Diagnostic Evaluation of Infantile Cholestasis

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Objective: *To evaluate diagnostic accuracy of some important clinical manifestations and different investigations in infantile cholestasis.*
Material and Method: *Infants diagnosed with prolong conjugated hyperbilirubinemia and admitted to Chiang Mai University Hospital between Jan 1999 and Feb 2003. Demographic and clinical data were recorded. Routine biochemical tests, and serology for TORCHS infections were carried out. An abdominal ultrasonography, DISIDA scan and percutaneous/open liver biopsy were performed. Hyperechoic band at the level of portal bifurcation, named triangular cord (TC) sign was blindly assessed on ultrasonography by the same radiologist. The patients were diagnosed as BA if either operative findings of atretic common bile duct/ gallbladder or evidence of bile duct obstruction demonstrated by intraoperative cholangiography was noted.*
Results: *Sixty-one patients were diagnosed as BA (n = 31) and NH (n = 30) with an average age at diagnosis of 88.6 and 63.1 days respectively. Concerning clinical presentations, only the presence of acholic stool was significantly different between BA and NH (p = 0.006). The GGT level of greater than 500 IU/L was significantly found in BA (p < 0.001). The acholic stool and GGT level more than 500IU/L were highly specific for BA at 100 and 96.6% respectively. In addition, the sensitivity and specificity of US-TC and DISIDA scan were 87.4, 100 and 89.7, 92.0% respectively. The accuracy for diagnosis of BA were highest by DISIDA scan (96.3) followed by US-TC (86.9), GGT level of > 500 IU/L(81.0) and acholic stool(80.3) in order.*
Conclusion: *There was no single laboratory investigation that could precisely make a definite diagnosis of BA. The acholic stool and GGT level of higher than 500 IU/L were highly specific for BA. The TC in ultrasound is noninvasive and easily available tests when combined with acholic stool and the GGT level is suggested plan of management.*

Keywords: *Cholestasis, Jaundice, Neonatal, Biliary atresia*

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Infantile cholestasis has remained a challenging problem for general practitioners and pediatricians. If left untreated, some can progress to end-stage liver disease and ultimately require liver transplantation, particularly in biliary atresia (BA). Therefore, early cost-effective accurate diagnosis and prompt intervention are of importance. Seventy percent of prolonged neonatal jaundice comprises biliary atresia (BA) and idiopathic neonatal hepatitis (NH)[1]. Compared to NH which is a much more benign condition, BA is a progressive cholangiopathy, characterized by complete fibrotic obliteration of the lumen of all or part of the extrahepatic biliary tree within the first three months of life[2]. Its pathogenesis has still been obscure. However, various prenatal and perinatal insults are postulated, including infections, vascular abnormality, toxin exposure, defective morphogenesis, disorder of immunologic mechanism, and genetic factors. Despite early hepaticoportoenterostomy, BA has still been the most common indication for pediatric liver transplantation in the United States[2].

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Numbers of investigations involving in diagnostic evaluation of infantile cholestasis, such as biochemical tests, ultrasonography, hepatobiliary scintigraphy (DISIDA scan), and liver biopsy are basically used, but no such single test can definitely differentiate BA from NH, unless performing intraoperative cholangiography which is considered as a gold standard diagnosis and is invasive. Investigators, therefore, have continued to find a new reliable, rapid, and noninvasive diagnostic tool for BA. Recently, using ultrasonography to identify a triangular cord sign, triangular or tubular echogenic density cranial to the portal vein bifurcation, has become one of the promising method[3,4]. Other more advanced investigations are duodenal aspiration, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiography and the detection of lipoproiein X[5]. The aim of the present study was to review and evaluate all the diagnostic value of the clinical and laboratory investigations in the authors' hospital for further planning and management on these patients.

Material and Method

Infants who presented with cholestatic jaundice, admitted from Jan 1999 to Feb 2003 were enrolled. After clinical assessment, all of these patients were investigated for liver profiles, serum markers of congenital infections, ultrasonography, and hepatobiliary scintigraphy. The ultrasound examination was performed after at least 4 hours fasting using 10 MHz linear transducer looking for the gallbladder and the presence of triangular cord sign (TC) by a single pediatric radiologist. Hepatobiliary scintigraphy with Tc-99m (DISIDA) was carried out after phenobarbital priming 5mg/kg/day for 5 days. The DISIDA scan images were obtained at 15, 30, 60, 120 minutes and 24 hours. If there was no excretion into the intestine within 24 hours, percutaneous liver biopsy or intraoperative cholangiography was scheduled. If there was evidence of atretic common bile duct/gallbladder or bile duct obstruction demonstrated during operation and IOC, the patient would be diagnosed as BA.

