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Analysis of clinical parameters that contribute to the misdiagnosis of biliary atresia

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Abstract

Background: Biliary atresia (BA) is one of the most common and perplexing causes of neonatal cholestasis. Each year many cases of neonatal cholestasis are misdiagnosed as BA, resulting in unnecessary exploratory surgery. Therefore, the aim of our study was to analyze the clinical features and parameters that contribute to the misdiagnosis of BA. We used a retrospective study to compare BA and similar neonatal cholestatic diseases, which were confirmed by intraoperative cholangiography.

Methods: Six hundred and two infants that were suspected to have BA were recruited for the study. All cases were divided into a non-BA group and a BA group according to intraoperative cholangiography. In addition, each group was divided into three subgroups according to the patients age at surgery (group i, <60 d; group ii, 60–90 d; and group iii >90 d). The annual misdiagnosis rate of non-BA patients was calculated. Age at onset of jaundice and the liver function and ultrasound results were compared between the two groups and subgroups. Moreover, the positive predictive value and false positive rate of hepatobiliary scintigraphy in the diagnosis of BA were calculated. Finally, the disease spectrum of the non-BA group was analyzed.

Results: Of the 602 cases, 83 patients were diagnosed as non-BA. The remaining 519 cases were confirmed to have BA. There was no significant decline in the misdiagnosis rate of suspected BA cases by year. The age at onset of jaundice, total bilirubin (TBIL), direct bilirubin (DBIL), DBIL/TBIL and alanine aminotransferase (ALT) values before the exploratory operation showed no statistically significant difference ($P>0.05$) in the non-BA versus BA groups. However, the mean level of gamma-glutamyl transpeptidase (γ-GT) was 263.2 mmol/l in the non-BA group and 902.7 mmol/l in the BA group ($P<0.01$). The length of the liver below the ribs was detected with ultrasound and found to be smaller in the non-BA group than that of the BA group (2.99 cm±1.62 vs. 3.61 cm±1.26, respectively; $P<0.05$). Among the 498 infants who received hepatobiliary scintigraphy examination, the false positive rate was 13.3% (66/498) and the positive predictive value was 86.7% (432/498). In the non-BA group, 58 infants suffered from hepatitis syndrome, 16 cases were biliary dysplasia, 5 cases were TPN related cholestasis, 2 cases were bile duct perforation and 2 were bile-plug syndrome.

Conclusion: The similarity of liver function tests and excessive dependence on hepatobiliary scintigraphy may contribute to the misdiagnosis of infants with jaundice. The age at onset of jaundice, the level of γ-GT and the liver length below the ribs may be helpful in the differential diagnosis of jaundice in infants.

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Biliary atresia (BA) is a rare neonatal disease, which manifests as progressive cholestasis [1–3]. BA is characterized by periductular inflammation and fibrosis that is associated with the progressive obliteration of the bile ducts [1–3]. In addition, BA is the leading indication for pediatric liver transplantation worldwide. The majority of untreated BA patients die from cirrhosis within one year after birth [4]. The outcome of BA patients is largely dependent upon receiving a prompt Kasai portoenterostomy to re-establish bile flow [5].

The inability to distinguish between cholestatic syndromes and extrahepatic BA can lead to the misdiagnosis of BA in many cases of neonatal jaundice due to the lack of high specificity current non-invasive screening methods. Unfortunately, the misdiagnosis of BA in non-biliary atresia (non-BA) patients results in unnecessary exploratory surgeries, which are both unproductive and potentially harmful due to surgical complications. Therefore, there is a critical need for obstructive jaundice in neonates to be accurately differentially diagnosed [6–8].

The goal of our retrospective study was to evaluate the differences in the clinical parameters of infants with a suspected BA diagnosis that underwent exploratory surgery at our institution. Evaluation of the parameters that lead up to the misdiagnosis of BA may reveal possible methods to improve the differential diagnosis of BA from other causes of neonatal cholestasis.

1. Materials and methods

1.1. Clinical data

From 2004 to 2010, 602 (345 males and 257 females) infants that underwent operative cholangiography in the Surgery Department of Children's Hospital of Fudan University were included in our retrospective study. All the patients received operative cholangiography at an average age of 74.4 days. Clinical data, including the age at onset of jaundice, total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), gamma-Glutamyltransferase (γ-GT), the liver length below the ribs and hepatobiliary scintigraphy examination were collected. The Children's Hospital of Fudan University approved this study.

1.2. Diagnostic criteria

The confirmed diagnosis of BA was based on intraoperative cholangiography. The gallbladders or the remnants of gallbladders were found and punctured with an entry needle in a laparoscopy or laparotomy operation. Next, water-soluble contrast medium was injected and an upper abdominal X-ray was taken (Fig. 1). BA was confirmed if the extrahepatic bile duct and (or) intrahepatic bile ducts were not developed. The patients were divided into a BA group (519 cases) and a non-BA group (83 cases) according to the above criteria.

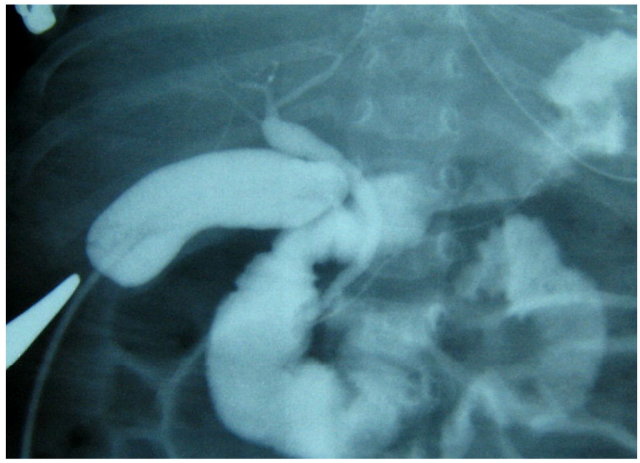

Fig. 1 Intraoperative cholangiography. The picture shows that the contrast medium can enter into the duodenum and hepatic ducts of grade II and III after lavage with saline. Therefore, BA can be excluded.

1.3. Statistical methods

The annual misdiagnosis rate of non-BA patients from 2004 to 2010 was analyzed using a trend chi-square test. The age at onset of jaundice, TBIL, DBIL, DBIL/TBIL, ALT, γ-GT and ultrasound results from the two groups were compared by t-test. The TBIL, DBIL, ALT and γ-GT also were compared according to different age categories. Moreover, the positive predictive value and false positive rate of the hepatobiliary scintigraphy in the BA group were calculated. Finally, the disease spectrum of the non-BA group patients was analyzed.

2. Results

The proportion of non-BA diagnoses that received operative cholangiography from 2004 to 2010 was evaluated for each year [0.162 (6/37), 0.047 (2/43), 0.031 (2/64), 0.123 (9/73), 0.196 (18/92), 0.176 (24/137), and 0.141 (22/156)]. There was no significant trend by year ($P>0.05$) (Table 1).

Table 1 There was no significant trend in the proportion of non-BA infants that received cholangiography from 2004 to 2010.

Time (year)	2004	2005	2006	2007	2008	2009	2010
Non-BA	6	2	2	9	18	24	22
BA	31	41	62	64	74	113	134
Total	37	43	64	73	92	137	156
Misdiagnosis rate (%)	16.22	4.65	3.13	12.33	19.57	17.52	14.10