Factors Predictive of an Obstructive Pathology among Filipino Infants with Neonatal Cholestasis

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ABSTRACT

Objective. To determine factors predictive of obstructive neonatal cholestasis among Filipino infants and to describe their outcome.

Methods. Jaundiced infants within the first eight weeks of life with liver biopsy were included. Excluded were cholestasis secondary to metabolic or infective causes. Retrospective chart review (2009-2012) and prospective recruitment of patients (2013) were done. A final diagnosis of non-obstructive or obstructive neonatal cholestasis was made on clinical, biochemical, ultrasonographic, and histologic findings, using histology and/or operative cholangiogram as the gold standard. The outcome was assessed on the 6th and 12th months from diagnosis. The crude odds ratio for obstructive jaundice was computed. Multiple logistic regression on significant variables (p-value <0.05) was done.

Results. Two hundred sixty-three (263) patients were included: 161 with non-obstructive and 102 with obstructive cause. Mean age at first consult was higher in those with obstruction. On logistic regression, females (OR:2.3), absence of a family history of idiopathic neonatal hepatitis (OR:4), and persistently pale/acholic stools (OR:13) were predictive of obstruction. 85% of patients with a non-obstructive cause are alive and well, while 80% of patients with obstruction have died.

Conclusion. Among jaundiced infants females, the absence of a family history of idiopathic neonatal hepatitis and persistently pale yellow/acholic stools were predictive of obstruction. The outcome was poor in patients with obstructive jaundice.

Keywords: neonatal cholestasis, biliary atresia, neonatal hepatitis, acholic stools

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INTRODUCTION

Neonatal cholestasis is the persistence of jaundice in infants 15 days of life or more with a serum direct bilirubin levels of more than 20% of the total[1] or direct/conjugated bilirubin level of > 1.0 milligrams per deciliter (mg/dl) or 17 micromoles per liter (umol/L).[2] It affects approximately 1 in every 2500 term infants.[3,4] Of the many conditions that can present with jaundice in infancy, extrahepatic biliary atresia and idiopathic neonatal hepatitis are the most common causes, accounting for 44.53% and 23.36%, respectively, of cases presenting in the United Kingdom in 1976.[5] A systematic review done four decades later, on conjugated hyperbilirubinemia in the infancy of 1692 subjects, revealed both conditions remain the most common causes of neonatal cholestasis, but now have similar frequencies, 26% for idiopathic neonatal hepatitis and 25.89% for extrahepatic biliary atresia. But the latter study had significant limitations, including inconsistencies of diagnostic approach and variations among sample populations.[6] Locally, 68% of liver

biopsy patients are diagnosed with neonatal cholestasis, 42% have an obstructive pattern on histology indicative of extrahepatic cause, and 72% with hepatocellular cholestasis and widespread giant cell transformation of hepatocytes, suggestive of intrahepatic disease.[7] Other reported causes of neonatal cholestasis are seen in Table 1.

It is crucial to determine the etiology of jaundice in infants. In those with obstructive causes like extrahepatic biliary atresia or choledochal cyst, prognosis depends on the age at which an operation is performed. On the other hand, in those with known causes of non-obstructive disease such as metabolic or infectious etiology, specific treatment is available and should be instituted once confirmed. Identifying any drug or toxin causing cholestasis is also essential. Idiopathic neonatal hepatitis is a diagnosis of exclusion. In the meta-analysis done by Gottesman in 2015, the most common identified causes of non-obstructive jaundice include infection (11.47%), total parenteral nutrition (TPN)- associated cholestasis (6.44%), metabolic disease (4.37%), alpha-1 anti-trypsin deficiency (4.14 %), and perinatal hypoxia/ischemia (3.66 %). CMV was the most common infection identified (31.51 %). The most common metabolic disease etiology was galactosemia (36.49 %).[6] Countries included in the study belong to the United States (3 studies), Turkey (2 studies), United Kingdom, South Africa, Iran, Nigeria, England, and Asia-Pacific countries such as Bangladesh, China, Australia (2 studies), India, and Thailand.[6] In a study done in Malaysia, the most common cause of intrahepatic cholestasis is idiopathic (38%), followed by infectious (12.5%), TPN-associated (5%), endocrine and metabolic (4.1%), progressive familial intrahepatic cholestasis (4%), and Alagille syndrome (0.7%).[8] In the Philippines, where workups for neonatal hepatitis are limited, we consider it idiopathic after other etiologies like a structural, metabolic, or a possible infectious cause have been excluded.

