intracranial bleeding from vitamin K deficiency.

In conclusion, INH and EHBA are the most common causes of neonatal cholestasis. Due to advance management and nutritional support in critically ill premature infants, TPN-related cholestasis is found more often. Inborn error of metabolism related to neonatal cholestases is uncommon in Thai infants. Overall short term prognosis of neonatal cholestases is good.

Keywords: Cholestasis, Neonatal hepatitis, Biliary atresia, Total parenteral nutrition

J Med Assoc Thai 2005; 88(Suppl 8): S9-15

Full text. e-Journal: <http://www.medassocthai.org/journal>

Neonatal cholestasis (NC) is the most common liver problem in infants. It is defined as impaired canalicular biliary flow resulting in accumulation of biliary substances in blood and extrahepatic tissues usually occurring in the first month of life. 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 neonatal cholestasis in Western countries is estimated to occur around 1 in 2500 live birth^(1,2).

The most common causes of neonatal cholestasis are idiopathic neonatal hepatitis (INH) and extrahepatic biliary atresia (EHBA). Idiopathic neonatal hepatitis has been reported to have an incidence of 1 in 4800 to 9000 live births⁽³⁾, while the incidence of EHBA has been estimated to be about 1:15000⁽⁴⁾. The remaining cases are caused by various other disorders, including infection, metabolic disorder, endocrine disorder, and other rare disorders.

Due to advance investigations, other genetic etiologies are increasingly recognized. While more information of diseases related to neonatal cholestasis are becoming increasing apparent, there are limited data on Asian infants. Etiologies could be different due to race, environment, and infection. Due to limitation of advance investigation, some metabolic diseases can

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not be diagnosed accurately. The objective of this study was to study etiologies and outcome of neonatal cholestasis in Thai infants.

Material and Method

Medical records of infants aged less than 3 months with diagnosis of neonatal cholestasis in Department of Pediatrics, Siriraj Hospital from 1993 to 2004 were retrospectively reviewed. Cholestasis is defined as having conjugated bilirubin level more than 1 mg/dL with total bilirubin less than 5 mg/dL, or equal to more than 20% of the total bilirubin level when total bilirubin is greater 5 mg/dL persisting more than 2 weeks. Etiologies were diagnosed by history, physical examination, and proper investigations. The following investigations were performed: TORCH titers (except for reovirus 3, adenovirus, coxsackie virus, human herpes virus 3, parvovirus), thyroid function, abdominal ultrasound, hepatobiliary scintigraphy, liver biopsy, intraoperative cholangiography, and some metabolic investiga-

tions for inborn error of metabolism such as alpha-1 antitrypsin deficiency, tyrosinemia, organic acidemia and other storage diseases. Appropriate investigations were selected depend on preliminary diagnosis and progression of disease. Treatments included specific and supportive therapies such as antibiotics, hormone, surgery, choleretic agents, nutrition and vitamin supplements. Patients were followed at least 3 months.

Results

There were 252 infants diagnosed to have neonatal cholestasis. They were 135 males (53.6%) and 117 females patients (46.4%). The etiologies were INH (23%), EHBA (22.2%), TPN-related cholestasis (18.3%), infection (9.9%), miscellaneous causes (9.1%), endocrine cause (6%), choledochal cyst (5.6%), Down syndrome (4.4%) and hemolytic anemia (1.6%) respectively (Table 1).

In the cases of INH, there was no history of neonatal jaundice in their family. All cases had

Table 1. Etiologies of neonatal cholestasis in Thai children

Etiology	Male	Female	Total (%)
Idiopathic neonatal hepatitis	37	21	58 (23%)
Biliary atresia	24	32	56 (22.2%)
TPN-related cholestasis	22	24	46 (18.3%)
Infection	12	13	25 (9.9%)
Endocrinologic causes	9	6	15 (6%)
Choledochal cyst	8	6	14 (5.6%)
Down syndrome	6	5	11 (4.4%)
Hemolytic anemia	1	3	4 (1.6%)
Miscellaneous causes	16	7	23 (9.1%)
Total	135 (53.6%)	117 (46.4%)	252 (100%)

Table 2. Miscellaneous causes of neonatal cholestasis

Etiology	Male	Female	Total
Hypoxia	4	2	6
Unknown causes with normal GGT	4	1	5
Unknown causes with high GGT	2	-	2
Alagille syndrome	1	1	2
Neonatal lupus erythematosus	2	-	2
Inborn error of metabolism	1	-	1
Hydrocephalus	1	-	1
Inspissated bile plug	1	-	1
Cleidocranial dysostosis	-	1	1
Cardiomyopathy,hydrop fetalis	-	1	1
Renal tubular acidosis	-	1	1
Total	16	7	23

cholestasis resolved completely except one case who died from intracranial bleeding. TPN-related cholestasis was found mostly in premature baby (except 5 full term infants). However, TPN was not a single cause since there could be other causes such as hypoxia, sepsis, and drug-induced.

