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Original article

INFANTILE CHOLESTASIS SYNDROME AT CHIANG MAI UNIVERSITY HOSPITAL FROM 1994–1998

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Abstract Objective To study the different etiologies of jaundiced infants and compare them with the clinical findings of common etiologies.

Methods A prospective collective study of jaundiced infants who were admitted at the Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai from January 1994 to December 1998. The collected data included clinical findings and investigations.

Results The common etiologic findings were biliary atresia, 31 cases (48%) and neonatal hepatitis, 23 cases (33%). The biliary atresia patients were diagnosed at an average age of 93.4 days (18-285). A clay or pale yellow stool was significantly common in biliary atresia patients (p<0.001), but the LFT was not helpful in differentiating between the these 2 conditions. Ultrasonography showed 58.2% sensitivity and 58.2% specificity. The HIDA scan was highly sensitive (100%) with a specificity of 64.7%. An intraoperative cholangiogram was helpful for a definite diagnosis of 5 neonatal hepatitis patients (22.7%).

Summary Biliary atresia and neonatal hepatitis were two common etiologies of jaundiced infants admitted at Chiang Mai Hospital. Both of them were diagnosed at a late stage. The clay or pale yellow stool was the only statitical significance found in biliary atresia patients. The HIDA scan was very sensitive and less specific. An intraoperative cholangiogram was helpful for a definite diagnosis. In a cholestatic infant with pale or yellow stool, an early transfer is essential. **Chiang Mai Med Bull 2003;42(1):17-23.**

Keywords : Infentile cholestasis, biliary atresia, clay stool

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Either structural abnormalities or functional disorders of the hepatocytes and intra- and extra-hepatic bile ducts can be responsible for etiologies of the cholestasis in infants. These patients usually present with a prolonged jaundice. The most common cause includes neonatal hepatitis (NH) and biliary atresia (BA). Besides a prolonged neonatal jaundice, the patients can have hepatosplenomegaly, normal to clay-colored stools, and dark urine. Biliary atresia is the most serious condition that, if left untreated, always leads to early death during the childhood period. These patients require immediate surgery within 60 days of age, in which the normal bile flow can be reestablished in 80% of the patients.[1] This condition accounted for 40% of patients with infantile obstructive cholangiopathy, reported by Phuapradit *et al.*[2] In that study, they used hepatobi liary scintigraphy and intraoperative cholangiography to differentiate NH from BA. However, the success rate of the Kasai operation on BA patients was not good (24%).[2]

Since early diagnosis and treatment are essential in the outcome, a prospective study was carried out to evaluate the clinical manifestation, diagnostic investigations, and treatment of the patients referred to our hospital with prolonged neonatal jaundice. This information might be useful for establishing effective and practical guidelines for this group of patients.

Materials and methods

All infants with prolonged neonatal jaundice, admitted to Chiang Mai University Hospital, were enrolled into the study from 1994–1998. Clinical presentation and a complete physical examination were recorded. Blood samples were obtained for liver function tests, prothrombin time (PT), partial prothrombin time (PTT), and serology for congenital infections, including HBs Ag, HBs Ab, toxoplasmosis titer, rubella IgM, cytomegalovirus (CMV) IgM&IgG, herpes simplex virus (HSV) IgM, and VDRL. An abdominal ultrasonography and hepatobiliary scintigraphy scan (HIDA scan) were carried out. Phenobarbital at a dose of 5 mg/kg/day was administered to the patients for 5 days before the HIDA scan. Other specific investigations were performed according to specific indications, such as hemoglobin typing, hemocultures and a CT scan. A liver biopsy was not carried out routinely in this study. If a definite diagnosis could not be made, an exploratory laparotomy would be performed with an intraoperative cholangiography (IOC) to exclude the BA. BA was diagnosed by exploratory laparotomy in the absence of a patent extrahepatic bile duct or the presence of obstructed intrahepatic or extrahepatic bile ducts that were demonstrated by intraoperative cholangiography. Idiopathic neonatal hepatitis (INH) would, on the other hand, be diagnosed if there were evidence of radioisotope activity seen in the small

bowel. A modified Kasai operation was then performed in the patients with BA.

Results

There were 63 infants with prolonged neonatal jaundice in this study. The most common causes of this condition were BA and NH, which comprised 82% of cases. The other causes responsible are shown in Table 1. There were no metabolic liver diseases or congenital infections in this study. The serology for CMV IgG was positive in both BA and NH. (40.8% *v.s.* 50.2%). Females were slightly predominant in BA, compared with NH. The patients came to seek medical attention be latedly. The mean ages of the patients at admission were 93.4 and 84.7 days in BA and NH, respectively. Six patients, 2 in BA and 4 in NH, had a convulsion as an initial symptom, resulting from an intracranial hemorrhage. Acholic and pale yellow stools were statistically significant in BA compared to those in NH ($p<0.001$). However, 54.5% of NH also had acholic stools. Table 2 summarizes the clinical manifestations of BA and NH. As shown in Table 2, the physical examination was similar in both BA and NH, except for hepatomegaly, which was more commonly noted in BA. Signs of chronic liver diseases were observed at the time of diagnosis in both groups. Associated anomalies and other clinical findings

Table 1. The etiologies of the patients with prolonged neonatal jaundice from 1994-1998.