Different studies have been done to identify clinical, biochemical, ultrasonographic, and histological features that will differentiate non-obstructive and obstructive causes of neonatal cholestasis. In a prospective study in a tertiary hospital in the United Kingdom, 80% of infants with biliary atresia were jaundiced at birth, and 83% had acholic stools.[5] On the other hand, a Taiwanese study reported that the onset of jaundice before 15 days of life and clay or pale-yellow color of stools failed to differentiate biliary atresia and severe neonatal hepatitis. In comparing the two disorders, the diagnostic method with the highest accuracy was percutaneous liver biopsy (92%) and duodenal juice color (90%).[9] Using histopathologic features in a mathematical model, the presence of six variables, namely, portal duct proliferation, bile plugs, portoportal bridges, neutrophils, hepatocyte swelling, and multinucleated giant hepatocytes, were able to identify an obstructive pathology with a 100% sensitivity and 74% specificity.[10] Histological confirmation will require a liver biopsy, which specialists could only do, thus requiring a referral to a tertiary center. This often causes a delay in identifying an obstructive pathology like extrahepatic biliary atresia that requires immediate surgical intervention.

Presently, no local study on a sufficient number of patients has identified the different features of infants predictive of an obstructive type of neonatal cholestasis, using histology and/or operative cholangiogram as a gold standard. Knowledge of this will alert the primary care physician on the need for further evaluation and management and urgent referral to a specialist. This study determined the clinical, biochemical, and ultrasonographic factors predictive of an obstructive cause among Filipino infants with neonatal cholestasis. The outcome of these infants will also be described.

Table 1. Differential diagnoses of neonatal cholestasis based on liver histology

Obstructive NC	Non-obstructive NC
• Biliary atresia • Choledochal cyst • Gallstones or bile sludge • Neonatal sclerosing cholangitis	• Alagille syndrome* • Alpha1-antitrypsin deficiency • Endocrine disorders (hypo-thyroidism, panhypopituitarism) • Inborn error of bile acid metabolism • Inborn error of metabolism (galactosemia, tyrosinemia type 1) • Infection • Neonatal hepatitis • Parenteral nutrition-associated liver disease

**May rarely present with obstructive features; NC= neonatal cholestasis*

MATERIALS AND METHODS

Definition of terms

A definite diagnosis of an obstructive cause of neonatal cholestasis was made if laparotomy with intraoperative cholangiography showed the absence of egress of dye into the duodenum, confirming the obliteration of extrahepatic bile ducts, and wedge liver biopsy showed an obstructive or fibrotic pattern. It was considered presumptive if an operative cholangiogram was not done. Still, an obstructive or fibrotic pattern was demonstrated on a needle biopsy, and the patient's clinical course is suggestive of an obstructive pathology, including the presence of progressive jaundice and complications related to cirrhosis. A non-obstructive etiology such as neonatal hepatitis was verified by the predominant histology of giant cell pattern in the absence of bile duct proliferation and by following the natural course of the patient, including the disappearance of jaundice and normalization of serum bilirubin levels.

Study design and setting

This was both a retrospective and a prospective cohort study conducted at the Division of Pediatric Gastroenterology, Hepatology and Nutrition of the University of the Philippines - Philippine General Hospital, a government tertiary referral center in the country. Since 2001, the

Division employed a systematic protocol in investigating cholestatic infants, which included a detailed history, physical examination, biochemical studies, appropriate serological investigations, imaging studies, and, if possible, a percutaneous liver biopsy. The research was reviewed and approved by the institution's Ethics Review Board.

Subjects investigated

Consecutive pediatric patients with jaundice within the first eight weeks of life who underwent percutaneous liver biopsy using the Menghini technique were included. Excluded were patients with incomplete records, inadequate liver biopsy specimen, a known cause of cholestasis, including those with an inborn error of metabolism, infection/sepsis proven by cultures, and those whose cholestasis is secondary to paucity of interlobular bile ducts by liver biopsy.

For the retrospective study from 2009 - 2012, the names of the infants who had a liver biopsy for cholestasis were obtained from the monthly census data. Their medical records were reviewed, and relevant data were recorded. For the prospective part conducted in 2013, all infants who fulfilled the inclusion criteria were recruited after the nature of the investigation was explained and informed consent was obtained.