Statistical analysis

Unpaired t-test was performed to compare between liver profiles mean of biliary atresia (BA) group and neonatal hepatic is (NH) group. Chi-square test was used to compare categorical data. All p-values less than 0.05 were based on two tailed test of significance. Diagnostic test were evaluated for all indicators.

Results

Sixty-one patients were enrolled, in which 31 were diagnosed as BA. The average age of BA and NH were 88.6 days (22-180) and 63.1 days (14-177), respectively. Clinical demographic data and presentation are shown in Table 1. Acholic stool was the only significant finding presenting in 18 of 31 BA patients and none was found in NH. On the contrary, pale yellow stool was noted in 13 of BA and 12 of NH patients, whereas none of BA patients had normal stool color. Seizure secondary to intraventricular hemorrhage presented in 3 cases of BA and 1 in NH patients. Signs of chronic liver disease such as ascites and palmar erythema were rarely observed in both groups. The associated clinical findings in NH were comprised of Down syndrome (n = 3), sepsis (n = 2), CMV infection (n = 2) and HIV infection (n = 1).

The basic liver function tests were compared in Table 2. Cholesterol and globulin levels were

Table 1. Clinical manifestation of BA and NH patients

Clinical manifestation	Biliary atresia (n = 31)	Neonatal hepatitis (n = 30)
Age (average, days)	88.6	63.1
(range)	(22-180)	(14-177)
F:M	20:11	14:16
Acholic stool	18	0
Pale-yellow stool	13	12
Yellow stool	0	18
Seizure	3	1
Palmar erythema	5	3
Ascites	3	1

Table 2. Liver profiles of BA and NH patients

Liver profiles	Biliary atresia (n = 31)	Neonatal hepatitis (n = 30)	p-value
Albumin (g/dl)	3.67	3.72	NS
Globulin (g/dl)	2.74	2.10	0.008
Cholesterol (mg/dl)	256.80	194.70	0.03
Alkaline phosphatase (IU/L)	629.56	573.03	NS
AST (IU/L)	221.19	186.75	0.35
ALT (IU/L)	159.07	109.75	0.05
TB (mg/dl)	17.23	15.03	0.35
GGT (IU/L)	755.14	179.48	<0.001
Prolonged PT* (sec)	8	5	NS

Data are presented with mean
* PT > 2 time control PT

Table 3. Diagnostic clinical and investigations of BA and NH patients

Indicator	Result	BA (n = 31)	NH (n = 30)	Sensitivity %	Specificity %	Accuracy %
Acholic stool	Presence	18	0			
	Absence	13	30	58.0	100	80.3
GGT	> 500 IU/L	19	1			
	< 500 IU/L	10	28	65.5	96.6	81.0
US-TC	Presence	27	2			
	Absence	4	28	87.4	89.7	86.9
DISIDA scan	No excretion	29	2			
	Excretion	0	23	100	92.0	96.3
Liver biopsy	Definite BA/NH	15	9			
	Not Diagnostic	1	0	93.8	100	60.0

(Missing number in some investigations due to not done or unavailable)

significantly higher in BA patients than those of NH patients, in which it represented a more progressive to chronic liver disease. However, no perfect cut-off value could be identified. Gammaglutamyl transpeptidase enzyme (GGT), an enzyme located in the epithelial lining of the biliary tree and canaliculi, was the only marker that showed a significant predominance in BA compared to NH. When tabulating the frequency of the patients at the different cut-off level, GGT higher than 500 IU/L showed a strong significance discrimination between BA and NH. In the present study, 19 of 29 BA and 1 of 29 NH had GGT greater than 500 IU/L. Marked prolonged prothombin time > 100 seconds were more common in BA (4/8) than in NH (2/5).