Diagnosis	Number of the patients
Biliary atresia	31
Neonatal hepatitis	23
Biliary hypoplasia	2
Choledochal cyst	1
Bile peritonitis	1
Breast milk jaundice	3
Others (sepsis, elliptocytosis)	2

Table 2. Clinical manifestations of biliary atresia and neonatal hepatitis.

Clinical manifestation	Biliary atresia (%)	Neonatal hepatitis (%)	p value
Sex (M:F)	14 : 17	13:10	0.58
Age of admission, mean±SD(day)	93.4±61.05	84.7±60.9	0.00
Duration of Jaundice (1 wk: 1-4 wks: >4 wks)	9:9:13	7:9:6	0.51
Stool color (acolic : pale-yellow : normal)	27:3:1	12:1:10	0.01
Convulsion	2	4	0.20
Bleeding disorder	1	6	0.02
Jaundice	31 (100)	23 (100)	1
Fever	6 (19)	5 (23)	1
Hepatomegaly	31 (100)	16 (70)	0.00
Splenomegaly	20 (65)	14 (60)	0.99
Ascites	7 (23)	3 (13)	0.48
Palmar erythema	1 (3)	5 (22)	0.46
Superficial vein dilatation	5 (16)	2 (9)	0.47

Table 3. Liver function profiles.

Parameters	Biliary atresia mean±SD	Neonatal hepatitis mean±SD	p value
Albumin, gm/dL	3.60±0.74	3.59±0.80	0.96
Globulin, gm/dL	2.88±0.89	2.61±1.15	0.33
Alkaline phosphatase, U/L	526.13±275.00	477.52±217.27	0.52
Cholesterol, mg/dL	223.81±82.88	206.09±77.31	0.43
AST, U/L	230.90±110.78	419.09±707.15	0.50
ALT, U/L	161.94±114.20	202.35±183.32	0.32
Direct bilirubin, mg/dL	8.58±4.56	8.12±4.83	0.72
Total bilirubin, mg/dL	14.03±5.18	14.53±8.04	0.63
PT, sec	20.24±22.04	14.30±14.35	<.01
PTT, sec	54.37±34.98	41.17±33.83	<.01

were also found in both groups. The association with the translocation of chromosome 8p, 11q, patent ductus arteriosus (PDA), ventricular septal defect (VSD), thalassemia, indirect inguinal hernia, and umbilical hernia was noted in BA, whereas, Down syndrome, tetralogy of Fallot (TOF), unidentified anemia, G6PD deficiency, and HIV seropositive without clinical AIDS were associated with the NH patients.

The biochemical tests shown in Table 3 were unhelpful in differentiating BA from NH. Prolonged PT and PTT were more common in BA, which was due to vitamin K malabsorption. The presence of gallbladder on the abdominal ultrasound was found to be similar in both groups (42%). All cases with BA showed no excretion on the HIDA scan, compared to 37% with NH (p<0.002). The IOC was helpful in establishing the diagnosis of NH in 5 patients (22.70%). The sensitivity and specificity of the ultrasound to diagnose BA and NH were 58.3% and 41.6%, respectively, whereas, the percentages were very much higher in the HIDA scan (100% and 64.7% in sensitivity and specificity, respectively).

Discussion

Biliary atresia and neonatal hepatitis were the common causes of prolonged neonatal jaundice in our study, as seen in Western countries. In 1987, Balliseri reported that BA and NH accounted for nearly 55%–65% of all prolonged jaundice infants.[3] However, with the advent of sophisticated investigation, metabolic liver diseases, in particular alpha 1 – antitrypsin deficiency and progressive familial intrahepatic cholestasis, have been increasingly reported in literature, and consist of 12.8%–23% of the cases.[4-5] In our study, there were no metabolic liver diseases noted. This might have resulted from the lack of specific laboratories available at our center at the time. The serological evidence of congenital infections, especially CMV, was equally positive in both conditions (BA and NH) and did not show any causative correlation. This

might not be true for a test with less specificity. Therefore, it would not be worth investigating yet, unless there are more specific tests available or clinical indications.

Biliary atresia was more common at Chiang Mai University Hospital, possibly because it is a referral center in the North. The patients of this study came to seek medical attention belatedly. The ages at admission ranged from 6–282 days. This was similar to a report from India, in which the mean age at admission for BA was 120±60.5 days.[6] Inadequate health education, ignorant parents, unassessable medical care, and late referral from the primary physician might have been responsible for this issue. The late referral resulted in progressive liver damage and eventually cirrhosis. In our study, approximately one-third of the patients developed signs of chronic liver disease. Acholic and pale yellow stools kept the physician alert and eager in investigating the patients for BA, since it was more commonly seen in BA compared with NH. Some had suggested "Yellow Alert" as the screening policy for BA in the neonatal period.[6] CNS bleeding was another presentation that occurred in both groups and this has to be stressed. This was caused by prothrombin complex deficiency, which was the result of inadequate vitamin K absorption or impaired synthetic function. The liver function tests were similar in both conditions. The HIDA scan was very sensitive and statistically significant when differentiating BA from NH, but the specificity for BA was low (64.7%). The role of the ultrasonography was somewhat limited. However, there were studies that reported the presence of a triangular cord sign as an early diagnostic marker on the ultrasound for BA, which had a 95% positive predictive value.[7-8] The IOC was the final procedure that made a correct diagnosis of 5 patients with NH. As it was apparent that a laparotomy was performed in every case of acholic or pale yellow stools in these patients, it would be worthwhile to do a laparotomy as quickly as possible after each positive triangular cord sign. Other helpful diagnostic investigations were reported to empower a definite diagnosis, as laparoscopy was also mentioned for direct visualization of the liver and gallbladder, which could save 42% of unnecessary laparotomies.[9] Magnetic resonance of cholangiography was reported to demonstrate the biliary pathway clearly and quickly.[10] However, these investigations need further evaluation.