Parameters investigated

Pertinent clinical, biochemical, ultrasonographic, and histological features were obtained in all patients. This included the family, birth, maternal history of the infant and the type of feeding given at the onset of cholestasis. The onset of jaundice was categorized as less than (<) 15 or (≥) 15 days or more to enable us to focus on the infants with early onset of jaundice. High-grade hepatomegaly was defined as a palpable liver edge of more than 5 cm below the costal margin, and splenomegaly was considered if it is palpable below the left costal margin.

The biochemical parameters included standard liver function tests and prothrombin time, reported as the number of seconds the patient's value is prolonged compared to the control. In writing the data of this study, a total bilirubin > 10 mg/dL was used as a cutoff since it is the midpoint of 7 and 14 mg/dL, two values used in previous studies[5,9] which showed low likelihood ratios or LR (LR of 1.8 for total bilirubin > 7 mg/dL; and LR of 0.9 for > 13.7 mg/dL). For the same reason, the direct bilirubin cutoff value for this study was increased to > 7mg/dL as the reported value of ≥ 4 mg/dL has only a likelihood ratio of 0.001.[9] For aspartate serum transaminase (AST), alkaline phosphatase (ALP) and prothrombin time (PT) the cutoff values were decreased to > 300 international units per liter (IU/L), > 200 IU/L and ≥ 4 seconds off from control, respectively, as low LR arrived with higher levels.[9] For gamma-glutamyltransferase (GGT), the same reported cutoff value of ≥ 300 IU/L was employed.[9]

Ultrasonographic findings of the hepatobiliary tree were registered either as normal, contracted, or absent gall bladder and presence or absence of hepato- and or splenomegaly, ascites, and liver parenchymal liver disease.

All needle liver biopsies were performed by the consultants or the fellows of the Division. The percutaneous liver biopsy was performed using the Menghini needle either blindly, ultrasound-guided, or with a mark at the biopsy site confirmed by ultrasound. Wedge liver biopsies were done only among infants who underwent exploratory laparotomy. The assessment of all the liver biopsies was done by a single Pediatric histopathologist who only had the information on the patient's age. Based on hematoxylin and eosin staining, all liver biopsy specimens were evaluated under a light microscope. Additional staining was requested as necessary. An inadequate liver biopsy was defined as one that has less than five portal tracts in the specimen.

Outcome

A final diagnosis of a non-obstructive or obstructive type of neonatal cholestasis was made after carefully considering the clinical, biochemical, ultrasonographic, and histologic findings. The patients were monitored at the outpatient clinic monthly, with repeat laboratory workups done as needed to monitor the course of the disease.

The outcome of the patients was assessed using two different endpoints: 6th and 12th months from the time they were diagnosed to have liver disease. For the prospective part, patients were followed-up until June 2014, at least six months from the last recruitment date. The outcome of the patients was described as follows: (1) alive with no clinical or biochemical signs of liver disease; (2) alive with sequelae if with clinical and/or biochemical signs of liver disease; and (3) died if the patient has expired or required a liver transplant.

Sample size estimate

The sample size was computed using the formula by Hsieh *et al.* for studies that used multiple regression for analysis.[11] Based on a reported minimum difference of 12% between the two groups, with a 10% significance, 80% power, and minimum correlation between data of 30% using the formula, the sample computed is 222 patients.[5]

Statistical analysis

Data were analyzed using STATA 9 (Stata Corporation, Texas USA). Discrete data were presented as numbers (percentages) while continuous data as mean (standard deviation or SD). Comparison of categorical values was performed using x^2 test or Fisher's exact test as appropriate. The non-parametric Mann-Whitney test was used for the comparison of continuous data. The crude odds ratio for obstructive jaundice was estimated for each identified potential factor. Variables that were statistically significant on univariate analysis were entered into a multiple logistic regression to identify factors predictive of obstructive etiology of neonatal cholestasis. A p-value less than 0.05 was considered significant.

RESULTS

Three hundred eleven patients fulfilled the inclusion criteria during the study period, but 48 were excluded: 42 with incomplete medical records and six with inadequate liver biopsy specimens. A total of 263 patients were included, of which 178 were analyzed retrospectively, and 85 were followed up prospectively. One hundred sixty-one patients were classified as non-obstructive and 102 with obstructive neonatal cholestasis. Of the 102, 95 (93%) had extrahepatic biliary atresia (37 diagnosed via intraoperative cholangiography and 58 based on needle liver biopsy), and seven (7%) had neonatal sclerosing cholangitis. Table 2 depicts the patient characteristics. Among the 37 patients who confirmed biliary atresia via intraoperative cholangiogram, 28 infants underwent Kasai portoenterostomy.