Although the presence of acholic stool had a 100% specificity for BA, its sensitivity was low (58%). However, it was the first readily significant clinical presentation that could lead to extensive diagnostic evaluation on BA. Concerning radiological investigation, ultrasonography is the cheapest and easiest tool. However, it requires high skill trained radiologists. Using the triangular cord sign as diagnostic criteria for BA, its sensitivity and specificity in the present study was 87.4% and 89.7%, respectively. Three out of 4 BA with absence of TC had severe cirrhosis; 2 cases had periportal thickening and marked fibrosis. Besides ultrasonography, DISIDA scan is commonly performed to diagnose BA before deciding to do surgery. Its sensitivity and specificity was 100% and 92%, respectively. Nonetheless, major limitations of DISIDA scan were high investment and time-consuming procedure, in which some needed phenobarbital priming. Among those, liver biopsy was the most reliable investigation for making the diagnosis of BA with a sensitivity and specificity of 93.8 and 100%, respectively, but it was invasive. Table 3 shows summarized sensitivity, specificity and accuracy of different diagnostic methods used in the present study.

Discussion

Timely fashioned diagnostic evaluation and management of infants with conjugated hyperbilirubinemia are essential, particularly in some certain surgical correctable conditions, such as biliary atresia and choledochal cyst. In case of delayed diagnosis, progressive liver damage becomes an inevitable event. Reestablishment of bile flow can occur if hepatoportoenterostomy is performed before the age of 2 months[6]. Although liver transplantation is a hope for a patient with progressive liver disease, it is costly and needs long-term follow up and management.

Hepatobiliary scintigraphy with technetium-labeled iminodiacetic acid derivatives has been accepted to differentiate BA from other non-obstructive causes[7]. In BA, the hepatic uptake of the radioisotope is not impaired, but there is no excretion into the intestine. In contrast to NH, the uptake is impaired, but there is still evidence of excretion into the small bowel, except in a case of severe hepatitis. The sensitivity of DISIDA scan in the diagnosis of BA has been reported as high as 83-100%[5]. However, a false negative result can be noted in a few patients with BA who are subsequently diagnosed. This can be explained by early testing while the patients still have incomplete obstruction in the evolutionary disease process. Compared to its sensitivity, the specificity for BA or other obstructive causes is rather low 33-100%. In those patients without anatomic obstruction may not excrete tracer[5]. In the

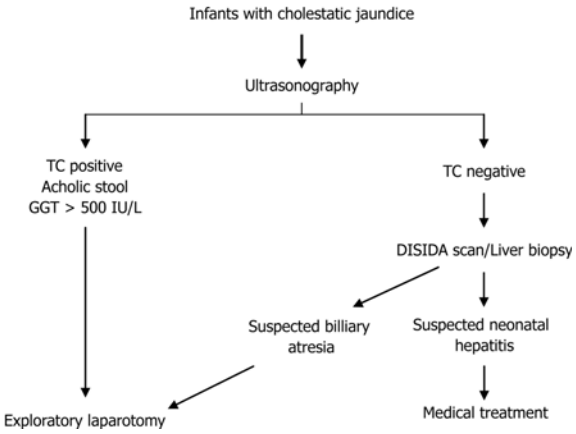

Fig. 1 Suggested plan of diagnosis and management of infantile cholestasis

present study, the sensitivity, specificity, and accuracy of DISIDA scan for diagnosis of BA were 100%, 92%, and 96.3%, respectively. The high diagnostic values found in the present study might result from a relatively old age at diagnosis of BA. This makes DISIDA scan a good test for detecting the biliary obstruction condition, however, it is a time consuming procedure.

Ultrasonography is a noninvasive and rapid diagnostic procedure for the cholestatic infants. Kotb et al reported a 100% sensitivity and specificity using the triangular cord sign[8]. Recent studies have reported high specificity of 98-100% when using TC as a diagnostic criterion for BA[5]. The present study showed the sensitivity, specificity, and accuracy of 87.4%, 89.7% and 86.9%, respectively. The lower results may be explained by 3 cases of the 4 absence TC in BA showed marked liver cirrhosis, two had periportal thickening and marked fibrosis lead to severe cirrhosis with marked fibrosis that masked the TC sign and the technical error of loss of the objectivity of the TC sign which was recently reported[9]. Other possible explanations of the false negative TC sign reported in some studies may be explained by too small periportal fibrosis mass seen on ultrasound, or unusual hepatic radicals such as hypoplastic, or fibrous hepatic duct[10,11]. The sensitivity, specificity and accuracy of biliary atresia patients will be higher when a combination of the TC sign and the gallbladder length as all reported 95.7%[12].

