Original Article

Etiology and Clinical presentation of cholestatic jaundice during infancy period in Thammasat University Hospital

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Abstract

Background: The diagnosis of cholestasis during infancy is challenging because of its diverse etiology.

Objective: To determine the etiology and clinical profile of cholestatic jaundice during infancy in Thammasat University hospital.

Methods: The medical records of all patients with the diagnosis of cholestatic jaundice between January 2012 and January 2017 were reviewed retrospectively. Demographic characteristic, investigation, and etiology of cholestasis were collected.

Results: We enrolled 122 infants in our study (74 boys). The mean age at presentation of jaundice was 46.6 ± 62.6 days. Preterm infants numbered 68 (55.7%). Parenteral nutritional-associated liver disease (PNALD) in infants was the most common cause of cholestatic jaundice (29.5%) and occurred more often in preterm infants (75.5%). Idiopathic neonatal hepatitis (17.2%) and septicemia (13.1%) were common. Sixteen infants (13.1%) had biliary tract abnormalities, biliary atresia (BA) in 14 (11.5%) and choledochal cyst (2%), respectively. In biliary atresia, the mean age of jaundice by parental history was 47.1 days but the mean age at the first medical visit was 80.6 days.

Conclusions: PNALD in sepsis infants is the most common etiology of cholestatic jaundice in our setting, particularly in preterm infants. Identification of the possible disorders of cholestatic jaundice and accurate diagnosis are important for successful management and a better outcome.

Keyword: Parenteral nutritional-associated liver disease, Cholestasis, Cholestatic jaundice, Biliary atresia

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Introduction

Cholestasis during infancy is a rare condition but potentially a serious problem, affecting approximately 1 in 2,500 infants.[1-3] The typical findings in an infant who has cholestasis are protracted jaundice, scleral icterus, light colored stools, dark colored urine, and hepatomegaly. Any infant with cholestatic jaundice or liver disease should be immediately evaluated. The effects of cholestasis are profound and widespread that lead to worsening liver disease and systemic illness.

Cholestatic jaundice can thus be classified into intrahepatic or extrahepatic cholestasis, depending upon the level of obstruction to bile flow. Extrahepatic cholestasis or obstructive cholestasis is due to excretory block outside of the liver, along with the extrahepatic bile ducts particularly biliary atresia (BA)and choledochal cyst. Other extrahepatic causes of biliary obstruction in young infants include inspissated bile/plug syndrome, gallstones or biliary sludge and neonatal sclerosing cholangitis. Intrahepatic cholestasis can be due to a disease involving the liver parenchymal cells and/or the intrahepatic bile ducts such as neonatal hepatitis, metabolic/genetic caused (galactosemia, tyrosinemia type I, panhypopituitarism, bile acid synthetic defects, progressive familial intrahepatic cholestasis (PFIC), Alagille syndrome, parenteral nutrition-associated liver disease (PNALD) and a broad array of generally rare disorders.

Biliary atresia (BA) is the most common cause of cholestatic jaundice in the first months of life, occurring in 25-41% of patients, followed by idiopathic cholestasis (13%), progressive familial intrahepatic cholestasis (PFIC, 10%), cholestasis of preterm infants (10%), alpha-1 antitrypsin deficiency, Alagille syndrome, portocaval shunts, mitochondriopathy and biliary sludge.[1-6]

Aanpreung et al and Osatakul S et al reported the etiology of cholestasis in Thai infant include idiopathic neonatal hepatitis (INH) 23-55%, extrahepatic biliary atresia (EHBA) 22.2-67%, TPN-related cholestasis 18.3%, infection 1-9.9%, endocrine causes 6%, choledochal cyst 5.6%, Down syndrome 4.4%, hemolytic anemia 1.6%, and miscellaneous causes 9.1%, respectively.[7-8]

The objective of this study was to investigate the etiology and clinical characteristic of neonatal and infant cholestasis in Thai setting.