Miscellaneous causes of cholestasis included hypoxia (6 cases), unknown causes with normal GGT

(5 cases), unknown causes with high GGT (2 cases), Alagille syndrome (2 cases), neonatal LE (2 cases) and others (6 cases). Seven cases of unknown causes with normal and high GGT had signs of chronic liver disease during follow-up period. However, they had yellow-colored stools and therefore, obstruction of biliary tract could be excluded. Inborn error of metabolisms was suspected in these patients. There

Table 3. Infectious causes of neonatal cholestasis

Etiology	Male	Female	Total
CMV(IgM positive)	2	5	7
HIV	2	1	3
Rubella	2	1	3
Syphilis	1	2	3
Toxoplasmosis	2	-	2
Sepsis	2	-	2
Other infections	-	2	2
Urinary tract infection	1	-	1
Tuberculosis	-	1	1
IAHS	-	1	1
Total	12	13	25

IAHS : infectious associated hemophagocytic syndrome

Table 4. Endocrine causes of neonatal cholestasis

Etiology	Male	Female	Total
Panhypopituitarism	1	3	4
Panhypopituitarism, hydranencephaly	2	1	3
Panhypopituitarism, septo-optic dysplasia	2	-	2
Panhypopituitarism,microcephaly	1	-	1
Panhypopituitarism,schizencephaly	-	1	1
Congenital hypothyroidism	-	1	1
Total	9	6	15

Table 5. Etiologies of neonatal cholestasis in the first week of life

Etiology	Male	Female	Total
Hemolytic anemia	1	3	4
Hypoxia	2	1	3
Congenital rubella	1	1	2
Unknown intrauterine infection	-	2	2
Biliary atresia	1	-	1
Alagille syndrome	1	-	1
Down syndrome, myeloproliferative disorder	1	-	1
Idiopathic neonatal hepatitis	-	1	1
Panhypopituitarism , schizencephaly	1	1	-
IAHS	-	1	1
Total	7	10	17

were some limitations of investigations and therefore definite diagnoses in these patients could not be determined (Table 2).

There were 25 infants whose infections were concluded as the etiologies of NC. The diagnosis had been made by clinical manifestation and/ or positive serologic test or blood cultures (Table 3).

Among those with endocrinologic causes, panhypopituitarism with or without other malformations was the most prevalent causes. Eleven cases of panhypopituitarism were found along with other anomalies such as hydranencephaly, septo-optic dysplasia, microcephaly, and schizencephaly. The second com-

mon causes were congenital hypothyroidism (Table 4).

Seventeen cases developed cholestasis early during the first week of life due to hemolytic anemia, intrauterine infection, hypoxia and others (Table 5). All cases of hemolytic anemia had hemolytic blood pictures and increased conjugated bilirubin level in which their etiologies were due to minor blood group incompatibility, homozygous Hb-Constant Spring, and congenital spherocytosis. One case had marked jaundice and hepatosplenomegaly since birth. Bone marrow aspiration showed hemophagocytosis which may be related to infection.

Table 6. Mortality related to causes of liver disease during short term follow-up

Etiology	Cause of death	Number
TPN-related cholestasis	sepsis, liver failure	1
Idiopathic neonatal hepatitis	intracranial bleeding	1
Unknown cause with low GGT	liver failure	1
Inborn error of metabolism	liver failure	1
Choledochal cyst	liver failure	1
CMV	liver failure	1
IAHS	liver failure	1
Total		7 (2.8%)

Table 7. Comparative data : etiologies of neonatal cholestasis

Etiology	Non TPN cholestasis		Included TPN cholestasis	
	Mieli-Vergani G 1989 (%)	Mclin VA 2004 (%)	Stormon MO 2001 (%)	Aanpreung P 2005 (%)
Idiopathic neonatal hepatitis	30.5	15	25	23
Biliary atresia	34.7	25-30	-	22.2
Obstructive cause	-	-	20	-
Choledochal cyst	3.1	-	-	5.6
TPN related cholestasis	-	-	20	18.3
Infection	-	-	9	9.9
Other hepatitis	8.7	-	-	-
Bacterial sepsis	-	2	-	-
CMV	-	3-5	-	-
Miscellaneous causes	-	-	-	9.1
Endocrine causes	-	1	-	6
Inborn error of metabolism and genetic syndrome	-	-	23	-
Alpha-1 antitrypsin deficiency	17.4	7-10	-	-
Galactosemia	-	1	-	-
Inborn error of bile acid biosynthesis	-	2-5	-	-
Intrahepatic cholestasis syndrome	-	20	-	-
Intrahepatic bile duct hypoplasia	5.6	-	3	-
Down syndrome	-	-	-	4.4
Hemolytic anemia	-	-	-	1.6

