Original Article

Clinical Features Differentiating Biliary Atresia from Other Causes of Neonatal Cholestasis

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Abstract

Introduction: This study determined any clinical features which may help to differentiate biliary atresia (BA) from other causes of neonatal cholestasis (NC). Materials and Methods: A prospective and observational study was conducted on consecutive infants with NC referred to the University of Malaya Medical Centre, Malaysia, between November 1996 and May 2004. Results: The 3 most common causes of cholestasis among the 146 infants with NC studied were idiopathic neonatal hepatitis (n = 63, 43%), BA (n = 35, 24%) and congenital cytomegalovirus hepatitis (n = 13, 9%). Common clinical features at presentation were jaundice (100%), hepatomegaly (95%), splenomegaly (52%) and pale stools (47%). Three clinical features noted to be sensitive for BA were the presence of acholic or variably acholic stools on admission, a liver which was firm/hard in consistency and a palpable liver of ≥4 cm (sensitivity of 77%, 80% and 94%, respectively), but the corresponding specificity was poor (51%, 65% and 39%, respectively). The stools of 2 children with BA were pigmented initially but became acholic subsequently. Conclusions: We did not find any single clinical feature with sufficient sensitivity and specificity to differentiate BA from other causes of NC. Repeated inspection of stools colour is necessary as occasionally, patients with BA may have initial pigmented stools. Biochemical assessment and imaging studies are important in the assessment of any infant with NC.

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Introduction

Causes of neonatal cholestasis (NC) are long and diverse but the responses of newborn liver, either physiological or anatomical, are limited.[1] This is because the ability of a developing liver of responding in the face of a variety of insults are limited.[1] Thus infants with NC usually presented with variable degrees of jaundice, dark urine, pale stools and enlarged liver, all of which are non-specific features of NC.[2]

Biliary atresia (BA) is an important cause of NC.[3] Early diagnosis and surgery for BA is important to ensure higher success rates for surgery and better long-term outcomes.[3] BA usually presents shortly after birth with persistent jaundice, pale stools, and dark urine in term infants with normal birth weights.[3-7] However, jaundice, pale stools and dark urine, individually, are imperfect ways of differentiating BA from other causes of cholestasis in NC.[8] Jaundice is a frequent and early presenting feature of NC,[9] but persistent jaundice at 2 weeks of age is also a relatively common finding, being observed in 2.4% to 15% of all newborns.[10,11] In addition, visual screening of jaundice for hyperbilirubinaemia may yield many false positive results.[11] Stools of an infant with BA are often acholic, but in the early course of the disease, the incomplete or evolving obstruction may cause the stools to appear normally pigmented or intermittently pigmented.[3]

The objective of this study was to determine if persistent jaundice, pale stools and enlarged liver and/or spleen in infants first admitted with NC could differentiate BA from other causes of NC.

Materials and Methods

This prospective, descriptive study was conducted at the Department of Paediatrics, University of Malaya Medical Centre (UMMC), Kuala Lumpur and was approved by the institutional medical ethics committee.

Patients

All patients with NC referred to the Department of Paediatrics, UMMC between November 1996 and

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May 2004 were enrolled in the study. NC was defined as the onset of clinically apparent jaundice within the first 4 months of life, with the conjugated bilirubin >17 μmol/L if the total bilirubin was <85 μmol/L, or the conjugated bilirubin >20% of the total bilirubin if the total bilirubin was <85 μmol/L.[8]

Clinical Features on First Admission

History taking and physical examination of all patients were conducted by the first author whenever feasible. If the initial clinical encounter was not conducted by the first author, the first author would interview the parents and performed physical examination personally during subsequent visits. History, which included basic demography, perinatal histories, family history of liver diseases or other medical histories, was obtained directly from the parents. The following data were obtained during physical examination: growth parameters, presence of associated physical anomalies, abdominal examination, enlarged liver and/or spleen and ascites. The size and consistency of palpable liver and/or spleen were determined, if present. Other significant physical findings were also noted.