The mean age at first consult was higher in those with obstructive cause [3.95 (SD 3.06) months vs. 2.59 (SD 1.55), $p < 0.001$]. In the non-obstructive group, more infants were male and with a family history of idiopathic neonatal hepatitis. Persistently pale to acholic stools, the presence of high-grade hepatomegaly and splenomegaly were more common in those with obstruction.

The biochemical parameters showed significantly higher mean baseline serum AST (390 IU/L versus 311, p-value 0.01, n=80) and ALT (259 IU/L versus 220, p-value 0.0454, n=83) in the non-obstructive group while the GGT levels (914 IU/L versus 181, p-value < 0.001, n=21) were markedly elevated in patients with obstruction. Mean baseline serum albumin levels were normal for age in both groups; however, it was significantly lower in the obstructive group (31 versus 36, p-value < 0.001, n=91).

Comparison of maximum biochemical abnormalities and sonographic findings of the hepatobiliary tract at presentation as shown in Table 3 revealed that GGT ≥ 300 IU/L and hepatomegaly on ultrasonography were more common in the obstructive group. On the other hand, a normal ultrasonography finding was more common in those with non-obstructive causes.

Factors predictive of an obstructive pathology among Filipino infants with neonatal cholestasis that were statistically significant on the univariate analysis included: female sex, persistently pale yellow to acholic stools, high-grade hepatomegaly and splenomegaly on physical examination, GGT ≥ 300 IU/L, and presence of hepatomegaly on hepatobiliary tree ultrasound. Family history of idiopathic neonatal hepatitis and normal hepatobiliary tree ultrasound were significantly more common in infants with non-obstructive causes. Due to an inadequate sample size (n=50), GGT > 300 IU/L was not included in the final model. Multiple logistic regression showed that of the seven variables, only female sex (odds ratio [OR] of 2.32) and persistently pale yellow to acholic stools (OR 12.99) were significantly related to the occurrence of obstruction.

Table 2. Demographic and baseline clinical factors of 263 Filipino infants diagnosed with obstructive and non-obstructive neonatal cholestasis at the UP-PGH

Demographic and clinical factors	Obstructive NC	Non-obstructive NC	*p*-value	Crude odds value
Female sex	**45/102 (44.1%)**	49/161 (30.43%)	**0.026**	**1.804**
Onset of jaundice at <15 days old	53/100 (53%)	72/137 (52.55%)	1.000	0.982
Maternal age at birth (years)				
≤20	14/91 (15.38%)	20/130 (15.38%)	0.809	1.139
21-30	49/91 (53.85%)	77/130 (59.23%)		
31-40	24/91 (26.37%)	29/130 (22.31%)		
>40	4/91 (4.40%)	4/130 (3.08%)		
Positive maternal history for any illnesses or exposures during pregnancy	28/91 (30.77%)	45/127 (35.43%)	0.516	0.810
Firstborn	39/95 (41.05%)	64/134 (47.76%)	0.348	1.317
Family history of idiopathic neonatal hepatitis	**6/74 (8.11%)**	24/102 (23.53%)	**<0.001**	**0.287**
Low birth weight (<2.5 kg)	3/30 (10%)	15/54 (27.78%)	0.094	0.289
Prematurity	7/94 (7.45%)	17/127 (13.39%)	0.193	0.521
Feeding type				
Pure breastfeeding	39/67 (58.21%)	57/111 (51.35%)	0.654	0.833
Mixed feeding	16/67 (23.88%)	29/111 (26.13%)		
Bottle feeding	12/67 (17.91%)	25/111 (22.52%)		
Persistently pale yellow to acholic stools	**89/101 (88.12%)**	49/131 (37.40%)	**<0.001**	**12.412**
High-grade hepatomegaly	**52/88 (59.09%)**	38/130 (29.23%)	**<0.001**	**3.497**
Splenomegaly	**53/89 (59.55%)**	54/134 (40.30%)	**0.006**	**2.181**
Presence of congenital anomalies	13/98 (13.26%)	24/135 (17.78%)	0.371	0.707

n/m wherein n = number of subjects fulfilling the parameter and m = total number of subjects tested; NC = neonatal cholestasis