During the 3 month follow-up period, 7 cases died due to liver diseases. All cases had progressive liver dysfunction except a case of idiopathic neonatal hepatitis with intracranial bleeding due to vitamin K deficiency (Table 6).

Discussion

This study demonstrated causes of NC in Thai infants which were somewhat different from data from Western countries (Table 7). Both INH and EHBA were the most common etiologies of NC. However, it is relatively lower than previous reports. Studies by Mieli-Vergani G, et al⁽⁵⁾ and Mcln VA, et al⁽⁶⁾ did not include TPN-related cholestasis as the etiology of NC. The prevalence of infectious cause and TPN-related cholestasis in our study and those of Stormon MO, et al⁽⁷⁾ were similar.

Inborn error of metabolism as the cause of cholestasis in this study were very low while alpha-1 antitrypsin deficiency is the most common inborn error of metabolism causing NC in Western countries⁽⁸⁾. In our study alpha-1 antitrypsin levels were measured in some cases. However, no case was diagnosed during long term follow-up period. There was one case that had failure to thrive, vomiting, acidosis, suggesting inborn error of metabolism, but no definite diagnosis can be made. There were 7 cases with normal or high gamma glutamyl transferase (GGT) and signs of chronic liver disease which could be categorized in this group. The low or normal level of GGT is found in some children who have progressive familial intrahepatic cholestasis and inborn error of bile acid metabolism. If these patients were included in this category, those NC caused by inborn error of metabolism would have been 8 cases (3.2%) which are still less than what appeared in the Western data. These results suggest that inborn error of metabolism related to NC is not common in Thai infants.

Idiopathic neonatal hepatitis has two different categories, i.e., sporadic cases and familial cases. Prognosis of idiopathic neonatal hepatitis is variable. For sporadic cases the prognosis is very good with 90% resolution by age 1 year⁽¹⁾. In our study, all cases in this group had jaundice resolved completely without any signs of chronic liver disease except for one who died due to intracranial bleeding. In familial cases, the prognosis is poor as its causes may be inborn error of metabolism⁽¹⁾. In the present study, no familial history of jaundice in siblings was noted; thus, familial causes were unlikely. The criteria for diagnosis in this study were different from previous studies.

Liver biopsy was not routinely performed, so the diagnosis was made mainly by exclusion of other causes. Previous reports showed that mortality of idiopathic neonatal hepatitis is 13-25 %^(9,10). Prognosis in our data was better than in previous reports. Treatments with choleric agents, nutrition and vitamin supplements are appropriate for these patients.

Extrahepatic biliary atresia is another common cause of NC and needs urgent diagnosis before 8 weeks of age. It is an idiopathic inflammatory process resulting in obstruction of the biliary tract, chronic cholestasis, and progressive fibrosis and eventually progress to biliary cirrhosis⁽¹⁾. Delayed diagnosis is still the major problem in Thailand. Unfortunately, virus-associated with EHBA was not demonstrated due to limitation of investigations in this study.

TPN-related cholestasis was found more often due to advance management and nutritional support in critically ill premature infants. These patients have high risk for developing cholestasis due to prolonged hypoxia, recurrent infection, starvation, necrotizing enterocolitis, short bowel syndrome, and drug toxicities^(11,12). Treatment with choleric agents and vitamin supplements were appropriated for these patients. Prognosis of these patients depended on underlying diseases. There was one case of short bowel syndrome that died due to liver failure and severe sepsis.

Diagnosis of intrauterine infection is not difficult in cases of small for gestational age, hepatosplenomegaly, microcephaly, hydrocephalus, thrombocytopenia, and cholestasis⁽¹³⁾. Serological viral studies in patients and mothers, X-ray long bone and skull, eye examination should be performed to establish the diagnosis. Diagnosis of CMV infection in this study might be not conclusive because CMV IgM antibody was done in the second month of life. The serological studies do not distinguish congenital from early postnatal infection. One case with CMV infection had progressive liver failure and died. The remaining patients had jaundice resolved completely which their diagnoses may be CMV infection, idiopathic neonatal hepatitis or other causes.