Definitions and Diagnostic Criteria

Neonatal jaundice was defined as the presence of jaundice with predominantly unconjugated bilirubin within the first 2 weeks of life. The colour of the stools was inspected during the first admission by the first author, and was classified as follows: pale (completely and uniformly devoid of any green or yellow pigments), slightly pale (contains mixture of pale and normally pigmented stools, or uniform in colour but not normally pigmented), or normally pigmented (uniformly and normally pigmented). The degree of jaundice was classified into mild (mild yellowish discolouration mainly confined to the sclera and on the face), moderate (obvious yellowish discolouration involving the most part of the body), and severe (deep yellowish discolouration involving the entire body). The size of liver (in centimetre, measured with a non-stretchable measuring tape) was measured along the mid-clavicular line below the right costal margin. Hepatomegaly was defined as a palpable liver of ≥2 cm below the right costal margin along the mid-clavicular line. The upper border of the liver was not determined because of the imprecise nature of such measurement. Splenomegaly was defined as a palpable spleen of any size below the costal margin. The size of spleen was measured between its tip and the left costal margin. The upper border of the spleen was not determined.

BA was diagnosed based on the criteria described by McKiernan et al[12] and Fischler et al.[13] All cases of BA were confirmed with operative cholangiogram, or demonstration of atretic gall bladder and/or extrahepatic biliary tree intra-operatively.[12,13] All surgery were either performed by a single paediatric surgeon, who has more than 30 years' experience in the field of paediatric surgery, or by his trainee under his supervision.

Diagnosis of other causes of NC were made according to standard clinical practices.[14,15] Diagnosis of progressive familial intrahepatic cholestasis (PFIC) was made based on the criteria of Whittington et al,[16] which consisted of all of the following: chronic unremitting cholestasis with onset in infancy; exclusion of anatomical and metabolic aetiologies after a thorough clinical, laboratory and radiological evaluation; typical biochemical markers of cholestasis, including increased levels of conjugated bilirubin and alkaline phosphatase, but low to normal levels of serum γ-glutamyl transferase. A positive family history was necessary if γGT was not low.[17]

Cytomegalovirus (CMV) hepatitis was diagnosed based on the following criteria: NC and a positive CMV IgM antibody in the absence of other aetiologies.[18] Alpha-1 antitrypsin (α1AT) deficiency was diagnosed by performing serum α1AT levels and phenotypes. Neonatal haemochromatosis was diagnosed on the presence of neonatal acute liver failure in association with at least 2 of the following: (i) positive family history and/or prenatal history, (ii) high serum ferritin levels, (iii) histological confirmation (Perl's stain) of hepatic and extrahepatic non-reticuloendothelial iron deposition, (iv) magnetic resonance imaging confirmation of iron overload in organs other than the liver.[19] An infant is considered as having idiopathic neonatal hepatitis (NH) after thorough history, physical examination and laboratory evaluations fail to identify an underlying cause of the NC.[20]

A final review on the diagnosis of all cases of NC was made in May 2007, 3 years after the enrollment of the last patient. For the purpose of comparison, all patients with NC were divided into 2 groups, either BA or non-BA (i.e. all other diagnoses). Only patients who were adequately investigated with a known final outcome were included in the final analysis.

Statistical Method

Data were entered using Statistical Package for Social Science 11.0 (Social PSS; Chicago, Illinois) for Windows XP. Data are quoted as medians and range. Chi-square tests were used for categorical data while student *t*-test was used for comparison of numerical data.

Results

During the study period, a total of 146 patients who fulfilled the inclusion criteria of NC were studied. The underlying aetiologies of NC in these 146 patients are shown in Table 1. The most common identifiable cause of NC in the present cohort was BA (n = 35, 24%).

Demography and Birth History

The clinical features at initial presentation of these 146 patients are shown in Table 2. BA was more common among females when compared to other aetiologies of NC. There were no difference between BA and non-BA in terms of gestational age or birth weight. Majority of the infants with NC were delivered at term (median gestational age for BA: 40 weeks, for non-BA: 39 weeks, Table 2). No patient with BA had similar problem among other family members. One patient with PFIC has an elder brother who died of progressive cholestasis during infancy at another hospital. The cause was undetermined.