Methods

A retrospectively, chart review study, performed at Thammasat University hospital during 2012-2017. It was approved by the Ethics committee of the Faculty of Medicine, Thammasat University. We included term and preterm infants with cholestatic jaundice that developed before they reached 12 months (m) of age. Cholestasis was defined as either: (i) a direct bilirubin > 1 mg/dL with a total bilirubin < 5 mg/dL or (ii) direct bilirubin > 20% when the total bilirubin > 5 mg/dL.[5] PNALD is defined as a decrease in bile flow, independent of mechanical obstruction in patients receiving prolonged parenteral nutrition (PN) and with no other underlying cause of liver disease.[9-11] Clinical diagnoses of PNALD includes serum direct bilirubin >2 mg/dL or ALT > 2 × the upper limit of normal.[5, 9]

The exclusion criteria were age >12 m, loss to outpatient follow up due to any causes, and incomplete medical record data. All children underwent a full history and physical examination, which included an eye examination by ophthalmologists and echocardiogram if a cardiac abnormality was found. Stools were examinated to look for pale-colored or acholic stool. Information collected includes demographic data, gender, age of presentation, blood chemistry, diagnostic imaging test, liver histology and genetic/metabolic testing.

Data were recorded on the standard case report forms. The data analysis includes descriptive statistics of means with standard deviations, medians, and ranges by using SPSS.

Result

One hundred twenty-two infants [74 boys (60.7%)], with cholestatic jaundice met the inclusion criteria. 44.3% of infants were term newborn. Clinical characteristics of cholestatic jaundice are shown in Table 1. The mean age onset of jaundice was 46.68 ± 62.6 days, but the mean age at presentation of parental concern was 55.54 ± 65.59 days. Most BA infants (78.6%) had acholic stools at their first presentation. However, acholic stools were found in non BA group 6.6%, such as idiopathic neonatal hepatitis (n=4), PNALD (n=2), Alagille syndrome (n=1) and congenital syphilis (n=1).

The etiologies of cholestatic jaundice was shown in Table 2. PNALD was the most common cause (40.2%) neonatal and infant cholestasis and often occurred in preterm infants [n=37, (75.5%)]. Thirteen patients (10.7%) were PNALD, characterized cholestasis >2 weeks associated with TPN. Thirty-six patients were (29.5%) had PNALD combine with a confirmed bacterial infection either spontaneous or related to the TPN. Eight of whom were preterm infant with intestinal atresia and five cases were term infants with underlying gastroschisis, NEC or intestinal atresia, PPHN and HIE.

Sixteen patients (13.1%) had biliary tract abnormality. BA and choledochal cyst were found in 14 and 2 cases, respectively. The mean age of the first medical visit in BA group was 80 days, but mean age of onset that parental concern was 47.1 days. The ultrasonography for diagnosis of biliary atresia based on the appearance of the gall bladder revealed a false negative result of 75% (9 in 12) and false positive result of 4.4% (3 in 68). The triangular cord sign was positive in three cases of biliary atresia and biliary cirrhosis with ascites were found in 2 cases. Technetium 99m-iminodiacetic acid hepatobiliary scintigraphy was done in 5 cases of suspected BA and only 2 cases presented no evidence of tracer excretion into the biliary system. Two patients underwent a percutaneous liver biopsy and histology showed the classic histologic features of biliary obstruction, such as bile duct proliferation, perilobular fibrosis and periportal bridging, with preservation of the basic hepatic lobular architecture. The intraoperative cholangiogram and histologic examination of the duct remnant were done in 7 cases.

In 108 patients of non-BA group, 87 cases (80.6%) had neonatal hepatitis with an identifiable cause and 21 cases (19.4%) were idiopathic neonatal hepatitis. Infants with TORCHs infections were CMV hepatitis (n=3), confirmed by urine CMV, PCR for CMV, and liver histology. One infant had clinical features of congenital syphilis associated with an elevated rapid plasma reagin (RPR) test. Infants who had infection (16 cases; 13.1%) were identified by presented of clinical SIRS[11]. In non-BA group, liver biopsy was performed in 18 (16.7%) patients.

Infants with genetic diseases (12 cases; 9.8%), comprised eight cases of trisomy 21 that was confirmed by karyotyping. Four cases had trisomy 21 with transient abnormal myelopoiesis (TAM), one case was hypothyroidism and three case were idiopathic cause. Complete metabolic screening was performed in seven cases but all were negative even though metabolic disease was suspected strongly because of seven patients presented with hypoglycemia, with positive reducing sugars in urine and high alpha-fetoprotein (AFP). One infant had primary hyperlactatemia based a high serum lactate.

Three cases were diagnosed Alagille syndrome. All of them presented peripheral pulmonary artery stenosis, butterfly vertebrae and liver histological finding compatible with Alagille syndrome. One patient was positive for posterior embryotoxon by slit lamp eyes examination. Clinical diagnosis can be confirmed with genetic testing by finding a mutation with sequence analysis of JAG1 or NOTCH2 on Fluorescence in situ hybridization (FISH).