Cortisol deficiency and hypothyroidism can cause cholestasis in neonate. Panhypopituitarism is associated with neonatal hepatitis syndrome in 30-70%^(14,15). Intractable hypoglycemia is another clue to diagnose panhypopituitarism. Some cases may have midline defect or dysmorphic skull. Hormone therapy can improve cholestasis but some cases need additional choleric agent. Hypothyroidism is usually

associated with unconjugated hyperbilirubinemia but may be associated with the neonatal cholestasis. Thyroid function test would be the routine investigation in neonate with unexplained jaundice.

Intrauterine infection and hypoxia were the common causes of cholestasis during the first week of life. Generally, hemolytic anemia produces increased unconjugated bilirubin which could cause jaundice. However, it can also cause cholestasis as seen in this study. Severe intrauterine hemolysis could produce conjugated bilirubin which accumulates in biliary tract establishing cholestasis as in inspissated bile plug syndrome. In a case of infectious associated hemophagocytic syndrome (IAHS), signs of chronic cholestatic liver disease were seen since birth. Investigations were performed to exclude other diseases such as neonatal hemochromatosis, uncommon viral infection, inborn error of metabolism and familial erythrophagocytic lymphohistiocytosis. Final diagnosis was revealed from autopsy, though the causative infectious agent could not be demonstrated.

Overall short term prognosis of NC was good. The mortality rate in our study was 2.8%. In these cases, the mortality was related to liver failure during the 3 month follow-up period. One case of idiopathic neonatal hepatitis died of intracranial hemorrhage due to vitamin K deficiency. Correction of vitamin K deficiency or other blood component in all cases of cholestasis should be given to prevent such complication. The infants with extrahepatic biliary atresia and cirrhosis due to unknown etiologies require long term follow-up and managements to ascertain their outcome.

In conclusion, EHBA and INH are the most common causes of NC in this study. Because of advance management and nutritional support in critically ill premature infants, TPN-related to choleostasis is increasingly found. Inborn error of metabolism related to NC is not common in Thai infants. Overall short term prognosis of NC is good.

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ภาวะตัวเหลืองจากน้ำดีคั่งในเด็กทารกแรกเกิด

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Neonatal cholestasis เป็นปัญหาโรคตับที่พบได้บ่อยที่สุดในเด็กทารก การศึกษานี้มีจุดประสงค์เพื่อหาสาเหตุที่ทำให้เกิดภาวะดังกล่าวและผลการรักษา โดยทำการศึกษาย้อนหลังในผู้ป่วยทารกที่มีอายุน้อยกว่า 3 เดือนที่มีปัญหา cholestasis ในภาควิชากุมารเวชศาสตร์ตั้งแต่ปี พ.ศ. 2536 ถึง ปี พ.ศ. 2547 โดยพบว่ามีผู้ป่วยทั้งหมด 252 ราย เป็นเด็กชาย 135 ราย (53.6%) และเด็กหญิง 117 ราย (46.4%) ซึ่งมีสาเหตุจาก idiopathic neonatal hepatitis (INH) 23%, extrahepatic biliary atresia (EHBA) 22.2% ภาวะ cholestasis เนื่องจากได้สารอาหารทางเส้นเลือด 18.3% การติดเชื้อ 9.9% โรคต่อมไร้ท่อ 6% choledochal cyst 5.6%, Down syndrome 4.4% และ hemolytic anemia 1.6% สาเหตุอื่นๆ 9.1% ภาวะ cholestasis เนื่องจากได้สารอาหารทางเส้นเลือดพบได้มากขึ้นเนื่องจากความก้าวหน้าในการดูแลทารกคลอดก่อนกำหนดที่ป่วยหนัก โรค inborn error of metabolism พบได้น้อยมากซึ่งมีผู้ป่วย 8 ราย (3.2%) อาจเป็นโรคดังกล่าว ผู้ป่วย 17 ราย (6.7%) มี cholestasis ในช่วงสัปดาห์แรกหลังเกิดโดยมีสาเหตุจาก hemolytic anemia การติดเชื้อในช่วงตั้งครรภ์ ขาดออกซิเจน และอื่นๆ ได้ติดตามผู้ป่วยอย่างน้อย 3 เดือน พบว่ามีผู้ป่วยเสียชีวิต 7 ราย (2.8%) ที่มีสาเหตุการตายเนื่องจากตับวาย 6 รายและเลือดออกในสมอง 1 รายเนื่องจากขาดวิตามิน K