Table 1. Final Diagnosis of 146 patients with Neonatal Cholestasis Referred to Department of Paediatrics, University of Malaya Medical Centre, Kuala Lumpur between 1996 to 2004

Final diagnosis	**n**	**%**
Bile duct obstruction		
Cholangiopathies		
Biliary atresia	35	24
Choledochal cyst	1	0.7
Alagille syndrome	1	0.7
Caroli disease	1	0.7
Other		
Inspissated bile syndrome /mucous plug	1	0.7
Neonatal hepatitis		
Idiopathic		
Idiopathic neonatal hepatitis	63	43
Viral		
Cytomegalovirus	13	9
Herpes-simplex virus	2	1.5
Bacterial		
Urinary tract infection	3	2
Cholestatic syndromes		
Progressive familial intrahepatic cholestasis	5	4
Endocrine		
Congenital adrenal hyperplasia	1	0.7
Congenital hypothyroidism	3	2
Congenital hypopituitarism	1	0.7
Metabolic		
Galactossaemia	1	0.7
Neonatal haemachromatosis	2	1.5
Acute liver failure, undefined	4	3
Toxic		
Parenteral nutrition associated- cholestasis	7	5
Miscellaneous		
Perinatal asphyxia	2	1.5
Total	146	100

Age of Onset of Jaundice and Age of Referral

The history of neonatal jaundice was present in 68% (n = 98 of 142 infants with information available) of all infants at birth (Table 2). In approximately two-thirds of all these infants (68%), the neonatal jaundice persisted and blended into cholestatic jaundice of NC. For infants with no history of preceding neonatal jaundice, the onset of cholestatic jaundice was 14 days for BA, which was significantly earlier than the 19 days for non-BA ($P = 0.006$). However, there was a significant delay in referral for infants with NC for further diagnosis (median age at referral: BA 60 days vs non-BA 58 days, $P = 0.045$).

All patients with PFIC had the neonatal jaundice with the onset of jaundice within the first few days after birth (median 3 days). The jaundice subsequently persisted in all patients beyond the neonatal period and blended into the cholestatic jaundice.

Physical Examination on Admission

Jaundice (100%), hepatomegaly (94%), splenomegaly (52%) and presence of acholic stools (47%) were common physical findings in NC. There was no difference in the degree of jaundice between infants with BA and non-BA. Hepatomegaly was equally common in both groups of patients (BA 100% vs non-BA 94%). Patients with BA were more likely to have a palpable liver which was bigger in size (median size of palpable liver, BA 4 cm vs non-BA 3 cm, $P < 0.001$) and also firmer in consistency (BA vs non-BA, $P < 0.001$).

A palpable spleen was seen in approximately half of all infants on admission, irrespective of the underlying cause of cholestasis (BA 51% vs non-BA, 52%, $P = 0.13$). There was no difference in the size of spleen between the 2 diagnostic groups (median size of spleen, BA 2 cm vs non-BA 3 cm; $P = 0.13$).

The degree of pigmentation of stools on admission was variable, with 30% (n = 44) of patients who had pigmented stools on admission, while another 47% (n = 69) were completely acholic. The remaining 23% (n = 33) had variably acholic stools. The presence of acholic stools was more commonly seen in patients with BA (BA vs non-BA, $P < 0.001$). However, only 29 (83%) of 35 infants who had BA had pale stools on admission. In the remaining 6 patients, 4 had slightly acholic stools while the other 2 had pigmented stools on first presentation. In the latter 2 patients, the stools became completely acholic during the course of disease.

Ascites were uncommon on admission (n = 10, 7%) and

Table 2. History and Clinical Features Differentiating Biliary Atresia from Other Causes of Neonatal Cholestasis