We founded an array of miscellaneous etiologies of cholestatic jaundice in infants. For example, a patient with congenital tuberculosis was cholestatic jaundice due to isoniazid (INH) and hereditary spherocytosis with hemosiderosis was confirmed by liver histology.

Table 1 Clinical characteristic of neonatal and infant cholestasis

	neonatal and infant cholestasis n=122 (%)
Mean age onset of jaundice (mean± SD) (days)	46.68 ± 62.6
BA group	47.1
Non-BA group	41.6
Mean age at the first medical visit (mean± SD) (days)	55.54 ± 65.59
BA group	80.6
Non-BA group	46.6
Acholic stool (n [%])	
BA	11/14 (78.57)
Non-BAgroup	8/122 (6.55)
Hepatomegaly (n [%])	54 (44.26)
Splenomegaly (n [%])	23 (18.85)
Ascities (n [%])	5 (4)
Encephalopathy (n [%])	5 (4)

Table 2 Etiology of neonatal and infant cholestasis

Etiology	N (%) n = 122	
BILE DUCT ANOMALY		
Biliary atresia	14	(11.5)
Choledochal cyst	2	(1.6)
Alagille syndrome	3	(2.5)
TOXIC OR SECONDARY DISORDERS		
PNALD	49	(40.2)
Drug (isoniazid)	22	(18)
Hemosiderosis of liver	1	(0.8)
INFECTIOUS DISORDERS		
bacteria, fungus	16	(13.1)
TORCHs	4	(3.3)
Genetic disorder		
Trisomy 21	8	(6.6)
a) TAM	4	
b) Hypothyroid	1	
c) Idiopathic	3	
IMMUNOLOGICAL DISORDERS		
Langerhan's cell histiocytosis	1	(0.8)
VASCULAR MALFORMATIONS		
Hepatic hemangioma	1	0.8
MISCELLANEOUS		
Idiopathic neonatal hepatitis	22	18

PNALD: parenteral nutrition-associated liver disease, TORCHs: Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes infections, TAM: Transient abnormal myelopoiesis

Discussion

In the present study, we have shown that PNALD combined with sepsis was the most common etiology of jaundice, followed by idiopathic neonatal hepatitis and BA. PNALD combined with sepsis was found higher rate than the other previous study because we included both term and preterm infants including underlying disease intestinal atresia, gastroschisis, necrotizing enterocolitis, persistent pulmonary hypertension of the newborn, and hypoxic ischemic encephalopathy.[7, 12] PNALD had multifactorial risk factors, including preterm birth, intestinal failure, oxidative stress, infection, nutrient deficiencies, and contaminants in PN products, as well as macronutrient provisions in the form of intravenous fat emulsion and proteins.[10, 13-15] In addition, small for gestational age is a strong independent risk factor for neonatal cholestasis.[16]

However, they were not the clinical guideline of cholestasis in the preterm infant for prolong PN used. We suggested to close follow-up and serial measurements of fractionated bilirubin levels early in life are important, monitoring growth, and tolerance of enteral feedings. In the future research and clinical interventions would be helpful to resolve many pending issues in this field.

Previous studies reported that the most common causes of cholestatic jaundice in the first months of life are BA (25%–40%).[1-6] This study showed a BA rate of 11% which was much less than previous studies. In our series, infants with BA presented with delay in mean age of the first medical visit (80 days), but the mean age of onset that parental concern was 47.1 days. Matthai et al. reported the mean age of the first medical visit of BA to hospital in their series was 2.9 months, similar to this study[16] Karim also reported a considerable delay of diagnosis, a mean of 3.5 months[4]. The discrepancy of color recognition significantly contributed to delay in the detection of BA. The affected infants may present with pigmented stools after birth, and a prolonged jaundice maybe easily misinterpreted as physiological or breast milk jaundice. As a result, they were often referred too late to obtain the optimal benefit from surgical treatment. Two studies from Taiwan reported better outcomes when an Infant Stool Color Card screening program was implemented. These studies compared outcomes before and after screening revealing significant increases in the proportion of patients undergoing Kasai operation before 60 days of life.[17, 18]

Acholic stools are almost found in obstructive cause particularly BA and choledochal cyst. Although it presented in the idiopathic neonatal hepatitis, PNALD, Alagille syndrome and congenital syphilis. However, persistent acholic stools with jaundice is the most common clinical presentation of BA and should be high on the differential diagnosis.