Table 3. Comparison of maximum biochemical abnormalities and sonographic findings of the hepatobiliary tract at presentation in 263 Filipino infants with neonatal cholestasis, classified as the obstructive and non-obstructive cause

Result	Obstructive NC	Non-obstructive NC	*p*-value	Crude odds ratio
Maximum biochemical abnormality on initial consult				
TB >10 mg/dl (171 µmol/l)	66/102 (64.71%)	96/161 (59.63%)	0.437	1.241
DB >7 mg/dl (119.7 µmol/l)	54/102 (52.94%)	84/161 (52.17%)	1.000	1.031
AST >300 IU/L	38/80 (47.5%)	72/136 (52.94%)	0.440	0.804
Alkaline Phosphatase >200 IU/L	45/47 (95.74%)	64/66 (96.97%)	0.728	0.703
GGT ≥300 IU/L	**16/21 (76.19%)**	**5/29 (17.24%)**	**<0.001**	**15.36**
PT ≥4 sec. off from control	14/100 (14%)	13/151 (8.61%)	0.213	1.728
Sonographic findings of the hepatobiliary tract				
Normal	24/89 (26.97%)	**59/139 (42.45%)**	**0.024**	**0.501**
Hepatomegaly	**25/89 (28.09%)**	20/139 (14.39%)	**0.016**	**2.324**
Splenomegaly	4/89 (4.49%)	6/139 (4.32%)	1.000	1.043
Contracted/ absent gallbladder	49/89 (55.06%)	66/139 (47.48%)	0.280	1.355
Ascites	2/89 (2.25%)	3/139 (2.16%)	1.000	1.042
Liver parenchymal disease	5/89 (5.62%)	13/139 (9.35%)	0.451	0.577

n/m wherein n = number of subjects fulfilling the parameter and m = total number of subjects tested; NC = neonatal cholestasis

Table 4. Association between diagnosis and outcome of 263 Filipino infants with according to the type of neonatal cholestasis

Outcome	Obstructive NC, n= 102(%)	Non-obstructive NC, n= 161(%)	*p*-value
Alive without liver disease	1 (1)	137 (85.1)	
Alive with liver disease	19 (18.6)	9 (5.6)	**< 0.001**
Died or required a liver transplant	82 (80.4)	15 (9.3)	

N = number of subjects fulfilling the parameter; NC = neonatal cholestasis

On the other hand, a family history of idiopathic neonatal hepatitis decreased the risk of obstruction (OR 0.25).

The overall mean duration of follow-up was 8.5 months, with a longer period noted in those with obstruction [10 (SD 25) months vs. 7.6 (SD 4.1)]. Association between diagnosis and outcome (Table 4) showed that most infants with a non-obstructive cause are alive without liver disease. In contrast, most patients with obstruction have died or required liver transplants. The study could not determine who among these patients proceeded with liver transplantation and survived since the outcomes were assessed only at the 6th and 12th months from diagnosis.

DISCUSSION

Our present study showed that among Filipino infants presenting with jaundice within the first two months of life, predictors of an obstructive cause were: female gender, absence of a family history of idiopathic neonatal hepatitis, and presence of persistently pale or acholic stools. These findings underscore the importance of visual inspection of the stool color by an experienced physician in evaluating a cholestatic infant.

Our study used histology with or without an operative cholangiogram in making a final diagnosis of obstructive or non-obstructive cholestasis. Galluci et al. showed that liver biopsy exhibits a 100% sensitivity and 76% specificity in diagnosing biliary atresia, the most common cause of bile duct obstruction in infants.[10] The predominant histological pattern was reported by Vitug et al., with a giant cell pattern associated with neonatal hepatitis, which is non-obstructive, and an obstructive or fibrotic pattern with biliary atresia and other bile duct disorder, such as neonatal sclerosing cholangitis.[7]