		All (n = 146) N (%)	Biliary atresia (n = 35) N (%)	Other diagnoses (n = 111) N (%)	*P*
Male (%)		84 (58)	15 (43)	69 (62)	0.04
Gestational age; median (range; week)		40 (25-42)	40 (28-42)	40 (25-41)	0.56
Birth weight (median, kg)		2.90	3.00	2.90	0.22
Presence of neonatal jaundice,	Yes	99 (68)	23 (66)	76 (68)	0.60
	No	42 (29)	9 (26)	33 (30)	
	Uncertain	5 (3)	3 (9)	2 (2)	
Persistence of neonatal jaundice		67 (68)	18 (78)	49 (64)	
Onset of cholestatic jaundice, median (days)[a]		16	14	19	0.006
Age at referral; median (range; days)		59 (1-300)	60 (16-260)	58 (1-300)	0.045
Presence of other physical anomalies		16 (11)	4 (11)	12 (11)	0.60
Presence of clinical jaundice on admission		146 (100)	35 (100)	111 (100)	
Degree of jaundice:	Mild	41 (28)	5 (14)	36 (32)	0.09
	Moderate	59 (40)	19 (54)	40 (36)	
	Severe	35 (24)	9 (26)	26 (23)	
	Uncertain[b]	10 (7)	2 (6)	8 (7)	
Presence of hepatomegaly;	Yes	139 (95)	35 (100)	104 (94)	0.08
	No	7 (5)	0 (0)	7 (7)	
Consistency of liver	Soft	75 (54)	7 (20)	68 (61)	<0.001
	Firm	53 (38)	24 (69)	29 (26)	
	Hard	11 (8)	4 (11)	7 (6)	
Size of liver	2 cm	27	2	25	<0.001
	3 cm	34	6	28	
	4 cm	30	11	19	
	5 cm	29	10	19	
	≥ 6 cm	17	5	12	
Presence of splenomegaly		76 (52)	18 (51)	58 (52)	0.62
Size of spleen	1 cm	16	4	12	0.13
	2 cm	25	9	15	
	3 cm	21	1	20	
	4 cm	4	1	3	
	≥ 5 cm	15	3	8	
Presence of ascites		9 (6)	1 (3)	8 (7)	0.72
Colour of stools; Pigmented	44 (30)	2 (6)	42 (38)	< 0.001	
	Slightly pale	33 (23)	4 (11)	29 (26)	
	Pale	69 (47)	29 (83)	40 (36)	

[a] This group refers to infants without preceding neonatal jaundice.

[b] Uncertain: unable to ascertain degree of jaundice mainly due to dark complexion of skin.

Table 3. Diagnostic Usefulness of Various Clinical Features in Differentiating between Biliary Atresia and other Causes of Neonatal Cholestasis

Features	BA	non-BA	P-value	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
Size of liver [a]						
≥4 cm	27	51	0.001	77	51	55
<4 cm	8	53				
Consistency of liver						
Firm + hard	28	36	0.0001	80	65	68
Soft			7	68		
Colour of stools						
Slightly pale + pale	33	69	< 0.0001	94	39	51
Pigmented	2	42				

BA: biliary atresia
non-BA: non-biliary atresia, other diagnosis
[a]size of liver palpable below the right costal margin

was associated with an adverse outcome. The only patient who had ascites on admission and survived eventually was the one with the rupture of the choledochal cyst into the peritoneal cavity. One infant with BA who had ascites on admission had the embryonic form of BA. There was advanced liver cirrhosis upon laparotomy. Ascites was also seen in the other 4 patients who had neonatal acute liver failure and died subsequently. The remaining 4 patients who were diagnosed to have idiopathic neonatal hepatitis and ascites on admission were found to have advanced liver cirrhosis. All 4 died subsequently in the course of their illness.

Multiple logistic regression analyses showed statistically significant differences between the 2 diagnostic groups (BA vs non-BA) in 3 clinical parameters, that is the size and the consistency of liver and the colour of stools during the first admission. The presence of an enlarged and firm liver as well as acholic stools were more commonly seen in BA (Table 2). However, even though all these features were sensitive (sensitivity of 77%, 80% and 94%, respectively), none was specific (specificity 51%, 65%, and 39%, respectively) to differentiate BA from other causes of NC (Table 3).