The abdominal ultrasound is highly sensitive in excluding choledochal cyst or gallstone disease. Signs suggestive of BA include absent or abnormal gallbladder and the triangular cord sign. Retrospective review of ultrasonography for diagnosis of biliary atresia based on the appearance of the gall bladder revealed a false negative result of 75% and false positive result of 4.4%. The DISIDA scan is another useful investigation that measures the patency of the biliary tree. The best diagnosis modalities are intraoperative cholangiogram and histological examination of the duct remnant.

Though, in biliary atresia, cholestatic jaundice developed early but most of the case came to the hospital about 2 months. There are urgent need to create greater awareness about biliary atresia. This effort will salvage a number of infants and may help reduce the infant mortality rates in whom received surgical treatment before 60 days of age. Providing effective guidance, stool color card and counselling to families are necessary and may help early detection of cholestatic infant.

Infectious caused of cholestasis jaundice such as syphilis, rubella, toxoplasmosis, and herpes virus presented with small for gestational age, coagulopathy, and growth restriction. Screening for syphilis during antenatal care and treating seropositive mothers are essential for preventing congenital syphilis. In our series, only one child had congenital syphilis.

Our rate of Alagille syndrome was similar to previous studies that have reported the rate of 2-6%.[5, 19] Liver histology typically demonstrates a paucity of interlobular biliary ducts. The main diagnostic criteria of AS are typical facial signs such as a broad forehead, deepset eyes, a pointed chin, an ocular embryotoxon, cardiac abnormalities, and butterfly vertebrae. Our infants presented with three major diagnostic criteria, namely, peripheral pulmonary artery stenosis, butterfly vertebrae and typical liver histology. However, infants younger than 6 months of age may not present with a marked paucity of the bile ducts and some may have ductal proliferation. Therefore, a full work up is essential and should include a complete physical examination, ophthalmologic examination, liver histology and confirmed with genetic testing to detect the genetic mutation by sequence analysis of JAG1 or NOTCH2.

Our study was a retrospective case study bases on 122 infants. Some patients did not have full investigations like complete metabolic screening and gene mutation analysis.

References

1. Dick MC, Mowat AP. Hepatitis syndrome in infancy: an epidemiologic survey with 10-year follow up. Arch Dis Child. 1985;60:512-6.
2. Gottesman LE, Del Vecchio MT, Aronoff SC. Etiologies of conjugated hyperbilirubinemia in infancy: a systematic review of 1692 subjects. BMC Pediatr. 2015;15:192.
3. Andrianov MG, Azzam RK. Cholestasis in Infancy. Pediatr Ann. 2016;45:414-419.
4. Bazlul Karim AS, Kamal M. Cholestatic jaundice during infancy: experience at a tertiary-care center in Bangladesh. Indian J Gastroenterol. 2005;24:52-4.
5. Balistreri WF, Bezerra JA. Whatever happened to "neonatal hepatitis"? Clinic in Liver Dis. 2006;10:27-53.
6. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, et al. Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2017;64: 154-168.
7. Hoerning A, Raub S, Dechene A, Brosch MN, Kathemann S, Hoyer PF, et al. Diversity of disorders causing neonatal cholestasis-the experience of a tertiary pediatric centerin Germany. Front Pediatr. 2014;2:65.
8. Aanpreung P, Laohapansang M, Ruangtrakool R, Kimhan J. Neonatal cholestasis in Thai infants. J Med Assoc Thai. 2005;88:S9-15.
9. Osatakul S, Mo-suwan L, Patrapinyokul S. Neonatal cholestasis at Songklanagarind Hospital. Songkla Med J. 1989;7:6-12.
10. Duro D, Mitchell PD, Kalish LA, Martin C, McCarthy M, Jaksic T, et al. Risk factors for parenteral nutrition-associated liver disease following surgical therapy for necrotizing enterocolitis. J Pediatr Gastroenterol Nutr. 2011;53:583.
11. Diamond IR, Pencharz PB, Feldman BM, Ling SC, Moore AM, Wales PW. Novel lipid-based approaches to pediatric intestinal failure-associated liver disease. Arch Pediatr Adolesc Med. 2012;166:473-8.
12. Willis TC, Carter BA, Rogers SP, Hawthorne KM, Hicks PD, Abrams SA. High rates of mortality and morbidity occur in infants with parenteral nutrition-associated cholestasis. JPEN J Parenter Enteral Nutr. 2010;34:32-7.