Based on the present study, the presence of acholic stool, which had a high specificity, leads us to propose a stool color card as a screening tool for BA to the community and public organization. With this program, it is supposed to alert parents and lead to early medical attention as had been successful in Taiwan with the sensitivity and specificity of 89.7 and 99.9%, respectively[13]. Another proposed planning for investigating and management of cholestesis infants as Fig. 1. Abdominal ultrasonography will be the first investigation that can be done instantly and at the outpatient department. When combined, the finding of TC sign, acholic stool and serum level of GGT > 500 IU/L, exploratory laparotomy is suggested without waiting for DISIDA scan, which is considered a time-consuming procedure, particularly in a patient with late presentation. These suggested plans will bring the BA patients to early referral to the center and surgical intervention will be done earlier.

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การตรวจวินิจฉัยภาวะตัวเหลือง cholestasis ในเด็กเล็ก

ลำดวน วงศ์สวัสดิ์, ณัฐพงศ์ อัครผล, พรรณี วิศรุศรัตน, เจษฎา สิงห์เวชกุล, วินัยศักดิ์ ขัตติพัฒนพงศ์

วัตถุประสงค์*: เพื่อประเมินอาการทางคลินิก การตรวจทางห้องปฏิบัติการและรังสีวิทยาในการวินิจฉัยแยกโรคผู้ป่วยเด็กเล็กที่มีภาวะตัวเหลืองชนิด cholestasis*

วัสดุและวิธีการ*: ศึกษาผู้ป่วยเด็กที่เป็นท่อน้ำดีตีบและตับอักเสบ ตั้งแต่มกราคม ปี พ.ศ. 2542 ถึงกุมภาพันธ์ พ.ศ. 2546 โดยรวบรวมข้อมูลพื้นฐาน อาการทางคลินิก การตรวจทางห้องปฏิบัติการต่างๆ เช่น การทำงานของตับ การตรวจน้ำเหลือง โรคติดเชื้อ การตรวจ triangular cord (TC) จากอุลตราซาวนด์ช่องท้องโดยผู้เชี่ยวชาญคนเดียว การตรวจ DISIDA scan และการตรวจพยาธิสภาพจากเนื้อตับที่ได้จากการเจาะหรือการผ่าตัด ภาวะท่อน้ำดีตีบวินิจฉัยจากการพบท่อน้ำดีตีบจากการผ่าตัดหรือพบการอุดตันของท่อน้ำดีจากการทำ operative cholangiography*

ผลการศึกษา*: ผู้ป่วยทั้งหมด 61 คนเป็นท่อน้ำดีตีบ 31 คนและตับอักเสบ 30 คนโดยมีอายุเฉลี่ยขณะรับการรักษา 88.6 และ 63.1 วันตามลำดับ อุจจาระขาวซีดพบในผู้ป่วยท่อน้ำดีตีบมากว่าผู้ป่วยตับอักเสบ ($p = 0.006$) ทำนองเดียวกับระดับ gammaglutamyl transferase (GGT) ที่มากกว่า 500 ยูนิตต่อมิลลิเมตร ($p < 0.001$) อุจจาระขาวซีด และระดับ GGT ที่มากกว่า 500 ยูนิตต่อมิลลิเมตรมีความจำเพาะสูงต่อผู้ป่วยท่อน้ำดีตีบร้อยละ 100 และ 96.6 ตามลำดับ ขณะที่การตรวจ TC sign และ DISIDA scanมี ค่า ความไวและความจำเพาะ ร้อยละ 87.4,100 และ 89.7, 92.0 ตามลำดับ การตรวจ DISIDA scanจะมีความแม่นยำในการวินิจฉัยท่อน้ำดีตีบต้นสูงสุดร้อยละ 96.3 ตามด้วยการตรวจ TC sign ร้อยละ 86.9 และระดับค่า GGT ร้อยละ 88.1และอุจจาระสีซีดร้อยละ 80.3 ตามลำดับ*

สรุป*: ยังไม่มีการตรวจวินิจฉัยเฉพาะอย่างที่บ่งชี้มีความแม่นยำ.ในการวินิจฉัยโรคท่อน้ำดีตีบ อุจจาระขาวซีด และระดับ GGT ที่มากกว่า 500 ยูนิต ต่อ มิลลิเมตร มีความจำเพาะสูงต่อการมีท่อน้ำดีตีบ การตรวจหา TC sign ทำได้รวดเร็วไม่ต้องเตรียมผู้ป่วยนานเมื่อนำมาพิจารณาร่วมกับสีอุจจาระและระดับของ GGT ซึ่งมีความสำคัญในการวินิจฉัยโรคท่อน้ำดีตีบ*