Ninety-five percent of our patients with obstructive neonatal cholestasis were diagnosed with biliary atresia. The variables investigated in our study were based on their reported association with this disease. The age of onset of jaundice of less than 15 days was included. It was reported to be a sign of biliary atresia, suggesting that biliary injury starts before or soon after birth.[9,12,13] However, this was not demonstrated in our study. In terms of sex, the majority of our infants with obstructive cause were girls, consistent with the female predominance of the disease at 1.4:1.[14] Based on a 10-year Swedish national database comprising 1.2 million live births with 85 cases of biliary atresia identified, factors associated with this entity included high maternal age, parity of at least 4, low birth weight and history of prematurity, none of which were seen in our study.[15] On the other hand, low birth weight and prematurity were more common in non-obstructive jaundice in other studies.[5,12] A family history of idiopathic neonatal hepatitis was significantly more common

in the non-obstructive group in this study, and its presence decreases the risk of obstruction. Neonatal hepatitis has a 15-20% familial incidence, while biliary atresia's intrafamilial recurrence risk is negligible.[14] The stool color was also considered as the failure of bile to reach the duodenum, manifested as a pale yellow or acholic stool, which could signify a pathology anywhere from the hepatocytes to the ampulla of Vater. Eighty-eight percent of our patients with obstruction had a pale or acholic stool, similar to an 89 to 95% occurrence in other studies.[5,9] Of note, an abnormal stool color may also be seen among cholestatic infants with non-obstructive causes, as observed in 37% of our subjects and 27 to 43% in other reports.[5,9] Thus, stool color should be used as a screening for jaundiced infants, and its presence should alert the primary care physician on the need for an immediate referral to a specialty center. The institution has used a stool color card to screen for jaundiced infants with possible obstruction. This screening tool has been validated in Taiwan to decrease the number of late referrals among patients with biliary atresia.[16]

All our patients had liver function tests and the international normalized prothrombin ratio determination. Mean transaminases were slightly higher in those with non-obstructive cause, suggesting a greater degree of inflammation in the hepatocytes that releases these enzymes.[17] In agreement with previous reports, the bilirubin levels were not discriminatory on admission.[9,17] However, it has been observed that obstructive cholestasis had stable bilirubin levels (fluctuations < 51 umol/L or 3 mg/100 ml) while non-obstructive jaundice had a steady fall in bilirubin levels.[5] It has been shown in this study and other reports that gamma-glutamyl transpeptidase, an enzyme secreted by the bile ducts, was significantly higher among those with obstruction.[9,17] Serum gamma-glutamyl transpeptidase > 300 IU/L has been reported to have a sensitivity of 52% and specificity of 83% for biliary atresia.[9] Serum GGT was previously not routinely included on the liver function tests in our institution, and we only have the results on fifty patients. Therefore, we could not prove its utility in predicting and obstruction, as the variable could not be entered in the logistic regression.

In sonographic findings, intrahepatic ductal dilatation secondary to distal obstruction and decreased caliber of common bile duct has been shown to have an 80% accuracy for biliary atresia.[9] Other ultrasound findings suggestive of obstruction include absence or contracted gall bladder, dilatation of the bile ducts and biliary radicals, triangular cord sign, a tubular echogenic cord of fibrous tissue in portal hepatitis considered specific for biliary atresia.[14,18] In our study, only the presence of hepatomegaly on ultrasound was shown to differentiate an obstructive from a non-obstructive cause.[14,18] This may partly be due to subjectivity with ultrasound performed by different sonographers whose expertise and experience may be different knowing that an ultrasound examination is operator-dependent.

Eighty-five percent of our patients with non-obstructive neonatal cholestasis are alive without evidence of liver disease during the study period. A finding comparable to 84% and 86% reported in Taiwan and the United Kingdom, respectively, among patients with idiopathic neonatal hepatitis.[3,19] In this group of patients, the cause of jaundice was still unexplained after exclusion of a possible metabolic, infectious, or structural cause. Regarding genetic factors causing jaundice, alpha1-antitrypsin deficiency, the most common genetic cause of liver disease in Caucasian children, has a low incidence among Filipino infants presenting with neonatal cholestasis. Thus, genotype determination for alpha1-antitrypsin deficiency was not routinely done among our patients.[20]

CONCLUSION

The poor prognosis of our patients with obstructive causes, 80% had died, or required liver transplant confirms that early identification of these infants is essential if hepatic portoenterostomy for biliary atresia is to be carried out before 60 days life. Direct visualization alone of a pale yellow or acholic stool should already alert the primary physician to immediately refer jaundiced infants more than two weeks of life to a tertiary medical center for further evaluation. In this regard, the education and training of our physicians are essential.

We recommend that posters illustrating normal and abnormal stool color be made available in local health centers to increase parents' and physicians' awareness of the possible liver disease in a jaundiced infant instead of dismissing it as physiologic or breast milk jaundice.

Statement of Authorship

Both authors contributed in the conceptualization of work, acquisition of data and analysis, drafting and revising and approved the final version submitted.

Author Disclosure

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