13. Copple BL, Jaeschke H, Klaassen CD. Oxidative stress and the pathogenesis of cholestasis. Semin Liver Dis. 2010;30:195-204.
14. Spencer AU, Yu S, Tracy TF, Aouthmany MM, Llanos A, Brown MB, et al. Parenteral nutrition–associated cholestasis in neonates: multivariate analysis of the potential protective effect of taurine. JPEN J Parenter Enteral Nutr. 2005; 29:337-43.
15. Trauner M, Fickert P, Stauber RE. Inflammation-induced cholestasis. J Gastroenterol Hepatol. 1999;14:946-59.
16. Matthai J, Paul S. Evaluation of cholestatic jaundice in young infants. Indian Pediar. 2001;38: 893-8.
17. Lien TH, Chang MH, Wu JF, Chen HL, Lee HC, Chen AC, et al. Effects of the infant stool color card screening program on 5-year outcome of biliary atresia in Taiwan. Hepatology. 2011;53:202-8.
18. Hsiao CH, Chang MH, Chen HL, Lee HC, Wu TC, Lin CC, et al. Universal screening for biliary atresia using an infant stool color card in Taiwan. Hepatology. 2008;47:1233-40.
19. Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet. 2012;20:251-7.

บทคัดย่อ

สาเหตุและอาการทางคลินิกของภาวะน้ำดีคั่งในทารกที่พบในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

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บทนำ: ภาวะน้ำดีคั่งในทารกเป็นปัญหาที่พบบ่อย มีสาเหตุที่หลากหลาย ควรได้รับการวินิจฉัยอย่างแม่นยำและรวดเร็ว

วัตถุประสงค์: เพื่อหาสาเหตุและอาการทางคลินิกในทารกที่มีภาวะน้ำดีคั่ง ที่ได้รับการตรวจรักษาในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

วิธีการศึกษา: เป็นการวิจัยเชิงพรรณนา โดยศึกษาข้อมูลจากเวชระเบียน ตั้งแต่เดือนมกราคม พ.ศ. 2555 - 2560 เก็บข้อมูลพื้นฐาน ผลตรวจทางห้องปฏิบัติการเบื้องต้นและจำเพาะโรค

ผลการศึกษา: ภาวะน้ำดีคั่งในทารกพบทั้งหมด 122 ราย (เพศชาย 74 ราย) อายุเฉลี่ยที่เริ่มมี อาการเหลือง คือ 46.6 ± 62.6 วัน เป็นทารกที่คลอดก่อนกำหนด 68 ราย (ร้อยละ 55.7) สาเหตุที่พบมากที่สุด คือ ภาวะน้ำดีคั่งจากการให้สารอาหารทางหลอดเลือด (parenteral nutritional-associated liver disease) ร้อยละ 29.5 (49 ราย) ซึ่งส่วนใหญ่เป็นทารกคลอดก่อนกำหนด ภาวะที่พบรองลงมา ได้แก่ ภาวะตับอักเสบที่ไม่พบสาเหตุ (idiopathic neonatal hepatitis) ร้อยละ 17.2 ติดเชื้อในกระแสเลือด ร้อยละ 13.1 และโรคท่อน้ำดีอุดตัน (biliary atresia) ร้อยละ 11.5 ตามลำดับ นอกจากนี้ในโรคท่อน้ำดีอุดตันมีอายุเฉลี่ยของที่ผู้เลี้ยงดูสังเกตุว่าเริ่มมีภาวะเหลือง คือ 47.1 วัน ในขณะที่อายุเฉลี่ยเมื่อมาพบแพทย์ครั้งแรก คือ 80.6 วัน

วิจารณ์: ภาวะน้ำดีคั่งจากการให้สารอาหารทางหลอดเลือดเป็นสาเหตุของการเกิดภาวะน้ำดีคั่งในทารกที่พบมากที่สุด โดยเฉพาะในทารกที่คลอดก่อนกำหนด อย่างไรก็ตามการวินิจฉัยสาเหตุของภาวะน้ำดีคั่งในทารกต้องอาศัยการตรวจวินิจฉัยที่แม่นยำ เพื่อจะนำไปสู่การรักษาที่เหมาะสม

คำสำคัญ: ภาวะน้ำดีคั่งจากการให้สารอาหารทางหลอดเลือด, โรคทางเดินน้ำดีตีบ, ภาวะน้ำดีคั่งในทารก