Among the cholestasis syndrome infants, one has to consider biliary atresia and other treatable condition first such as choledochal duct cyst. The clinical condition of acholic or pale yellow stool must alert the clinician to transfer the patients. Helpful investigations are the HIDA scan, and IOC.

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กลุ่มอาการน่าดีไหลช้าในเด็กโรงพยาบาลมหาราชนครเชียงใหม่

ลำดวน วงศ์สวัสดิ์, พ.บ.,[1] วินัยศักดิ์ ขัตติพัฒนาพงษ์, พ.บ.,[2] เจษฎา สิงหเวชสกุล, พ.บ.,[2] ปาริชาติ รังคกูลนุวัฒน์, วท.ม.,[3] ณัฐพงษ์ อัครพล, พ.บ.[1]

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บทคัดย่อ **วัตถุประสงค์** ศึกษาสาเหตุต่างๆ ของผู้ป่วยเด็กที่มีอายุต่ำกว่า 1 ปี ที่รับไว้รักษาในโรงพยาบาลด้วยเรื่องตัวเหลือง ตาเหลือง รวมทั้งอาการทางคลินิกของผู้ป่วยเพื่อเป็นแนวทางการวินิจฉัย

ผู้ป่วยและวิธีการ รวบรวมผู้ป่วยแบบไปข้างหน้าของผู้ป่วยที่มีอายุต่ำกว่า 1 ปี ที่รับไว้รักษาที่ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ ตั้งแต่มกราคม พ.ศ. 2537 ถึงธันวาคม พ.ศ. 2541 โดยบันทึกสาเหตุของโรค อาการ อาการแสดง ผลการตรวจวินิจฉัยทางห้องปฏิบัติการ

ผลการศึกษา พบผู้ป่วยทั้งหมด 63 ราย ที่พบบ่อยได้แก่ท่อน้ำดีตีบตัน (biliary atrsia) 31 ราย (ร้อยละ 48) และตับอักเสบ (neonatal hepatitis) 23 ราย (ร้อยละ 33) ผู้ป่วยเหล่านี้ได้รับการวินิจฉัยช้ากว่ากำหนด โดยอายุเฉลี่ยขณะรับไว้รักษาในโรงพยาบาลที่ 93.4 วัน (18–285) และ 84.7 วัน (6–282) ในผู้ป่วยท่อน้ำดีตีบตัน และตับอักเสบตามลำดับ การมีอุจจาระขาวซีดหรือเหลืองอ่อนพบได้มากในผู้ป่วยท่อน้ำดีตีบตันอย่างมีนัยสำคัญทางสถิติ (p<0.001) การตรวจการทำงานของตับไม่ช่วยในการวินิจฉัยแยกโรค การตรวจโดย ultrasound มีความไว (sensitivity) และความจำเพาะ (specificity) ร้อยละ 58.2 และ 46.6 ตามลำดับ การตรวจ HIDA scan มีความไวและความจำเพาะร้อยละ 100 และ 64.7 ตามลำดับ การทำ intraoperative cholangiogram มีประโยชน์ช่วยในการวินิจฉัยชัดเจนขึ้นในผู้ป่วยตับอักเสบได้จำนวน 5 ราย (ร้อยละ 22.7)

สรุป พบผู้ป่วยท่อน้ำดีตีบตันมากกว่าตับอักเสบเนื่องจากเป็นศูนย์รับย้ายของผู้ป่วยซับซ้อนในภาคเหนือ ผู้ป่วยได้รับการวินิจฉัยที่แท้จริงช้าโดยมีอาการของโรคเรื้อรังร่วมด้วย การมีอุจจาระขาวซีดหรือเหลืองอ่อนพบได้บ่อยในผู้ป่วยท่อน้ำดีตีบตันอย่างมีนัยสำคัญ การตรวจ HIDA scan มีความไวสูงร้อยละร้อย และมีความจำเพาะร้อยละ 64.7 การทำ intraoperative cholangiogram ช่วยชี้ชัดการวินิจฉัยตับอักเสบ **เชียงใหม่เวชสาร 2546;42(1):17-23.**

คำสำคัญ : ตัวเหลืองในเด็กเล็ก ท่อน้ำดีตีบตัน อุจจาระขาว