Discussion

There are continuing efforts to alert primary care clinicians and paediatricians worldwide to recognise neonates with cholestatic jaundice at the earliest opportunity.[3,14,16] It is now recommended that BA should be excluded in all term infants who still have jaundice at 3 weeks of age.[3]

The evaluation of an cholestatic infant remains a challenge due to the diversity of cholestatic syndrome, their obscure pathogenesis and the non-specific clinical and pathologic features.[17] No single clinical feature or laboratory parameter have been found to show sufficient sensitivity and specificity to differentiate between BA and other causes of NC.[3,16] Diagnosis is often difficult.[14] However the surgery for BA should be performed as early as possible as the elimination of BA, to a great extent, depends on early surgery, therefore early referral should be made.[12,15]

In the present study, we found that common clinical features in NC were pale stools, an enlarged and firm liver and a palpable spleen. Jaundice was a universal finding, being seen in all infants with NC. Antecedent neonatal jaundice, which was present in slightly more than two-thirds of all patients, was equally common in infants with BA or other causes of NC. In approximately two-thirds of these infants, the neonatal jaundice persisted and blended into subsequent cholestatic jaundice of NC. We have previously observed that this may lead to a misdiagnosis of cholestatic jaundice as prolonged neonatal jaundice, the parents being falsely reassured, caused a delay in taking appropriate action.[14] In those patients without preceding neonatal jaundice, the onset of cholestatic jaundice was significantly earlier in patients with BA than those with other causes.

There was a trend for patients with BA to have a more severe degree of jaundice as compared to those with other causes of NC. However, this comparison maybe imprecise as classification of the degree of jaundice is subjective. In addition, the appearance of jaundice is also influenced by the complexion of the skin of patients.

An enlarged liver was also a common finding, being present in more than 90% of infants irrespective of the underlying cause. The size of the liver in infants with BA was significantly bigger (P <0.001) and harder in consistency (P <0.001) than those with other underlying aetiologies, which had previously been reported.[8,9] However,

it should be cautioned that assessment of the consistency of the liver is also a very subjective skill. The advantage of this present study was that it was prospective and all abdominal examinations were performed by a single clinician consistently over many years.

A detailed clinical history and observation of the stool colour by an experienced paediatrician have been considered as the most essential step in the evaluation of patients with NC.[3] The presence of pale stools has been considered a sensitive feature for BA.[10] However, it is not diagnostic of BA because many severe intrahepatic cholestasis may also be associated with persistently pale stools.[17] In the present study, presence of pale stools on admission was the most sensitive (94%) but least specific (39%) clinical feature for BA.

Conversely, it is generally assumed that the presence of documented pigmented stools suggests the patency of the biliary system and generally excludes BA.[17] However, the stools colour of BA, which is regarded as a progressive fibro-obliterative disorder, may change in the course of the disease.[18] Pigmented stools had been reported in the early course of disease in patients with BA.[7] In the present study, we also noted that 2 of the 37 infants who had BA had pigmented stools while another 4 had variably pale stools at initial presentation. In the patients who had initial pigmented stools, the age at initial referral were 47 days and 74 days, respectively. The stools of both patients became completely acholic in the course of the disease. Thus the presence of normally pigmented stools, particular in young infants, does not necessarily exclude BA. In occasional patients, the colour of the stools may change in the course of illness from being pigmented to completely acholic. Many authors now stress the importance of serial inspection of stools colour.[17,19] It is only when the stools are persistently pigmented can BA be confidently excluded.[17,19]

The present study reinforced the overlapping nature of the presenting clinical features of BA and other aetiologies of NC. We advocate a systematic approach which includes detailed history and physical examination, as well as appropriate investigations to all infants with NC. It is mandatory for the clinician responsible to inspect the colour of the stools on more than one occasion, even if the initial stool appears to be normally pigmented. Although the presence of acholic stools at initial presentation is more indicative of a patent biliary tract, occasionally, patients with BA may also have pigmented stools at initial presentation, especially early in the course of illness.

Conclusions

In conclusion, we did not find any single clinical feature that has sufficient sensitivity and specificity to differentiate BA from other causes of NC. It is important to realise that in the clinical approach of an infant with NC, repeated inspection of stools colour is necessary as patients with BA may have initial pigmented stools. Biochemical assessment and imaging studies are also important to assist in the assessment of any infant with NC to arrive at a timely diagnosis for appropriate management.

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